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Special Issue Reprint

Commemorative Issue Celebrating the 20th Anniversary of the Alzheimer's Foundation of America

Understanding and Treating Alzheimer's Disease

Edited by
Allison B. Reiss and Aaron Pinkhasov

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Commemorative Issue Celebrating the 20th Anniversary of the Alzheimer's Foundation of America: Understanding and Treating Alzheimer's Disease

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Aaron Pinkhasov

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Editors

Allison B. Reiss
NYU Long Island School of Medicine
Mineola, NY
USA

Aaron Pinkhasov
NYU Long Island School of Medicine
Mineola, NY
USA

Editorial Office
MDPI AG
Grosspeteranlage 5
4052 Basel, Switzerland

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About the Editors

Allison B. Reiss

Allison B. Reiss is an Associate Professor of Medicine at NYU Grossman Long Island School of Medicine and Head of the Inflammation Research Laboratory in the Department of Foundations of Medicine. She received her M.D. degree from the College of Medicine at SUNY Downstate Health Sciences University and completed her residency in internal medicine at the University of Medicine and Dentistry of New Jersey, Rutgers. She is a board-certified internal medicine physician, molecular biologist, and educator with over 30 years of experience in biomedical research. Her basic and translational research program focuses on understanding underlying pathological mechanisms in Alzheimer's disease as a means of finding effective therapies. She is well published in medical and scientific journals and has chaired symposia at national and international conferences. Dr. Reiss has served and serves on multiple editorial boards and is the Section Editor-in-Chief, Neurology, of the journal *Medicina*. Dr. Reiss is a member of the American Federation for Medical Research. She has received numerous awards and grants from the National Institutes of Health, the American Heart Association, and the Arthritis Foundation and is currently funded by the Alzheimer's Foundation of America. She has a strong passion for community outreach and is dedicated to improving healthcare, especially for older populations.

Aaron Pinkhasov

Aaron Pinkhasov, M.D., is the founding Chair of Psychiatry at NYU Langone Hospital–Long Island and is a Clinical Professor of Psychiatry and Medicine at NYU Grossman Long Island School of Medicine. He is a clinical investigator and a practicing clinician who completed a combined Internal Medicine and Psychiatry Residency program at SUNY Downstate Medical Center in Brooklyn, New York. His expertise extends to general psychiatry, psychosomatic medicine, and psychopharmacology. He has a specific interest in areas overlapping medical and psychiatric health. He has vast experience treating patients with a wide variety of psychopathologies. The author of multiple publications and presentations, his clinical expertise and areas of research include neurocognitive disorders as well as the role of psychiatry services in optimizing health outcomes. Together with Dr. Allison B. Reiss and Dr. Irving H. Gomolin, he has established NYU Langone Hospital–Long Island as a center for Alzheimer's treatment and research. He is currently an investigator on an Alzheimer's Foundation of America-funded study of Alzheimer's disease molecular pathways. Dr. Pinkhasov has received multiple professional honors, including the President's Award from the Office of the President, Borough of Brooklyn, and the Innovative Model for Integrated Care Award from the Association of Medicine and Psychiatry in 2017. He is a Distinguished Fellow of the American Psychiatric Association and a Fellow of the Academy of Consultation and Liaison Psychiatry.

Preface

The Alzheimer's Foundation of America (FA) has a mission statement that shows its dedication to persons with Alzheimer's disease and their families. Their mission is to "provide support, services, and education to individuals, families, and caregivers affected by Alzheimer's disease and related dementias nationwide and fund research for better treatment and a cure." In honor of this vision of a brighter future for those affected by Alzheimer's disease, we present this volume in commemoration of the 20th anniversary of the AFA. We have compiled 11 chapters addressing a variety of aspects of Alzheimer's disease pathogenesis, diagnosis, effect on quality of life, impact on family and caregivers, and therapeutic approaches. The authors of this compendium are experts in their fields and we believe that the information they have shared in this volume will be helpful to healthcare providers, caregivers, researchers, and people living with dementia and their loved ones. There are many recent innovations that are allowing those with dementia to live well while progress is being made. We express optimism that breakthrough treatments for Alzheimer's disease are on the horizon.

Allison B. Reiss and Aaron Pinkhasov
Editors

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Editorial

Special Issue "Commemorative Issue Celebrating the 20th Anniversary of the Alzheimer's Foundation of America: Understanding and Treating Alzheimer's Disease"

Allison B. Reiss * and Aaron Pinkhasov

Department of Medicine and Biomedical Research Institute, NYU Grossman Long Island School of Medicine, Mineola, NY 11501, USA

* Correspondence: allison.reiss@nyulangone.org

Alzheimer's disease (AD) is the most common form of dementia in older persons. It is a relentless, progressive neurodegenerative disorder, leading to cognitive impairment, deterioration of functional capacity and, ultimately, death [1,2]. The underlying causes of AD remain incompletely understood and, despite the allocation of huge resources towards finding a cure, progress has been slow. Pathologically, the AD brain is characterized by the accumulation of extracellular amyloid plaques and intraneuronal neurofibrillary tangles of phosphorylated tau protein [3]. Mitochondrial abnormalities, neuroinflammation, and synaptic dysfunction are also observed [4]. The economic burden and stress on caregivers and loved ones continues to grow as the population ages [5]. This compelling collection of articles provides a unique update on many practical aspects of navigating the care and treatment of persons with AD with a forward-looking perspective on promising therapeutic approaches.

In this Special Issue, we showcase several studies addressing the caregivers who take on the responsibilities of tending to the needs of a person with AD. This can take a heavy toll [6,7]. In their article, Sánchez-Alcón et al. present a descriptive correlational cross-sectional study of family caregivers studying dementia grief, which is the feeling of loss experienced by the caregiver prior to the physical death of the person with dementia [8]. Based on self-administered questionnaires, they found that dementia grief intensity was correlated to depressive symptoms and caregiver strain. Cohen and his team used a cross-sectional design in an exploratory analysis of the relationships among caregiver burden, physical frailty, race, and behavioral and psychological symptoms (BPSD) [9]. They found that frailty affected caregiver burden and BPSD functioned as a mediator between various predictor variables and caregiver burden. Hellis and Mukaetova-Ladinska present a review article covering the mental and physical demands placed on informal caregivers, with an emphasis on the need for support from within and outside the network of friends and relatives to mitigate some of the stress, anxiety and depression that can accompany caregiving [10].

Three articles draw attention to key aspects of making the diagnosis of AD. De Levante Raphael discusses the role of the primary care physician in recognizing dementia and the obstacles and difficulties involved. The author points out the need to educate primary care physicians so that they can perform cognitive assessment in older adults, detect impairment, and manage care [11]. Cummings and Kinney undertake a review of the rapidly evolving field of AD biomarkers [12]. They summarize the categories of biomarkers and their role in diagnosis, prediction, prognosis and monitoring of AD. Attention is given to the regulatory process in biomarker development, clinical validation, and the transition from use in clinical trials to application in clinical care. Dastgheib et al. report on their pilot study, applying electrovestibulography to 16 patients with AD, 13 with a mixed pathology of AD-cerebrovascular disease (AD-CVD), and 24 healthy age-matched controls [13]. They incorporated a cutoff Montreal Cognitive Assessment score, and then used their pilot

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electrovestibulography data to develop a hierarchy diagnostic algorithm to classify subjects as AD, AD-CVD, or control, and tested the robustness of the most informative features of the results against a blind testing dataset. They hope to use this algorithm to bring better accuracy to the challenge of distinguishing AD from AD-CVD.

The treatment of AD is the focus of three papers. Stecker gives a perspective on the broad issues in AD and the potential for implementing a new model encompassing large-scale collaborations and big data to achieve desperately needed innovations in treatment [14]. Angelopoulou et al. consider the value of telemedicine as a tool for bringing care to persons with dementia [15]. They point out the advantages of telemedicine in providing broad access to patient-centered, integrated care, especially for those living in remote areas and those with mobility issues. The convenience, reliability and reasonable costs associated with virtual visits are considered, and the limitations, such as need for digital proficiency and internet connectivity, are outlined. Reiss et al. investigate the current status of developments in AD therapy based on our escalating knowledge of brain biology at the molecular and genetic level [16]. They give a synopsis of novel approaches using small molecules, stem cells, repurposed drugs, deep brain stimulation, and dietary measures. New delivery systems and the shifting of resources away from anti-amyloid therapy brings optimism for future progress toward disease-modifying original therapeutics.

Ding et al. examine the value of a plant-based diet in maintaining cognitive health and mental sharpness [17]. In an organized fashion, they lay out the dietary guidelines and recommendations for nutrients and fiber that have been found to benefit brain health. Consideration is also given to the gut–brain axis and microbiome.

Together, the studies in this Special Issue highlight the importance of caregiving, diagnosis, treatment, and lifestyle in AD. We hope that the reader will find this collection to be a useful reference with tools and information dealing with both pragmatic and theoretical aspects of AD management.

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Article

Relationship between Depressive Symptoms, Caregiver Strain, and Social Support with Dementia Grief in Family Caregivers

Miriam Sánchez-Alcón [1,*], Almudena Garrido-Fernández [1], José María Cano-Rojas [2], José Luis Sánchez-Ramos [1] and Juan Diego Ramos-Pichardo [1]

[1] Nursing Department, Nursing Faculty, University of Huelva, 21007 Huelva, Spain; almudena.garrido@denf.uhu.es (A.G.-F.); jsanchez@uhu.es (J.L.S.-R.); juan.ramos@denf.uhu.es (J.D.R.-P.)
[2] Provincial Federation of Associations of Family Caregivers of People with Alzheimer's Disease and other Dementias of Huelva and Province, 21710 Huelva, Spain; afabollullos@alzheimerdehuelva.org
* Correspondence: miriam.sanchez@denf.uhu.es; Tel.: +34-959218130

Abstract: *Background and Objectives*: Dementia grief in family caregivers of people with dementia refers to grieving prior to the death of the care recipient. It is related to psychosocial risk factors that may have a negative impact on the health of these family caregivers. This study aimed to describe the relationship between depressive symptoms, caregiver strain, and social support with dementia grief in family caregivers of people with dementia. *Materials and Methods*: A descriptive correlational cross-sectional study was conducted. A total of 250 family caregivers of people with dementia participated. Dementia grief was the main variable, and depressive symptoms, caregiver strain, and social support were assessed. Additionally, socio-demographic data were collected. Descriptive statistics were calculated, and a bivariate correlation analysis and a multiple linear regression analysis were performed for dementia grief. *Results*: Higher scores for dementia grief were found in women, in family caregivers of patients at advanced stages of dementia, and in family caregivers with a low level of education. High levels of depressive symptoms and caregiver strain and low levels of social support indicated greater intensity of dementia grief. Depressive symptomatology was the variable with the greatest influence on dementia grief. Caregiver strain and social support also related to dementia grief, but to a lesser extent. *Conclusions*: In family caregivers, depressive symptoms, caregiver strain, and social support are related to the intensity of dementia grief, with a greater influence of depressive symptoms. Moreover, being female, having a low level of education, and caring for a care recipient at an advanced stage of dementia are factors associated with increased dementia grief. Concerning study limitations, the sample was restricted, belonging to a specific region of Spain and to a Provincial Federation of associations. It is necessary to exercise caution in generalizing results due to the sociodemographic and geographical characteristics of the sample.

Keywords: dementia grief; family caregiver; depressive symptoms; caregiver strain; social support

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1. Introduction

Dementia is currently considered a global public health challenge. With the ageing of the world's population, the prevalence of this disease has been on the rise, with more than 55 million people worldwide affected, and an estimated 139 million affected by 2050 [1].

Dementia not only affects those who suffer from it, but also has a significant impact on the lives of family members who provide care for people with this disease. Caring for people with dementia is a challenging and complex task, given that as the dementia progresses, family caregivers must adapt to the physical and mental deterioration of the care recipient. These changes impose a heavy workload on family caregivers, causing physical, psychological, and social problems that affect their health. In fact, they are often forced to give up a considerable part of their lives to devote to caring, with lifestyle and professional readjustments [2,3].

These conditions are highly stressful and generate a sense of loss in family caregivers prior to the death of the care recipient, which has recently been described as "dementia grief" [4]. Dementia grief is a complex phenomenon that is related to psychosocial and physical variables that can have a negative impact on the quality of life of family caregivers [5,6]. This concept refers to feelings related to the anticipation of future death together with losses (social, professional, emotional, and independence losses) that occur during the experience of caring for people with dementia [4,7,8].

This experience is characterized by progressive and continuous losses caused by the disease; prolonged and uncertain time of care; difficulties in patient-caregiver communication; disappearance of the identity of the loved one, who is physically present but psychologically absent; and deterioration of relationships owing to the new family roles [4,5,9]. Dementia grief is different from anticipatory grief. Anticipatory grief focuses exclusively on the feelings experienced by family caregivers before the death of a loved one occurs [10,11]. However, dementia grief is a broader concept, which also includes the emotional and psychological anticipation of family caregivers prior to the death of the person with dementia, along with the caregiver's own losses (social, professional, and independence losses, etc.) [6].

A recent review has shown a positive relationship between depression, burden, and social isolation with anticipatory grief in family caregivers of people with dementia. This association suggests that as levels of depression, burden, and social isolation increase, anticipatory grief will also increase. Furthermore, this relationship also indicates that these variables could be considered predictors factors of the onset of anticipatory grief [12]. However, in the literature, there are very few studies linking these variables to dementia grief.

Some studies have reported a relationship between depressive symptoms [4,13–15], strain and overload [8,15,16], and social support [17] in family caregivers with experienced dementia grief. However, few studies have analyzed these variables jointly. Therefore, the aim of this study was to describe the relationship between depressive symptoms, caregiver strain, and social support with dementia grief in family caregivers of people with dementia.

2. Materials and Methods

2.1. Research Design and Study Participants

A descriptive correlational cross-sectional study was conducted on a sample of 250 family caregivers of people with dementia from the province of Huelva (Spain). For inclusion in this study, the participants had to meet the following inclusion criteria: be at least 18 years of age, be a family caregiver of people diagnosed with dementia in the home and be able to read and speak Spanish. As exclusion criteria, family caregivers with any condition (visual, cognitive, etc.) that may hinder their ability to read and understand were not included.

2.2. Data Collection

All family caregivers belonging to the Provincial Federation of Associations of Family Caregivers of People with Alzheimer's Disease in Huelva who met the inclusion criteria were contacted. Group appointments were scheduled, at which the purpose of the research was made clear to the participants, and a brief description of the research was given to them in printed form. Those who agreed to participate received an informed consent form together with a data collection booklet containing the necessary measurement instruments. Participants completed the questionnaires in approximately 20 min.

2.3. Instruments

2.3.1. Marwit–Meuser Caregiver Grief Inventory-Short Form (MM-CGI-SF)

The Marwit–Meuser Caregiver Grief Inventory-Short Form [18] is a tool used to measure dementia grief in caregivers of people with dementia. It consists of 18 items distributed in three subscales, with 6 items each: (a) Personal Sacrifice Burden (PSB), which

assesses the personal sacrifices that the caregiver suffers as a consequence of caregiving; (b) Heartfelt Sadness and Longing (HS&L), which measures the emotional responses felt by the caregiver while providing care to the person with dementia; and (c) Worry and Felt Isolation (W&FI), which assesses the caregiver's perception of the lack of social interaction and support from others.

The items included in the questionnaire were assessed using a 5-point Likert-type response scale, which prompted participants to express their degree of agreement or disagreement with each item (from 1 = Strongly Disagree to 5 = Strongly Agree). The total scores for each subscale were calculated, and additionally, an overall score was obtained by adding the scores of the three subscales. The higher the MM-CGI-SF score, the more intense the grieving experience for the caregiver [19].

2.3.2. Patient Health Questionnaire-9 (PHQ-9)

This is a self-administered questionnaire that aims to assess the presence and severity of depressive symptomatology. It has 9 items that participants must answer using a Likert-type scale composed of 4 options, ranging from 0 to 3 points. The overall score of the questionnaire ranges from 0 to 27 points. Its interpretation is as follows: scores between 0 and 4 indicate minimal depressive symptoms; 5 to 9 suggest mild depressive symptoms; 10 to 14 indicate moderate depressive symptoms; 15 to 19 indicate moderately severe depressive symptoms; and a score of 20 to 27 reflects severe depressive symptoms [20,21].

2.3.3. Caregiver Strain Index (CSI)

This is a self-assessment questionnaire composed of 13 items with dichotomous responses (true-false). Its purpose is to measure the degree of perceived overload and the level of strain in the performance of the caregiving role of caregivers of severely dependent persons. The total score can vary between 0 and 13 points. A total score equal to or higher than 7 indicates a high level of strain on the part of the caregiver in caring for the dependent person [22,23].

2.3.4. Duke–UNC Functional Social Support Questionnaire

This is a questionnaire that assesses individuals' perceptions of the assistance and support provided by their family and friends [24,25]. It is a self-administered questionnaire with a structure composed of two dimensions: confidential social support, which addresses the possibility of having people to communicate with; and affective social support, which looks at demonstrations of love, affection, and empathy.

The questionnaire consists of 11 items, rated on a Likert-type response scale ranging from 1 to 5. Therefore, the total scores obtained can vary between 11 and 55 points. A score equal to or higher than 32 indicates perceived fair social support, while a score below 32 suggests perceived low social support.

Socio-demographic data of the participants were collected: age, sex, level of relationship with the care recipient, educational level, days per week caring for the patient, and years of caregiving. In addition, data on the stage of dementia of the care recipient were collected.

2.4. Data Analysis

For the description of the sample, descriptive statistics (means, standard deviations, ranges, medians, absolute values, and frequencies) were calculated. Parametric tests were used (Student *t*-test and 1-Way Anova) for the comparison of means.

Pearson correlations were calculated, linking the scores of the MM-CGI-SF and its subscales, and the rest of the variables. Subsequently, a multiple linear regression analysis was performed with the enter method, considering the total MM-CGI-SF and each subscale as dependent variables; in addition, the variables that had shown significant correlations in the correlation analysis were considered independent variables.

A data analysis was carried out using SPSS Statistics v.26 [26], and a 95% confidence level was established to determine statistical significance. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed [27].

2.5. Ethical Aspects

The study was approved by the Huelva Provincial Research Ethics Committee. Throughout the research, anonymity, confidentiality, and an appropriate handling of the participants' data were guaranteed. The ethical principles and fundamental research standards that govern all scientific research were rigorously maintained, in accordance with the Declaration of Helsinki.

3. Results

3.1. Descriptive Data of the Sample

A total of 250 family caregivers of people with dementia participated in the study, of whom 80.4% were women, with a mean age of 58.22 (SD = 12.7) years. The majority were daughters of the patients (62%; *n* = 155), with primary education (36%; *n* = 90), who had been caring for their relative presenting with moderate-stage dementia for several years ($\overline{X}$ = 5; SD = 3.6) (69.6%; *n* = 174), with a mean dedication of 6.1 (SD = 1.7) days per week.

With regard to dementia grief, the mean total score was 64.6 (SD = 14.8). Among the dimensions of the dementia grief, the W&FI scored the lowest ($\overline{X}$ = 18.5, SD = 5.7), and the HS&L, the highest ($\overline{X}$ = 23.3, SD = 5.4). The mean score for the PHQ-9 questionnaire was 11 (SD = 7); for the CSI, it was 7 (SD = 3.1); and for the Duke-UNC, it was 37.3 (SD = 10.4). Table 1 shows the descriptive data of the sample.

Table 1. Descriptive data of the sample.

Variables	*n* (%)	Mean	SD	Range	Median
Age		58.2	12.7	24–87	57
Sex					
Female	201 (80.4%)				
Male	49 (19.6%)				
Relationship with the care recipient					
Spouse/partner	79 (31.6%)				
Son/daughter	155 (62%)				
Other	16 (6.4%)				
Educational level					
No or incomplete education	29 (11.6%)				
Primary education	90 (36%)				
Secondary education	68 (27.2%)				
University education	53 (21.2%)				
Postgraduate education	10 (4%)				
Stage of dementia					
Mild	51 (20.4%)				
Moderate	174 (69.6%)				
Severe	25 (10%)				
Weekly days of care		6.1	1.7	1–7	7
Years of care		5	3.6	1–20	4
Personal Sacrifice Burden MM-CGI-SF(PSB)		22.7	5.4	6–30	23
Heartfelt Sadness and Longing MM-CGI-SF(HS&L)		23.3	5.4	6–30	25

Table 1. *Cont.*

Variables	*n* (%)	Mean	SD	Range	Median
Worry and Felt Isolation MM-CGI-SF(W&FI)		18.5	5.7	6–30	18
Dementia grief Total MM-CGI-SF		64.6	14.8	18–90	67
Depressive symptoms (PHQ-9)		11	7	0–27	10
Minimal	54 (21.6%)				
Mild	63 (25.2%)				
Moderate	58 (23.2%)				
Moderately severe	37 (14.8%)				
Severe	38 (15.2%)				
Caregiver Strain (CSI)		7	3.1	0–13	7
No high	105 (42%)				
High	145 (58%)				
Functional Social Support (Duke-UNC)		37.3	10.4	11–55	38
Low	69 (27.6%)				
Normal	181 (72.4%)				

SD: Standard deviation; MM-CGI-SF: Marwit-Meuser Caregiver Grief Inventory-Short Form; MM-CGI-SF(PSB): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Personal Sacrifice Burden); MM-CGI-SF(HS&L): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Heartfelt Sadness and Longing); MM-CGI-SF(W&FI): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Worry and Felt Isolation); PHQ-9: Patient Health Questionnaire-9; CSI: Caregiver Strain Index; Duke-Unc: Duke–UNC Functional Social Support Questionnaire.

Table 2 shows the mean scores of the dementia grief and its dimensions in relation to the rest of the variables. Differences were found in regards to sex, with higher scores in women, as well as regarding the educational level of the family caregiver, with higher scores in family caregivers with no or incomplete education, and in relation to the stage of dementia of the care recipient, with higher scores in cases of more advanced stages of dementia.

Table 2. Mean scores of the total MM-CGI-SF and its subscales in relation to the rest of the variables.

Variables	Personal Sacrifice Burden MM-CGI-SF(PSB)		Heartfelt Sadness and Longing MM-CGI-SF(HS&L)		Worry and Felt Isolation MM-CGI-SF(W&FI)		Dementia Grief Total MM-CGI-SF	
	Mean (SD)	*t*/*F* (*p*)	Mean (SD)	*t*/*F* (*p*)	Mean (SD)	*t*/*F* (*p*)	Mean (SD)	*t*/*F* (*p*)
Sex								
Female	23.1 (5.1)	–1.745 (0.056)	23.7 (5)	−2.057 (0.044)	18.9 (5.6)	–2.185 (0.030)	65.7 (14.1)	–2.439 (0.015)
Male	21.3 (6.3)		21.6 (6.4)		16.9 (5.8)		60 (16.7)	
Relationship with the care recipient								
Spouse/partner	23.6 (5.5)	2.075 (0.104)	24.2 (5.6)	1.401 (0.243)	19.6 (5.9)	1.972 (0.119)	67.6 (15.3)	2.140 (0.096)
Son/daughter	22.4 (5.4)		22.9 (5.4)		18.1 (5.6)		63.5 (14.8)	
Other	19.8 (4.5)		21.6 (4.7)		16.2 (4.2)		57.6 (10.8)	
Educational level								
No or incomplete education	25.3 (5.5)	3.068 (0.017)	26.4 (3.8)	4.983 (0.001)	22.7 (5.4)	6.459 (0.000)	74.5 (13.6)	5.793 (0.000)
Primary education	22.8 (5.1)		23.1 (5.7)		18.5 (5.4)		64.5 (14.4)	
Secondary education	22.5 (5.1)		23.5 (5.2)		18.4 (5.7)		64.4 (14.5)	
University education	22.2 (5.9)		22.5 (4.9)		16.9 (5.1)		61.7 (14.2)	
Postgraduate education	19.1 (5)		18.5 (5.9)		14.9 (5.3)		52.5 (13.7)	
Stage of dementia								
Mild	19.6 (6.5)	13.179 (0.000)	20.2 (6.4)	13.489 (0.000)	16.9 (6.6)	2.549 (0.080)	56.8 (18.2)	10.641 (0.000)
Moderate	23.2 (4.9)		23.8 (4.9)		18.8 (5.4)		66.0 (13.5)	
Severe	25.4 (3.7)		26 (3.7)		19.2 (5.3)		70.6 (9.7)	
Depressive symptoms (PHQ-9)								
Minimal	17.3 (5.3)	29.300 (0.000)	18.9 (6.2)	17.467 (0.000)	13.1 (4.2)	41.644 (0.000)	49.4 (14.1)	37.967 (0.000)
Mild	22.8 (4.2)		22.9 (4.9)		17.4 (4.5)		63.2 (11.4)	
Moderate	23.7 (4.8)		24.2 (4.4)		18.7 (4.7)		66.7 (12.4)	
Moderately severe	25.3 (3.8)		25.8 (3.8)		23.1 (4.1)		74.3 (9.5)	
Severe	26.4 (3.6)		26.1 (3.6)		23.2 (4.1)		75.8 (9.3)	
Caregiver Strain (CSI)								
No high	19.9 (5.9)	−7.283 (0.000)	21.5 (6.1)	–4.315 (0.000)	16.1 (5.8)	–6.132 (0.000)	57.6 (16)	–6.570 (0.000)
High	24.8 (3.9)		24.6 (4.4)		20.2 (4.9)		69.7 (11.5)	

Table 2. *Cont.*

Variables	Personal Sacrifice Burden MM-CGI-SF(PSB)		Heartfelt Sadness and Longing MM-CGI-SF(HS&L)		Worry and Felt Isolation MM-CGI-SF(W&FI)		Dementia Grief Total MM-CGI-SF	
Functional Social Support (Duke-UNC)								
Low Normal	24.6 (4.6) 22.0 (5.5)	3.404 (0.001)	24.6 (4.8) 22.8 (5.5)	2.344 (0.020)	21.7 (5.2) 17.2 (5.4)	5.886 (0.000)	71 (13.4) 62.1 (14.6)	4.336 (0.000)

t: Student t-test for independent samples; F: 1-Way Anova; *p*: significance level; SD: Standard deviation; MM-CGI-SF: Marwit-Meuser Caregiver Grief Inventory-Short Form; MM-CGI-SF(PSB): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Personal Sacrifice Burden); MM-CGI-SF(HS&L): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Heartfelt Sadness and Longing); MM-CGI-SF(W&FI): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Worry and Felt Isolation); PHQ-9: Patient Health Questionnaire-9; CSI: Caregiver Strain Index; Duke-Unc: Duke–UNC Functional Social Support Questionnaire.

Differences were also observed in dementia grief scores as regards depressive symptoms and caregiver strain, with higher scores in participants with more depressive symptoms and high caregiver strain. In terms of social support, the intensity of grief was higher in family caregivers with low social support.

3.2. Bivariate Correlations

Table 3 shows the correlations linking the MM-CGI-SF and its subscales, and the rest of the variables. Statistically significant positive correlations were found with depressive symptoms and caregiver strain, indicating a direct relationship. The correlation with perceived social support was also significant, although, in this case, with a negative value indicating an indirect relationship (the better the perceived social support, the lower the score in the MM-CGI-SF).

Table 3. Bivariate correlations between the MM-CGI-SF and its subscales in relation to the rest of the variables.

Variables	Personal Sacrifice Burden MM-CGI-SF(PSB)	Heartfelt Sadness and Longing MM-CGI-SF(HS&L)	Worry and Felt Isolation MM-CGI-SF(W&FI)	Dementia Grief Total MM-CGI-SF
Age	0.103 $p = 0.104$	0.075 $p = 0.238$	0.110 $p = 0.082$	0.107 $p = 0.90$
Sex	0.125 $p = 0.048$	0.149 $p = 0.018$	0.137 $p = 0.030$	0.153 $p = 0.015$
Relationship with the care recipient	−0.132 $p = 0.038$	−0.115 $p = 0.069$	−0.149 $p = 0.018$	−0.148 $p = 0.020$
Educational level	−0.181 $p = 0.004$	−0.210 $p = 0.001$	−0.270 $p < 0.001$	−0.247 $p < 0.001$
Stage of dementia	0.304 $p < 0.001$	0.308 $p < 0.001$	0.129 $p = 0.041$	0.273 $p < 0.001$
Weekly days of care	0.243 $p < 0.001$	0.116 $p = 0.067$	0.220 $p < 0.001$	0.216 $p = 0.001$
Years of care	0.180 $p = 0.004$	0.174 $p = 0.006$	0.114 $p = 0.071$	0.173 $p = 0.006$
Personal Sacrifice Burden MM-CGI-SF(PSB)		0.727 $p < 0.001$	0.720 $p < 0.001$	0.908 $p < 0.001$
Heartfelt Sadness and Longing MM-CGI-SF(HS&L)	0.727 $p < 0.001$		0.673 $p < 0.001$	0.890 $p < 0.001$
Worry and Felt Isolation MM-CGI-SF(W&FI)	0.720 $p < 0.001$	0.673 $p < 0.001$		0.893 $p < 0.001$
Dementia grief Total MM-CGI-SF	0.908 $p < 0.001$	0.890 $p < 0.001$	0.893 $p < 0.001$	
Depressive symptoms (PHQ-9)	0.537 $p < 0.001$	0.457 $p < 0.001$	0.640 $p < 0.001$	0.609 $p < 0.001$

Table 3. *Cont.*

Variables	Personal Sacrifice Burden MM-CGI-SF(PSB)	Heartfelt Sadness and Longing MM-CGI-SF(HS&L)	Worry and Felt Isolation MM-CGI-SF(W&FI)	Dementia Grief Total MM-CGI-SF
Caregiver Strain (CSI)	0.497 $p < 0.001$	0.379 $p < 0.001$	0.444 $p < 0.001$	0.490 $p < 0.001$
Functional Social Support (Duke-UNC)	−0.354 $p < 0.001$	−0.289 $p < 0.001$	−0.477 $p < 0.001$	−0.418 $p < 0.001$

p: significance level; MM-CGI-SF: Marwit-Meuser Caregiver Grief Inventory-Short Form; MM-CGI-SF(PSB): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Personal Sacrifice Burden); MM-CGI-SF(HS&L): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Heartfelt Sadness and Longing); MM-CGI-SF(W&FI): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Worry and Felt Isolation); PHQ-9: Patient Health Questionnaire-9; CSI: Caregiver Strain Index; Duke-Unc: Duke–UNC Functional Social Support Questionnaire.

With respect to the socio-demographic variables, the sex and educational level of the family caregiver, the stage of dementia in which the care recipient was, the family relationship between both of them, and the time devoted to caregiving were the variables that showed a relationship with the MM-CGI-SF (Table 3).

3.3. Multiple Linear Regression Analysis

Table 4 shows the multiple linear regression analysis results, considering total dementia grief and its three dimensions as dependent variables. For total dementia grief, the variable with the greatest weight was depressive symptomatology, followed by caregiver strain, stage of dementia, and educational level.

Table 4. Multiple linear regression results for each dependent variable.

Dependent Variables	Independent Variables	*B*	*SE*	*β*	*t*	*p*	Adjusted R^2
Personal Sacrifice Burden MM-CGI-SF (PSB)							0.447
	Constant	10.538	2.593		4.064	*<0.001*	
	Caregiver Strain (CSI)	0.588	0.98	0.344	6.010	*<0.001*	
	Depressive symptoms (PHQ-9)	0.235	0.046	0.302	5.065	*<0.001*	
	Weekly days of care	0.546	0.166	0.171	3.281	0.001	
	Stage of dementia	1.518	0.522	0.151	2.909	0.004	
Heartfelt Sadness and Longing MM-CGI-SF(HS&L)							0.312
	Constant	15.275	2.456		6.219	*<0.001*	
	Depressive symptoms (PHQ-9)	0.242	0.050	0.312	4.876	*<0.001*	
	Stage of dementia	2.045	0.572	0.204	3.577	*<0.001*	
	Caregiver Strain (CSI)	0.307	0.105	0.180	2.936	0.004	
	Educational level	−0.725	0.280	−0.141	−2.590	0.010	
Worry and Felt Isolation MM-CGI-SF(W&FI)							0.502
	Constant	15.037	2.548		5.902	*<0.001*	
	Depressive symptoms (PHQ-9)	0.325	0.046	0.398	7.078	*<0.001*	
	Caregiver Strain (CSI)	0.408	0.097	0.228	4.211	*<0.001*	
	Functional Social Support (Duke-UNC)	−0.095	0.029	−0.174	−3.319	0.001	
	Educational level	−0.785	0.258	−0.145	−3.046	0.003	
	Weekly days of care	0.339	0.165	0.101	2.049	0.042	
Dementia grief Total MM-CGI-SF							0.496

Table 4. *Cont.*

Dependent Variables	Independent Variables	*B*	*SE*	*β*	*t*	*p*	Adjusted R^2
	Constant	48.117	5.821		8.266	*<0.001*	
	Depressive symptoms (PHQ-9)	0.824	0.120	0.388	6.877	*<0.001*	
	Caregiver Strain (CSI)	1.206	0.249	0.258	4.849	*<0.001*	
	Stage of dementia	3.965	1.342	0.145	2.955	0.003	
	Educational level	−2.008	0.665	−0.142	−2.951	0.003	

B: Non-standardized regression coefficient; *SE*: standard error of the estimate; *β*: standardized regression coefficients; *t*: Student's test; *p*: significance level; MM-CGI-SF: Marwit-Meuser Caregiver Grief Inventory-Short Form; MM-CGI-SF(PSB): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Personal Sacrifice Burden); MM-CGI-SF(HS&L): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Heartfelt Sadness and Longing); MM-CGI-SF(W&FI): Marwit-Meuser Caregiver Grief Inventory-Short Form (Subescale Worry and Felt Isolation); PHQ-9: Patient Health Questionnaire-9; CSI: Caregiver Strain Index; Duke-Unc: Duke–UNC Functional Social Support Questionnaire.

As regards PSB, caregiver strain was the variable with the greatest weight, followed by depressive symptoms, weekly days of care, and stage of dementia. Regarding the HS&L model, depressive symptoms had the greatest weight, followed by stage of dementia, caregiver strain, and educational level.

In the linear regression analysis for the W&FI, the greatest weight was also found for depressive symptoms, followed by caregiver strain, social support, educational level, and weekly days of care. The explained variance for the W&FI model was higher (50.2%) than for the PSB, HS&L, and total dementia grief regression models (44.7%, 31.2%, and 49.6%, respectively).

4. Discussion

This study aimed to describe the relationship between depressive symptoms, caregiver strain, and social support with dementia grief in family caregivers of people with dementia.

In terms of socio-demographic variables, being female, having a low educational level, and caring for a care recipient who is at an advanced stage of the disease seem to be related to an increase in dementia grief.

Most of the family caregivers were women, and they had higher dementia grief scores than men. This may be caused because women are also often involved in other tasks, such as child and household care [28,29]. In addition, these caregivers lack free time and often limit their employment to part-time work or even sacrifice their job and opportunities for advancement, affecting family income and financial stability. In this sense, the family's finances fall on the spouse or partner, increasing the economic vulnerability of the household and the economic dependence of women on their partners [30–32]. Although there are studies showing that women experience more dementia grief [33,34], other articles have shown no association between sex and the level of dementia grief [16,35], showing that dementia grief may be more associated with individual factors (personality, psychosocial factors, etc.) rather than sex.

Family caregivers with higher educational levels experienced a lower intensity of dementia grief. This may be because they had more personal resources such as information, social contacts, and familiarity with the regulations, and very probably also greater economic resources. These results align with the findings of several studies [36–38]. With regard to the stage of dementia of the care recipient, higher dementia grief scores were observed for the family caregiver, especially when the care recipient was at an advanced stage of the disease. This association could be linked to an increase in the demands for care of the patient as the dementia progresses [12,39], as well as to the accumulation of care time when reaching these advanced stages, which can already be years or even decades [33,37,40].

Regarding the main variables of this study, it was observed that high levels of depressive symptoms and caregiver strain and low levels of social support indicated greater intensity of dementia grief.

Based on our findings, depressive symptomatology was the variable that showed the most weight and influence on dementia grief. Depressive symptoms are associated with deep feelings of sadness, hopelessness, and loss. They occur frequently in family caregivers of people with dementia, especially when they are aware that there will be no improvement for the care recipient. These feelings affect the family caregiver's motivation and enthusiasm for life [41,42]. Moreover, if even before the death of the recipient, family caregivers show depressive symptoms, once the death occurs, the risk of complicated grief or depression is much higher [43]. Our results are consistent with numerous studies linking depressive symptoms with increased dementia grief [4,13–15].

As for caregiver strain, it was observed that it could be a predictor of dementia grief. As expected, for the Personal Sacrifice Burden (PSB) dimension, caregiver strain was the variable with the greatest influence, as it precisely assesses this dimension. Caring for a person with dementia can be physically and emotionally demanding, causing family caregivers fatigue, stress, and emotional exhaustion. They often live tired due to the continuity of care, go through different stages of dementia for years, and are constantly confronted with the increasing needs of care recipients [44–46]. All of these factors may increase the sense of strain, and may therefore intensify dementia grief. These data are consistent with previous research showing that strain is associated with higher levels of pre-death grief in family caregivers of people with dementia [8,16,34,47].

The study findings also show that family caregivers with low perceived social support experienced a higher intensity of dementia grief. Furthermore, the variable with the highest weight in the Worry and Felt Isolation (W&FI) dimension was depressive symptomatology and not social support as we might expect. This may be because depressive symptoms cause the family caregiver to withdraw socially, gradually reducing their social circle, feeling less emotionally connected to others, and having a decreasing sense of social support. If this situation persists over the years of caregiving, it may even lead to the isolation of the family caregiver [12,48]. Recent studies [8,17,33] are in line with our data, indicating that social support may act as a buffer on the severity of dementia grief.

Multiple regression analyses showed that depressive symptoms, caregiver strain, and social support influence the intensity of dementia grief, with depressive symptomatology being the variable with the greatest influence on dementia grief and on two of its dimensions, Heartfelt Sadness and Longing (HS&L) and Worry and Felt Isolation (W&FI).

Therefore, there is a need for social and health professionals to assess the mood, strain, and perceived social support of family caregivers of people with dementia to identify individuals at risk and develop interventions aimed at preventing complicated grief after the death of the care recipient.

There are limitations to this study that should be mentioned. On the one hand, the sample size was insufficient for drawing a conclusion. However, it is important to take into consideration that the study is based on caregivers of people with dementia who face a significant burden of responsibilities. These caregivers are fully dedicated to the care of their loved ones and have very little time to devote to other activities, such as participation in research studies.

On the other hand, the sample was limited in geographical terms, since the data collection focused exclusively on the province of Huelva (Spain). Therefore, it is necessary to exercise caution when interpreting and generalizing the results, considering the sociodemographic and geographical characteristics of the sample. However, there are no significant cultural differences among the different geographical regions of Spain, and family caregivers joined associations for the services they offered, regardless of the caregivers' economic or educational resources. This leads us to consider that our results may offer a close representation of the situation of Spanish family caregivers.

It is noteworthy that the study sample consisted exclusively of family caregivers who belonged to the Huelva Provincial Federation of Associations of Family Caregivers of People with Alzheimer's Disease, so it was not possible to recruit family caregivers who were not members of this association. The analysis of this particular group of family caregivers

may have had a mitigating effect with regard to dementia grief scores, as the family caregivers who belong to this association have greater access to services. However, the results show that these family caregivers scored high in caregiver strain and low in perceived social support, thus influencing the intensity of dementia grief. Therefore, the inclusion of non-associated family caregivers in the sample would not have substantially altered the results and conclusions of this study.

5. Conclusions

In family caregivers of people with dementia, experiencing depressive symptoms and having a high strain and low social support are related to the intensity of dementia grief. According to our data, the variable with the greatest weight on dementia grief is depressive symptomatology. Moreover, being female, having a low level of education, and caring for a care recipient at an advanced stage of dementia are factors associated with increased dementia grief. Therefore, it is necessary to carry out assessments and interventions that consider these variables to prevent complicated grief after the death of the care recipient.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon request from the Nursing Department, University of Huelva, by contacting the first author, Miriam Sánchez-Alcón: miriam.sanchez@denf.uhu.es.

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The Relationships between Caregiver Burden, Physical Frailty, Race, Behavioral and Psychological Symptoms (BPSD), and Other Associated Variables: An Exploratory Study

Carl I. Cohen [1,*], Saeed Hashem [2], Kay Thwe Kyaw [1], Sharon A. Brangman [3], Suzanne Fields [4], Bruce R. Troen [5] and Michael Reinhardt [1]

[1] Division of Geriatric Psychiatry, SUNY Downstate Health Sciences University, MSC 1203, 450 Clarkson Avenue, Brooklyn, NY 11203, USA; drkaykyaw007@outlook.com (K.T.K.); michael.reinhardt@downstate.edu (M.R.)
[2] McLean Hospital, 115 Mill St., Belmont, MA 02478, USA; sahashem@mclean.harvard.edu
[3] Department of Geriatrics, SUNY Upstate Medical University, 175 Elizabeth Blackwell Street, Syracuse, NY 13210, USA; brangmas@upstate.edu
[4] Division of General, Geriatric and Hospital Medicine, Renaissance School of Medicine, Stony Brook University, 101 Nicolls Road, Stony Brook, NY 11794, USA; suzanne.fields@stonybrookmedicine.edu
[5] Division of Geriatrics and Landon Center on Aging, University of Kansas Medical Center and VA Kansas City Healthcare System, 4000 Cambridge Street, Kansas City, KS 66160, USA; btroen@kumc.edu
* Correspondence: carl.cohen@downstate.edu; Tel.: +1-646-342-9185

Abstract: *Background and Objectives:* For persons with dementia, the relationships between caregiver burden, physical frailty, race, behavioral and psychological symptoms (BPSD), and other associated variables are poorly understood. Only one prior study examined the relationships among these variables but did not include race, which is an important social determinant of health outcomes in the United States. To examine these interactions, we conducted a cross-sectional exploratory study based on a model by Sugimoto and colleagues. *Materials and Methods:* The sample comprised 85 patient–caregiver dyads (58% White) seen in four centers in diverse regions of New York State. All patients met DSM5 criteria for a major neurocognitive disorder, had a Clinical Dementia Rating sum score of $\geq$3, and Mini-Mental State Examination (MMSE) score of 10 to 26. Other measures included the SHARE-Frailty Instrument(FI), the Neuropsychiatric Inventory (NPI) to assess BPSD, Zarit's Caregiver Burden Interview (CBI), Lawton's Activities of Daily Living (ADL) Scale, the MMSE, the Cumulative Illness Rating Scale for Geriatrics (CIRSG), age, and gender. *Results:* In our sample, 59% met the criteria for prefrail/subsyndromal or frail/syndromal (SSF) on the SHARE-FI. SSF had significant direct effects on the NPI and significant indirect effects on the CBI mediated through the NPI; the NPI had significant direct effects on the CBI. Race (White) had significant direct effects on the CBI (higher) and SSF (lower) but did not have significant indirect effects on the CBI. MMSE, ADL, and CIRSG were not significantly associated with the NPI or the CBI. *Conclusions:* Our analysis demonstrated that frailty, race, BPSD, and caregiver burden may directly or indirectly influence one another, and therefore should be considered essential elements of dementia assessment, care, and research. These results must be viewed as provisional and should be replicated longitudinally with larger samples.

Keywords: dementia; frailty; caregiver burden; behavioral and psychological symptoms; neuropsychiatric symptoms; race

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1. Introduction

Dementia is thought to be one of the most serious public health challenges of the 21st century [1]. Not only does dementia affect the patient, but it can have a profound impact on caregivers. Perceived caregiver burden (CGB) among persons caring for dementia patients is associated with higher levels of stress, depression, and anxiety than in other

caregivers of non-dementia patients [2] and is associated with severe adverse outcomes for patients such as an increased likelihood of institutionalization [3]. Various factors have been associated with CGB, albeit not consistently, such as cognitive function, stages of dementia, depression, activities of daily living (ADL), and behavior and psychological symptoms of dementia (BPSD) [4,5].

BPSD is considered one of the most difficult problems for caregivers to deal with [6] and is associated with higher levels of CGB, more rapid cognitive and functional decline, hospitalization, and institutionalization [7]. Risk factors for BPSD include various sociodemographic factors, disease severity, ADL, and health-related factors [6,7].

The impact of ADL and physical functioning on CGB have been mixed. Garre-Olmo [8] reported that BPSD and ADL had indirect effects on CGB via caregiver distress due to BPSD. Kim [6] found that ADL had indirect effects on CGB through various BPSD symptoms such as hyperactivity, psychosis, and physical behavioral symptoms, indicating that BPSD exerted a complex mediating effect. Sugimoto [7] found that physical vitality had direct and indirect effects, mediated through BPSD, on CGB. On the other hand, Onishi [9] found that physical disability did not affect CGB. The literature has yielded inconsistent findings between cognitive status and CGB [10], while some reports, such as those by Kim [6] and Sugimoto [7], found indirect effects through BPSD.

Until recently, most studies that looked at the relationships between CGB, BPSD, ADL, cognitive status, and physical illness used correlations and/or regression analysis. This led Kim and colleagues [6] to conclude that studies regarding the causal relationship between BPSD in community-dwelling patients with Alzheimer's disease (AD) and caregiver burden "have not yet been established." However, as noted above, several studies have employed path studies that allowed for assessing the complexity of the interactions, e.g., both the direct and indirect relationships between these variables. While these studies provided more insight into these relationships, there has been an increased recognition that other variables, particularly physical frailty, can further contribute to the understanding of the interactions that affect CGB and associated variables. Over the past decade, there has been growing interest concerning physical frailty in dementia and what impact it may have on CGB and BPSD.

Like dementia, frailty is thought to be among the most challenging public health issues of this century [11]. Physical frailty is common in AD, with rates ranging from 11% to 50% [12]. All older adults are at risk of developing frailty, and it is associated with many adverse outcomes including diminished quality of life and increased rates of mortality, hospitalizations, falls, depression, and dementia [11]. It is a dynamic process that is potentially preventable, reversible, and treatable. A recognition of frailty and its risk factors can inform treatment decisions and prognosis.

Physical frailty has been conceptualized as a "risk accumulation" model [13]—i.e., an accumulation of diseases and impairments that create a predisposition for adverse outcomes—or as a "syndrome" model [14], i.e., a set of signs and symptoms that define a health condition or phenotype. The accumulation model allows for the inclusion of disabilities and comorbidities such as dementia or cardiovascular disease, whereas the syndrome model is a "primary" or "preclinical" state that is not associated directly with a specific disease or disability.

Both BPSD and physical frailty were found to be significantly associated with each other [7] and with CGB in dementia [7,15,16]. However, only Sugimoto and colleagues' [7] study in Japan has examined the interactions between physical frailty, caregiver burden, and BPSD in persons with Alzheimer's disease. They found that frailty acted directly onCGB, as well as indirectly through BPSD; the latter also had an independent effect on CGB.

Race is another variable that has been overlooked in its relationship with the CGB and its associated factors. In the United States, race has been linked to a variety of disparities in health outcomes [17]. This has been especially true for dementia. Although empirical estimates suggest that the prevalence of AD in minority individuals is highly variable, the most conservative finding is that compared to non-Hispanic White individuals, Black/African American individuals are twice as likely, and Hispanic/Latino individuals are 1.5 times

more likely to develop AD [18]. Race has been associated with CBG and physical frailty, with White individuals reporting a higher CGB but lower rates of frailty [2,19]. In dementia samples, frailty prevalence rates were nearly twice as high among Black and Hispanic individuals than among White individuals [19], and socioeconomic status and lower education exacerbated these racial differences [20]. In one study, racial differences tended to disappear after controlling for socioeconomic status [19], whereas another did not find this attenuation [20].

For caregivers in general, Black caregivers report a lower burden [2]. In dementia caregivers, the results are more mixed, ranging from no difference to less depression and more positive appraisals among Black caregivers [2]. There are also mixed findings for Hispanic caregivers, ranging from no differences compared to White caregivers, sometimes greater depression, and sometimes less perceived stress [2]. Greater racial differences were found in convenience samples. Factors contributing to this difference in CGB may include more positive perceptions of the caregiving role, greater religiosity, and more extended and supportive kin networks [2]. It must be underscored that although the caregiver burden may be perceived in a more favorable light, minority caregivers often experience substantial objective burdens, e.g., balancing work and caregiving, financial strains, and the accessibility and affordability of healthcare resources.

BPSD may be differentially expressed by race and is more likely to occur in Black participants with dementia than in White participants with dementia. In models adjusted for age, sex, and education, the odds of experiencing delusions and hallucinations were approximately doubled among Black individuals with dementia [21].

Several issues emerge from the review of the literature described above:

1. Despite extensive research on CGB and BPSD, their causal relationships have not been fully established because of modeling that did not include potential confounding associated variables or examine the direct and indirect effects of variables on CGB and BPSD.
2. There is increased recognition that physical frailty is common in dementia and may have direct and indirect effects on CGB and BPSD.
3. In the United States, race has been found to impact CGB, frailty, and BPSD, but has not been systematically examined together with other variables that affect CGB, BPSD, and frailty such as ADL, cognition, and physical health.

To address these three issues, we use an exploratory path analysis to examine the relationships between CGB, BPSD, frailty, race, and other associated variables based on a model developed by Sugimoto's team. In so doing, we provide guidance for larger confirmatory studies and discuss its implications for clinical care and research.

2. Materials and Methods

2.1. Study Population and Design

We used a cross-sectional design with data derived from the Alzheimer's Disease Assistance Centers at four State University of New York campuses in various regions of the state (Buffalo, Syracuse, Brooklyn, Stony Brook). The institutional review boards at each site approved the research, and for this report, the SUNY Brooklyn IRB (no. 688786-7) provided approval. Study dyads (patient and caregiver) were recruited consecutively from new intakes at the four sites between 2014 and 2015. Patient inclusion criteria consisted of a primary diagnosis that met DSM-5 [22] criteria for a major neurocognitive disorder (dementia), a Mini-Mental State Examination(MMSE) score of 10 to 26 [23], a Clinical Dementia Rating Scale sum of boxes score of $\geq$3 [24], age $\geq$ 55, having a caregiver, and being English-speaking. We excluded major neurocognitive disorders caused by traumatic brain injury, HIV infections, Parkinson's disease or Parkinson-related dementia, frontal dementia, substance abuse, or other medical causes. Of the 134 dyads screened, 85 met the study criteria. The sample was 67% female, had a mean age of 81.9 years (SD = 8.3), with a self-identified racial/ethnic distribution of 37% Black/African American, 58% White, 2% Hispanic/Latino, and 3% Other. Regarding living status, 22% lived alone, 34% with kin

(child, sibling, or several relatives including spouse), 33% with a spouse alone, 9% with an unrelated caregiver, or 1% other. The primary caregiver was a spouse (58%), a female child (29%), a male child (8%), other kin (2%), or a friend (4%). Comprehensive evaluations of patients included physical, neuropsychiatric, and neuropsychological testing, along with ancillary blood work and neuroimaging. The initial assessments suggested that 78% (n = 66) of the sample had AD or AD with another neurocognitive disorder ("mixed" dementia), 8% (n = 7) had probable vascular dementia, 8% (n = 7) had possible Lewy Body Dementia, and 6% (n = 5) had mixed dementia other than with AD.

Our research design was based on an adaptation of Sugimoto and coinvestigators' analytic model [7], as well as an incorporation of previous research on the relationship between race, caregiver burden, and frailty, described above. Although Sugimoto's team examined only Alzheimer's disease, many studies on caregiver burden have looked at dementia patients in general. We opted to focus on dementia patients to increase the power of our analysis and our concerns that many AD patients have mixed pathology [25]. However, a subanalysis of AD-diagnosed patients in our sample was also undertaken.

Within the overall model, caregiver burden was the dependent variable. Cognitive status, daily functioning, physical health, and race (White) were predictor variables, and BPSD was both a predictor and intervening variable between the latter variables and caregiver burden. In addition, SSF was conceptualized as a predictor variable of caregiver burden and BPSD, but also as an intervening variable for the relationship between race and caregiver burden. Cognitive status, daily functioning, and physical health were also conceptualized as having non-directional (symmetrical) relationships with SSF. Age and gender were used as covariates. This is depicted in Figure 1.

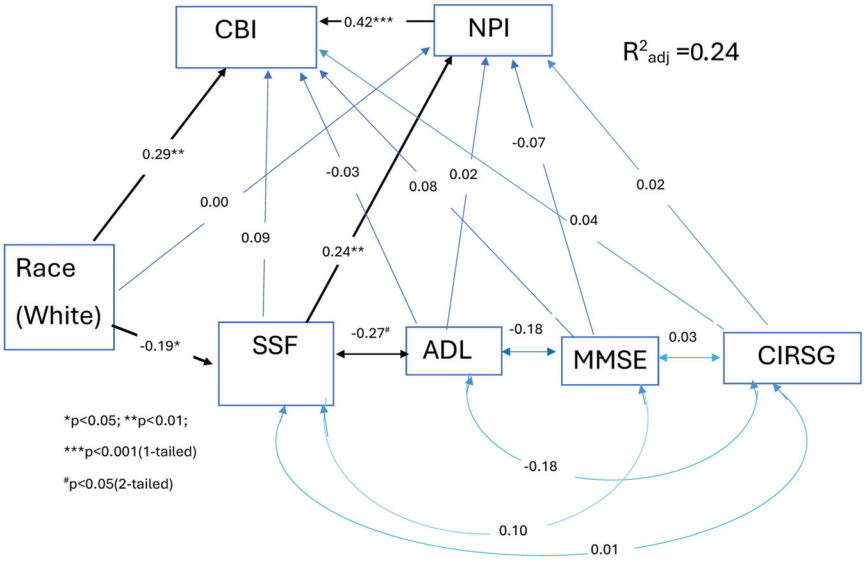

Figure 1. Path diagram representing the relationship between predictor variables. Abbreviations: SSF = subsyndromal/syndromal frailty; CBI = Caregiver Burden Interview; NPI = Neuropsychiatric Inventory; ADL= Activities of Daily Living Scale; MMSE= Mini-Mental State Examination; CIRSG = Cumulative Illness Rating Scale Geriatrics. Notes: 1. Indirect effect of SSF on CBI mediated by NPI: (0.24) (0.42) = 0.10. Sobel test: z-score = 1.77, p = 0.04 (1-tailed). 2. Indirect effect of race (White) on CBI mediated by SSF: (−0.19) (0.09) = −0.02. Sobel test: z-score = −0.76, p = 0.22 (1-tailed). 3. Indirect effect of race (White) on CBI mediated by SSF and NPI: (−0.19) (0.24) (0.42) = −0.02. Sobel test: z-score = −0.67, p = 0.25 (1-tailed).

2.2. Variables and Instruments

To operationalize the model, we first addressed the assessment of physical frailty. As noted above, physical frailty has been conceptualized as a "risk accumulation" model [13]—i.e., an accumulation of diseases and impairments that create a predisposition for adverse outcomes—or as a syndrome model [14], i.e., a set of signs and symptoms that define a health condition or phenotype. The accumulation model allows for the inclusion of disabilities and comorbidities, whereas the syndrome model is a "primary" phenotypical state that is not associated directly with a specific disease or disability. To obviate the conflation of disability associated with dementia with that of frailty, we chose the syndrome (phenotype) model and separately examined impairments in activities of daily living and physical disorders. We used the SHARE Frailty Instrument (Share-FI) [26], which is a summed score ranging from 0 to 5, with scores of 1–2 and 3–5 classified as prefrail (subsyndromal) and frail (syndromal), respectively. We dichotomized the scores into nonfrailty versus subsyndromal/syndromal frailty (SSF). For daily functioning, we used Lawton's Basic and Instrumental Activities of Daily Living (ADL) Scale [27] with a range of 0–14 (better); it was dichotomized using the median score of 7 as the cut point. To assess physical comorbidities, we used the Modified Cumulative Illness Rating Scale-Geriatrics (CIRSG) [28] that examines 14 medical systems and has a possible range of 0–56 (most severe); it was dichotomized using the median score of 7 as the cut point. The Neuropsychiatric Inventory (NPI) [29] was used to assess BPSD with a possible range of 0–144 (most frequent and severe symptoms). Caregiver burden was examined using the 4-item Zarit Caregiver Burden Interview (CBI) [30] with a possible range of 0–16 (most burdened). The MMSE (possible range in this study: 10–26) was used to assess cognitive status and was dichotomized into 17 and below ("severe") and 18 and above ("moderate/mild"). Race was dichotomized into White and non-White. Age (dichotomized into 55 to 79; 80 and above) and gender (male/female) were used as covariates. The internal reliabilities (Cronbach's alpha) of all scales were acceptable ($\geq$0.74), except for the CIRSG, which was 0.56, or minimally acceptable [31]. Interviewers were trained using instructional sessions and videotapes.

2.3. Statistical Analysis

To test the model design, we used a path analysis that entailed three linear regression analyses with CBI, NPI, and SSF as the dependent variables, respectively. The former two regression analyses met assumptions of normality, and the latter met the criteria proposed by Hellevik [32] for using a dichotomous dependent variable in regression analysis. We used Wright's method [33] to determine indirect effects; that is, we calculated the product of the betas ("compound correlations") of the single paths comprising the multiple paths between independent and dependent variables. The Sobel test [34] was used to calculate the significance of these indirect effects. Because causal direction was predetermined in the path analysis, we used 1-tailed *p*-values with a significance level of $p < 0.05$. For associations between exogenous variables where the direction was not specified, 2-tailed *p*-values were used. The regression analyses were powered to detect small to medium effect sizes ($f^2 = 0.07$). Any missing data, albeit rare, were replaced using mean imputation.

3. Results

Of the 59% (n = 50) of patients meeting the SSF criteria on the Share-FI, 46% (n = 23) scored 1–2 ("prefrail"/subsyndromal), and 54% (n = 27) scored 3–5 ("frail"/syndromal). Table 1 provides the mean values/percentages of the variables in the analysis. Table 2 provides the results of the three regression analyses. In Table 2, the unadjusted models show the bivariate relationships of the predictor variables with the dependent variables, and the adjusted model shows the independent (direct) effects of the variables when they are entered simultaneously into the analyses. No evidence of appreciable multicollinearity was found among the variables. The overall model predicting the CBI was significant [adjusted $R^2 = 0.24$, $F(8,76) = 4.36$, $p < 0.001$]. Significant relationships ($p < 0.05$) within

the various regression analyses were found for race, SSF, NPI, and CBI. Direct and indirect effects are shown in Figure 1. (The covariates, age and gender, were not included in the figure.) SSF had a significant indirect effect (compound correlation = 0.10) on the CBI mediated through the NPI (Sobel test = 1.77, $p = 0.04$). SSF did not have significant direct effects on the CBI ($\beta = 0.09$, $p = 0.21$), whereas the NPI had direct effects on the CBI ($\beta = 0.42$, $p < 0.001$). Race (White) had a direct effect on the CBI ($\beta = 0.29$, $p = 0.003$) and SSF ($\beta = -0.19$, $p = 0.03$); that is, race (White) was associated with a higher CBI and lower SSF. Race had no significant indirect effects mediated through SSF and the NPI (Sobel test= -0.67, $p = 0.25$) or SSF alone (Sobel Test = -0.76, $p = 0.22$). Neither the MMSE, CIRSG, or ADL scores were significant predictors of the CBI or the NPI, although ADL was significantly correlated with SSF (Figure 1). A post hoc analysis revealed that when the CIRSG vascular subscale was substituted for the CIRSG variable in the regression analyses, it had a significant relationship with the CBI ($\beta = 0.26$, $p < 0.005$) but not with the NPI ($\beta = -0.18$, $p = 0.06$).

Table 1. Demographic and clinical characteristics used in the analysis and inclusion criteria (N = 85).

Variable	Mean (SD)/%
Age	82.0 (8.3)
Gender (female)	67
Race (White)	58
Caregiver Burden Index	7.2 (3.9)
Neuropsychiatric Inventory	25.0 (21.6)
Activities of Daily Living Scale	7.0 (3.4)
Mini-Mental State Examination	19.2 (4.2)
Modified Cumulative Illness Rating Scale-Geriatrics	7.1 (3.7)
Clinical Dementia Rating Scale-Sum	7.4 (3.1)

Table 2. Linear regression analyses for path design.

		Dependent Variables											
		CBI [#]				**NPI** [##]				**SSF** [###]			
		Unadjusted Model		**Adjusted Model**		**Unadjusted Model**		**Adjusted Model**		**Unadjusted Model**		**Adjusted Model**	
Variables	**Mean (SD)/%**	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***
Age ≥ 80	71%	0.21	0.03	0.08	0.22	0.13	0.11	0.11	0.19	0.19	0.04	0.18	0.04
Female	67%	0.06	0.26	0.06	0.29	0.03	0.39	−0.05	0.34	0.33	0.001	0.27	0.005
White	58%	0.26	0.008	0.29	0.003	−0.04	0.38	0.00	0.49	−0.23	0.02	−0.19	0.03
MMSE ≤ 17	34%	0.07	0.27	0.08	0.22	−0.04	0.36	−0.07	0.27	—	—	—	—
ADL > 7	47%	−0.18	0.05	−0.03	0.39	−0.06	0.29	0.02	0.43	—	—	—	—
NPI	25.0 (21.6)	0.44	<0.001	0.42	<0.001	—	—	—	—	—	—	—	—
CIRSG > 7	48%	0.13	0.12	0.04	0.37	0.01	0.48	0.02	0.43	—	—	—	—
SSF	59%	0.17	0.06	0.09	0.21	0.24	0.01	0.24	0.03	—	—	—	—

Notes: N = 85; the unadjusted model is the effect of each variable before entering all the variables simultaneously into the regression analysis (adjusted model); *p*-values are 1-tailed; [#] R^2adj = 0.24, F(8,76) = 4.35, $p < 0.001$; [##] R^2adj = −0.01, F(7,77) = 0.87 $p = 0.53$; [###] R^2adj = 0.14, F(3,81) = 5.55, $p = 0.002$; Abbreviations: SSF = subsyndromal/syndromal frailty; CBI = Caregiver Burden Interview; MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living Scale; NPI = Neuropsychiatric Inventory; CIRSG = Cumulative Illness Rating Scale Geriatrics.

The item of education had too many missing cases (n = 12) to be included in the primary analysis. Also, in the Sugimato model, it was not significant. However, we

conducted a post hoc analysis that included education as a predictor variable in the analysis (n = 73) and found that education in the regression analyses was not significantly related to the CBI (β = 0.06, $p = 0.30$) or the NPI (β = 0.12, $p = 0.18$). It was significantly associated with SSF (r = −0.25, $p = 0.04$, 2-tailed) and race (White) (r = 0.33, $p = 0.004$, 2-tailed) and resulted in some attenuation of the relationship with the CBI in the case of White race (β = 0.15, $p = 0.10$) and with the NPI in the case of SSF (β = 0.20, $p = 0.08$).

Last, a subanalysis was performed with the patients diagnosed with AD (n = 66). As seen in Supplementary Table S1, all relationships among the variables remained the same, with no changes in significance for any of the variables.

4. Discussion

This study augments our understanding of the relationships between caregiver burden, physical frailty, race, BPSD, and other associated variables in persons with dementia. We partially confirmed Sugimoto and coinvestigators' [7] model, in that SSF had indirect effects on the caregiver burden as measured by the CBI, the latter being mediated through the NPI, which in turn had direct effects on the CBI. Moreover, a significant association between frailty (SSF) and BPSD (measured by the NPI) was also confirmed. Unlike Sugimoto's group, we did not find that SSF had direct effects on the CBI, although the beta in our study approximated the beta in their study. Also, consistent with the literature, White caregivers expressed higher levels of caregiver burden [2]. Conversely, being White was associated with significantly lower levels of SSF, an association that has been reported previously in non-dementia samples [19]. However, race had only direct effects on the CBI and did not have any significant indirect effects on the CBI through SSF or the NPI.

Our findings clarified some of the limitations of the Sugimoto team's study. Because they used a frailty measure that was based on the accumulation model, it was difficult to determine whether frailty primarily reflected impairments in ADL and comorbid physical illnesses. Because we used the frailty phenotype construct and examined ADL and physical health separately, we demonstrated that SSF had significant indirect effects on the CBI, whereas ADL and CIRSG did not have any direct or indirect effects. Other studies have found indirect effects of ADL on caregiver burden mediated through BPSD [6]. Cheng [10] postulated that ADL may have a more profound effect on caregiver burden in advanced dementia, whereas, in persons with milder cognitive symptoms, such as in the sample reported here, ADL has less of an impact. Physical diseases, especially vascular disorders such as strokes, have been associated with more BPSD and greater caregiver burden [7,35–37]. We did not find this association for overall physical disorders, but a post hoc analysis looking at the vascular subscale of the CIRSG was significantly associated with greater caregiver burden. Future studies may be able to clarify these findings. Moreover, contrary to the Sugimoto group's finding, we did not find that MMSE was associated with the NPI, although we did replicate their findings regarding the lack of an association between MMSE and caregiver burden. Indeed, the literature has yielded inconsistent findings between cognitive status and caregiver burden [10]. Finally, we were able to demonstrate the importance of race in this analysis, a variable that Sugimoto's group did not include.

A key takeaway from this study and previous research is the pivotal role that BPSD plays as a mediator between various predictor variables and caregiver burden. This may have important implications for interventions to reduce the caregiver burden. In our study, it was an important mediator between frailty and caregiver burden, whereas in other studies, it mediated between the caregiver burden and ADL, physical health, or cognitive status [6–8]. Some investigators have examined various cluster types of BPSD symptoms and their mediating position between other variables and caregiver burden. However, there have been considerable differences in the results of the cluster analyses, so it has been difficult to draw any definitive conclusions [6].

A strength of this study is the sample's multiracial composition and geographic diversity, as well as the fidelity of our analysis with the Sugimoto team's design. To our knowledge, it is the first study to look at the impact of race, a critical social determinant

of health outcomes in the United States, on the caregiver burden in dementia in concert with frailty and BPSD. Limitations include the cross-sectional design, meaning that causal direction cannot be verified; and the omission of potentially relevant variables such as nutritional status and various social determinants such as social class and living circumstances. Moreover, although Sugimoto's groups did not find education to be significant in their model, our findings that education may attenuate some of the effects of race on caregiver burden and the effect of frailty on the NPI suggests that education should be included in future research, especially when race is a predictor variable. Finally, because of the modest sample size (n = 85), there was a possibility of Type 2 errors, although the model was powered to detect small to medium effect sizes. Nonetheless, the findings must be viewed as provisional and need to be replicated longitudinally in other sites with larger sample sizes.

5. Conclusions

Our exploratory analysis demonstrated significant relationships between caregiver burden, frailty, race, and BPSD. The findings indicate that frailty, race, BPSD, and caregiver burden may directly or indirectly influence one another, and therefore should be considered essential elements of dementia assessment, care, and research.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina60030426/s1, Table S1. Linear Regression Analyses of Path Design for Patients Diagnosed with Alzheimer's Disease.

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Evaluating the Diagnostic Value of Electrovestibulography (EVestG) in Alzheimer's Patients with Mixed Pathology: A Pilot Study

Zeinab A. Dastgheib, Brian J. Lithgow and Zahra K. Moussavi *

Diagnostic and Neurological Processing Research Laboratory, Biomedical Engineering Program, University of Manitoba, Riverview Health Centre, Winnipeg, MB R3L 2P4, Canada; zeinab.dastgheib@umanitoba.ca (Z.A.D.); brian.lithgow@umanitoba.ca (B.J.L.)

* Correspondence: zahra.moussavi@umanitoba.ca; Tel.: +1-204-474-7023

Abstract: *Background and Objectives*: Diagnosis of dementia subtypes caused by different brain pathophysiologies, particularly Alzheimer's disease (AD) from AD mixed with levels of cerebrovascular disease (CVD) symptomology (AD-CVD), is challenging due to overlapping symptoms. In this pilot study, the potential of Electrovestibulography (EVestG) for identifying AD, AD-CVD, and healthy control populations was investigated. *Materials and Methods*: A novel hierarchical multiclass diagnostic algorithm based on the outcomes of its lower levels of binary classifications was developed using data of 16 patients with AD, 13 with AD-CVD, and 24 healthy age-matched controls, and then evaluated on a blind testing dataset made up of a new population of 12 patients diagnosed with AD, 9 with AD-CVD, and 8 healthy controls. Multivariate analysis was run to test the between population differences while controlling for sex and age covariates. *Results*: The accuracies of the multiclass diagnostic algorithm were found to be 85.7% and 79.6% for the training and blind testing datasets, respectively. While a statistically significant difference was found between the populations after accounting for sex and age, no significant effect was found for sex or age covariates. The best characteristic EVestG features were extracted from the upright sitting and supine up/down stimulus responses. *Conclusions*: Two EVestG movements (stimuli) and their most informative features that are best selective of the above-populations' separations were identified, and a hierarchy diagnostic algorithm was developed for three-way classification. Given that the two stimuli predominantly stimulate the otholithic organs, physiological and experimental evidence supportive of the results are presented. Disruptions of inhibition associated with GABAergic activity might be responsible for the changes in the EVestG features.

Keywords: feature selection; diagnostic algorithm; Electrovestibulography; Alzheimer's disease; cerebrovascular pathology; gamma-aminobutyric acid

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1. Introduction

Dementia is a progressive clinical syndrome, describing an array of brain disorders with debilitating cognitive and behavioral impairments [1]. Diagnosis of dementia is based on clinical symptoms, i.e., medical history, neuropsychiatric and neuropsychological assessments as well as brain imaging results and genetic tests [1,2]. Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia, and make up to around 60% and 30% of all cases, respectively [3]. Given that the chance to develop cerebrovascular disease (CVD) increases with age [4], AD patients often present with varying levels of CVD symptomology, and are considered as a dementia subtype called AD-CVD [5–7]. Differential diagnosis of AD and AD-CVD is challenging due to overlapping symptomologies [1,2]. Currently, brain autopsy is the only way to confirm dementia and its subtypes [8].

AD and AD-CVD have commonalities but also differences in their characteristics, which may both hinder and help their separation. Given that the AD-CVD pathology sits in the continuous spectrum between AD and VaD, and due to the involvement of cerebrovascular pathology, i.e., cerebrovascular lesions/blood flow reductions, AD-CVD has been found to be associated with a more rapid cognitive decline that often ends in a more severe form of dementia than predominant AD pathology [9,10]. On the other hand, AD-CVD pathology has been associated with a lower burden of Amyloid-β (Aβ) pathology than dementia with AD predominance [11,12], suggesting the presence of less AD pathology in AD-CVD compared to that in AD patients [13,14]. Regardless of the difference in origins, AD and AD-CVD both demonstrate neurodegenerative pathology, which makes their distinction complex due to similar symptoms, specifically, at early stages of the disease. While there are accepted criteria to diagnose AD and VaD [2,6,15], there is little consensus for the diagnosis of AD-CVD (mixed pathology) [16].

A common clinical method to identify AD, AD-CVD, and VaD cases is using the Hachinski ischemic score (HIS) [7,17]. A change in score range cut off for AD to 3 rather than 4 in HIS, i.e., modified HIS, improved the classification accuracy to 78.8% (from 73.3%) when AD was compared to a combined population of VaD and AD-CVD [18]. Another scale, the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) scale, identifies VaD (but not AD-CVD) cases more accurately compared to HIS by including the imaging results, which is the main limitation of HIS [6]. Nevertheless and to the best of our knowledge, no highly accurate separation of AD from AD-CVD (alone and not pooled with VaD) has been presented [19–21]. Presumably, mixed Alzheimer's, including AD-CVD, is considered as a category for underdiagnosed cases, and its diagnosis has an important clinical and prognostic value [16,19,22,23].

Electrovestibulography (EVestG), a non-invasive technique that detects vestibulo-acoustic neural activities [24], has shown promising results in the identification of various neurodegenerative [25,26], vertiginous [27–29], and neuropsychiatric disorders [30]. Given the extensive direct and indirect links between neuropathologies associated with dementia and the vestibular system [31,32], the distinct impact of AD and AD-CVD has been investigated using EVestG data [31,33]. Analysis of EVestG signals in response to some of its stimuli, as well as using the Montreal Cognitive Assessment (MoCA) score as one of the features, showed >80% accuracy in separating AD from AD-CVD and/or from age-matched healthy controls in our previous studies [31,34]. However, EVestG signals of the entire stimuli were not investigated [31]. Additionally, the time interval histogram (IH) of the detected field potentials (*FPs*), in addition to the average of spontaneous and driven vestibular *FPs* (FP_{ave}), were not considered in the previous studies [34]. In this study, the potential of EVestG for identifying AD, AD-CVD, and healthy control populations was investigated using both *FP* and IH characteristic curves of the EVestG signal in response to the entire stimuli. A novel hierarchy diagnostic algorithm based on the binary classification outcomes of its lower levels was developed and evaluated.

Low frequency range (proximal to 10 Hz) modulations of IH signals are hypothesized to occur in response to vestibular efferent or α band activity [35]. Spontaneous vestibular efferent activity is seen at 10–50 spikes/s [36] and the α band range is 8–13 Hz. As the experimental average detected gap between every two *FPs* is ~3.3 ms, a 33 *FP* gap approximately corresponds to about 100 ms (10 Hz). Thus, the normalized histogram of the time intervals between each 33 *FPs* (called the IH33 signal) could be of value to investigate for features. EVestG studies showed that the IH33 signal is shifted over the range of frequency depending on the pathology [25,35].

Furthermore, imaging studies showed AD biomarkers at an early stage are associated with decreased gamma-aminobutyric acid (GABA) interneurons signaling rather than cholinergic or glutamatergic dysfunction, i.e., due to Aβ and, particularly, Aβ oligomers (AβO) pathology [23,37–40]. Given that GABA could act as a facilitator in the spontaneous and driven discharge of the vestibular afferents, decreased GABAergic inhibitory function

may lead to the defacilitation of/reduction in afferent discharges [41,42]. Thus, an AD feature sensitive to changes in the afferents' firing pattern could be investigated. Accordingly, the IH33 curve of the AD population is speculated to shift to the lower frequency range or longer time intervals.

Conversely, studies have shown that the decrease in the cerebrovascular blood flow in animals and humans significantly increases the neuronal inhibition and GABAergic activity [43,44]. This was suggested as a mechanism to reduce the cell injury and enhance the tolerance of neurons to the ischemic and hypoxic condition [45]. Increased synaptic inhibition promotes synchrony of spiking among interneurons and between groups of excitatory neurons [42,46], while it also reduces slow timescale activity in a large population of neurons [47–49]. Moreover, a reduction in the blood flow to the vestibular periphery as a result of CVD leads to excitation of the vestibular nuclei, and via the efferent feedback loop, results in modulatory excitation of the vestibular afferents [50]. Based on these findings, we hypothesize that the IH33 curve of the AD-CVD population will shift to the higher frequency range or shorter time intervals compared to that of the AD group.

The main contribution of this paper is developing a novel hierarchy diagnostic algorithm based on the binary classification outcomes using unbiased features of the IH33 and FP_{ave} curves of selected EVestG stimuli. While this work is conceptually similar to our previous studies, here we propose a general hierarchical diagnostic algorithm for the separation of AD, AD-CVD, and controls using features of EVestG signals selected through an unbiased selection without any prior assumption(s).

2. Materials and Methods

2.1. Participants

EVestG data were collected either from the participants who were enrolled in one of the two clinical trial studies for monitoring and treatment of different types of dementia, or from healthy volunteers. From these, data of 16 individuals with AD, 13 with AD-CVD, along with data of 24 healthy controls, which were used in our previous study [34], were adopted for feature extraction, feature selection, and building the classification model. Additionally, the new data of 12 individuals with AD, 9 with AD-CVD, and a maximum of 8 healthy controls were acquired and used as a blind testing dataset. The healthy participants were carefully selected to be free of any significant cerebrovascular disease symptomology, particularly when compared to the AD-CVD population. Thus, two control participants were excluded from the test dataset versus the AD-CVD population (due to having focal neurologic signs).

All participants signed a consent form approved by the Biomedical Research Ethics Board of University of Manitoba prior to being enrolled in the study. The dementia subtype diagnosis was determined by medical specialists (neurologists and neuropsychiatrists) through several visits using clinical assessments and brain imaging results, i.e., magnetic resonance imaging (MRI) and/or positron emission tomography. All the diagnosed AD-CVD individuals also met the NINDS-AIREN criteria for "AD with CVD" [6]. All the diagnosed individuals were assessed based on the modified HIS [17,18], similar to our recent studies [31,34], using their full diagnostic reports (Table 1).

The participants went through a screening hearing test, MoCA [51], and Montgomery–Asberg Depression Rating Scale (MADRS) [52] before EVestG recording. Table 1 lists the participants' demographics. Except for one healthy control participant with a moderate MADRS score (22 out of 60), none of the participants had any significant depression at the time of testing.

Table 1. Control, Alzheimer's disease (AD), and AD mixed with levels of cerebrovascular disease (CVD) symptomology (AD-CVD) study participants' demographics.

	Age ($\mu \pm$ SD)	**Sex**	**MoCA** ($\mu \pm$ SD)	**Modified HIS** ($\mu \pm$ SD)	**MADRS** ($\mu \pm$ SD)
Control, N = 24	65.3 ± 7	9 M	27.6 ± 1.7	-	2.6 ± 5.7
AD, N = 16	72.5 ± 7.5	11 M	16.4 ± 4.8	1.8 ± 1.2	1.9 ± 2.8
AD-CVD, N = 13	75.8 ± 7.3	9 M	17 ± 4.4	5.6 ± 1.4	3.1 ± 4
Blind testing AD, N = 12	67.2 ± 7.1	9 M	16 ± 6.7	1.3 ± 1.3	4.7 ± 4.7
Blind testing AD-CVD, N = 9	71.3 ± 7.7	6 M	16.8 ± 6.7	4.6 ± 1	2.2 ± 3.6
Blind testing controls:					
- N = 8 used vs. AD	69.4 ± 5	4 M	26 ± 2.5	-	4 ± 3.4
- N = 6 used vs. AD-CVD	69.8 ± 4.1	3 M	27 ± 1.8	-	3 ± 3.2

($\mu \pm$ SD) values represent mean $\pm$ standard deviation.

2.2. Electrovestibulography (EVestG)

The detailed methodology for EVestG recordings has previously been presented in [24]. In brief, gelled wick cotton wool tip active and reference electrodes are placed bilaterally proximal to the tympanic membrane and on the outer ear canal, respectively (Figure 1a). A common electrode is placed on the forehead. While seated on a hydraulic chair (Figure 1b) inside an anechoic chamber, in a relaxed state and with eyes closed, the participant's ears signals are recorded in response to seven different tilting stimuli (Figure 1c) as follows: (a) 15 cm up/downward translation, while the participant is either in the upright sitting position (up/down tilt) or in the supine position (supine up/down tilt); (b) 40-degree rotation to the right side, either in the upright sitting position (rotation tilt) or in the supine position (supine rotation tilt); (c) 40-degree back/forward tilting in the upright sitting position (back/forward tilt); and (d) 40-degree tilting to the right side in the upright sitting position (ipsilateral right and contralateral left tilts), back to the center, and then 40-degree tilting to the left side in the upright sitting position (ipsilateral left and contralateral right tilts). The ipsilateral and contralateral tilts are abbreviated as IT and CT.

In each tilt, the chair returns to the center before starting another tilt. In every tilt, the chair movement has stationary (background or BGi), acceleration (OnAA), and deceleration (OnBB) phases that each take 1.5 s (Figure 1d). Corresponding to these phases and in each tilt, six 1.5 s segments of recorded EVestG signal are selected for each right/left ear as BGi, OnAA, OnBB, return to center (RTC) BGi, RTC OnAA, and RTC OnBB segments. The selected segments are analyzed offline via the Neural Event Extraction Routine (NEER V5.1) program [24], which detects and averages spontaneous and driven vestibular *FPs* to produce FP_{ave}. It also detects the time of occurrence of each *FP* and generates a normalized time interval histogram based on every 33rd detected *FP* (Figure 1e), i.e., ~100 ms time interval, named as IH33 (Figure 1f), during both static and dynamic conditions. It consists of 25 logarithmically spaced bins spanning the time interval or the frequency range (f = 1/time). The IH33 signal is used to focus on the low-frequency modulation of the *FPs*' firing pattern proximal to 10 Hz, which is hypothesized to be linked to the alpha band [35] and the lower end of vestibular efferent activity [36]. All the recordings were carried out at the EVestG lab, Riverview Health Center, Winnipeg, Manitoba, Canada. As the discriminative features in relation to the FP_{ave} signal were already selected in our previous study [34], here we explain the IH33 feature selection procedure and then use of the final selected features to develop the hierarchy diagnostic algorithm.

The noisy IH33 signals that occurred due to muscle artifacts, poor electrode placement, or jittery movement of the chair were checked manually and removed from the analysis (approximately 5% of the IH33 signals). Typically, IH33 signals corresponding to the following conditions were excluded if: (i) the registered times of occurrence of the detected *FPs* did not produce a smooth curve versus the *FPs*' number (similar to a stepwise rather than a semi-linear curve); (ii) the number of registered *FPs* was less than 350 or the times of occurrence of *FPs* spanned below 97% of the recorded segment duration (i.e., below 1.46 s

compared to 1.5 s); or (iii) the shape of the IH33 signal looked like a bimodal histogram rather than a normal one with the smaller peak exceeding more than 10 percent of the population.

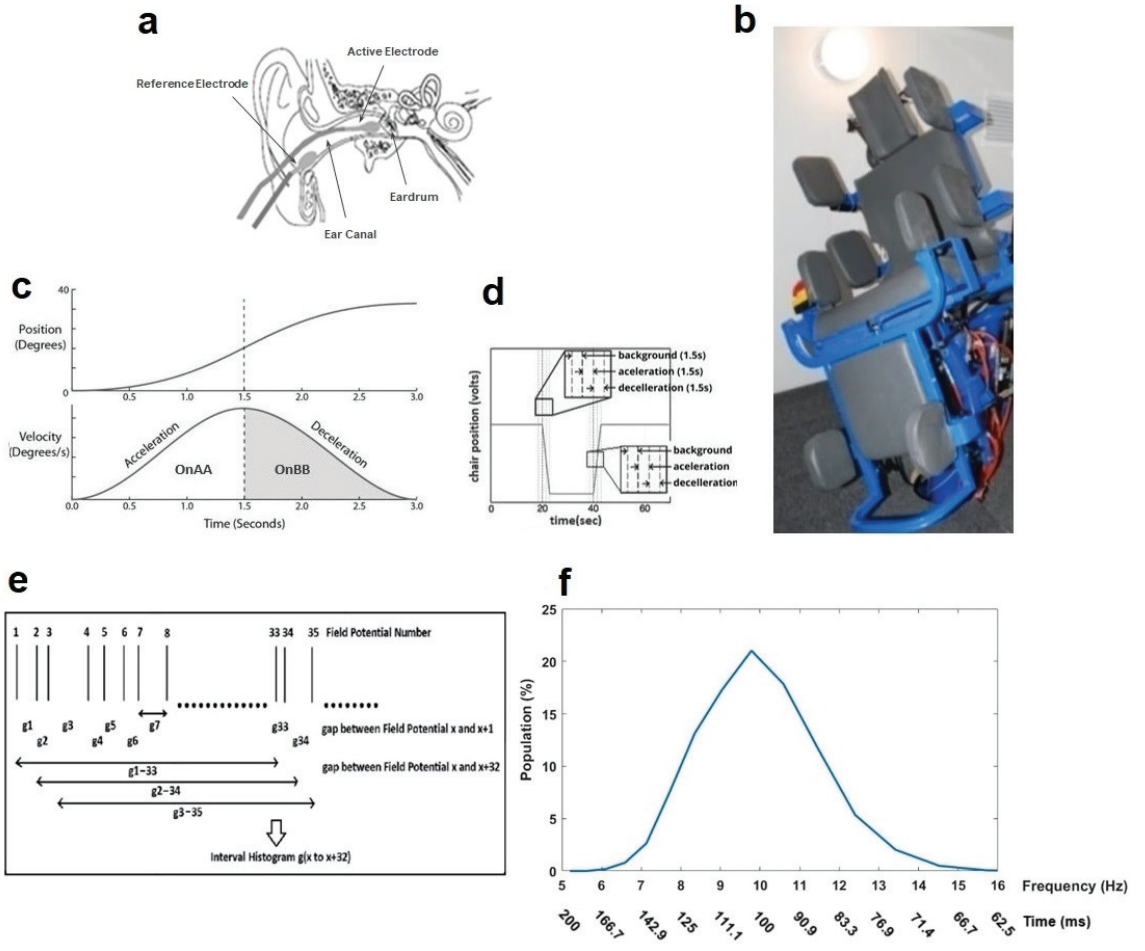

Figure 1. Electrovestibulography (EVestG) recording system and frequency response plot generated by the interval histogram of every 33rd detected field potential (IH33). (**a**) Active and reference electrode placement. (**b**) Hydraulic chair inside the anechoic room. (**c**) Chair position and velocity profiles during movement. (**d**) Chair entire movement pattern. (**e**) IH33 generation process. (**f**) A typical normalized IH33 (time = 1/f).

2.3. Signal Analysis

Figure 2 demonstrates a summary of the proposed approach for classification. The IH33 signals from every tilt were analyzed separately. Each tilt included IH33 signals of the six aforementioned segments for each (left/right) ear. Moreover, IH33 signals of the background segments (BGi or RTC BGi) of each ear, which were either in the upright sitting position (7 segments) or in the supine position (4 segments), were averaged to be used in the upright sitting or the supine tilt, respectively. These IH33 signals are named as "Upright average" and "Supine average" IH33 signals. Additionally, summation and subtraction (asymmetry) of the left and right ear BGi or RTC BGi IH33 signals were included

in the analysis ("LR" and "L-R" were added to the label for summation and subtraction, respectively).

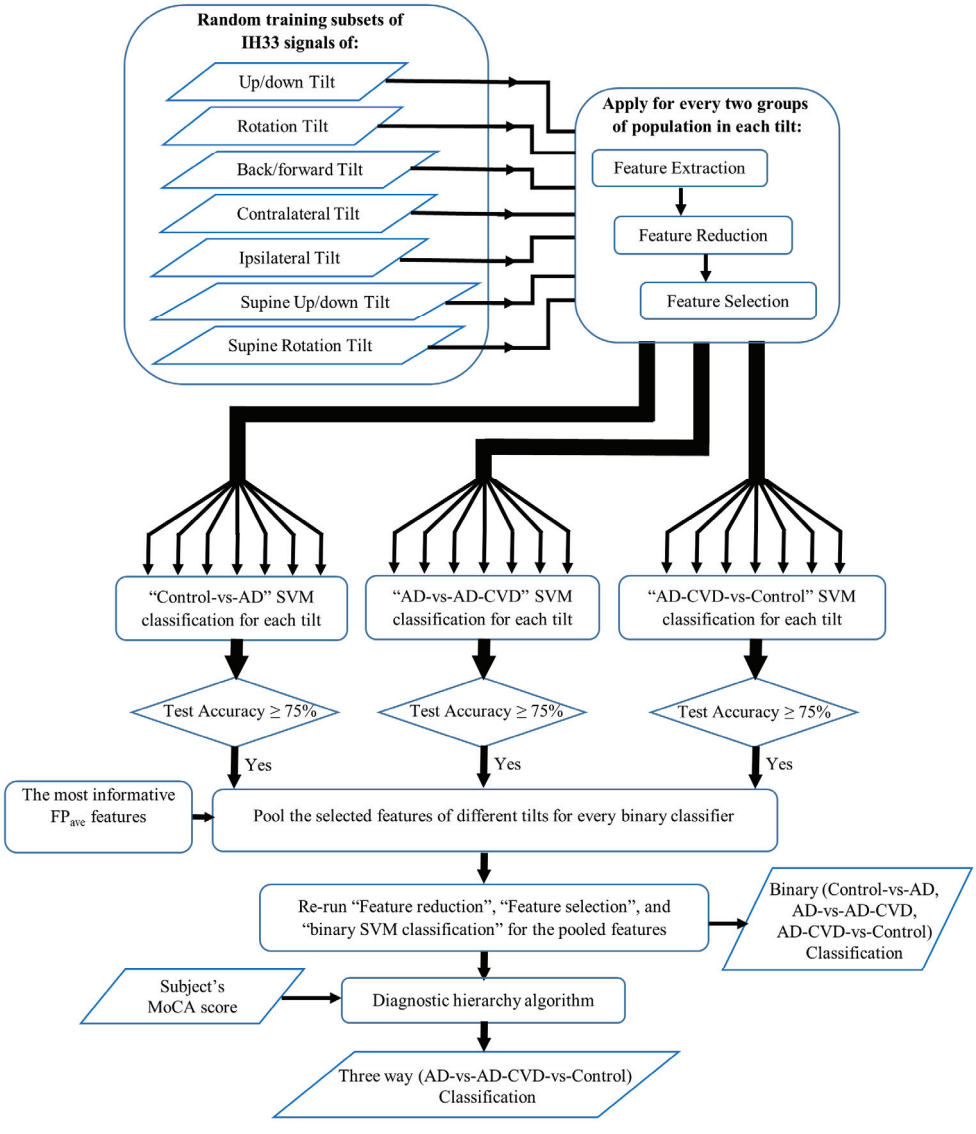

Figure 2. A summary of the proposed approach for classification.

Having data of seven different tilts from three populations (AD, AD-CVD, and Control), an unbiased feature extraction method, similar to our previous study (for a one-vs.-one classification approach [34]) was conducted. Thus, 21 binary classifiers, i.e., seven Control-vs.-AD, seven AD-vs.-AD-CVD, and seven AD-CVD-vs.-Control classifiers, were designed. The procedure for each binary classification is presented below.

2.4. Feature Extraction

To extract characteristic unbiased features from IH33 signals, subsets of the training data were selected as training sets by randomly leaving 20% of the training data of every

population out for testing. For binary classification, the minimum number of selected training sets for which all of the training data were used in a "left-out" set at least once was equal to 25 (5×5). Considering the small training dataset and to improve the stability of the outcome features, the number of random training sets was chosen as 1600 (40×40). In each training set, the standard error bands around the averaged IH33 signals of the two groups were searched for any mutual separation (i.e., the separation occurred if the lower standard error band of one group had higher values compared to the upper standard error band of the other group in time/frequency bins). In case of separation, and thus moving the standard error bands of the averaged IH33 signals of the two groups away from each other, two possible time/frequency regions at either side of the crossing of the two averaged IH33 signals were identified. The feature was computed as the average values of the bins of one region subtracted from those of the other region to magnify the shift in the IH33 signals. It is worth noting that the values of the first and last two bins, as well as the three bins corresponding to the peak value of the IH33 average signal of the two groups, were excluded as they were susceptible to noise (due to insignificant large differences in variance). Then, based on the normality test result calculated by the Shapiro–Wilk Normality test [53], either the non-parametric Wilcoxon–Mann –Whitney test [54] or the Unpaired *t*-test [55] was applied on the feature. If a feature was found to be significant (p-value < 0.05), it was saved as a selected feature in the training set. As the number of extracted features in each training set was large, feature reduction and selection were performed similar to the approach in [34] and summarized as follows:

2.5. Feature Reduction and Selection

In each training set and after imputation of the missing values, feature reduction was performed based on selecting (maximum of three) feature combinations, which resulted in the highest classification accuracy using supervised support vector machine (SVM) classification [56] in an exhaustive search scheme. In cases where the feature sets had the same classification accuracy, the feature set with the lowest number of missing values was selected (please find the detailed information of feature reduction in the Supplementary File of [34]). Assuming the first and second classes in a binary classification as the positive and negative classes, respectively, the classification accuracy in a binary classification was calculated as follows:

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN} \quad (1)$$

where *TP*, *TN*, *FP*, and *FN* are true positive, true negative, false positive, and false negative cases, respectively.

Using the reduced feature set in every training set, a supervised 10-fold cross-validation SVM classification was applied and the averaged training and testing performances were calculated. Then, the feature set that yielded the highest test accuracy and its features that were the most frequently repeated ones among the selected features across all the training sets was selected. Since the identified region(s) of the IH33 signal for the repeated features varied due to difference in the training set, the region(s) that was present for more than 50% of the repetitions, herein named as the common region(s), was selected to be used in the final classification. Given that the total number of possible training sets was larger than what was generated, the procedures of feature extraction, reduction, and selection were repeated three times with different random training sets to test if similar final features were selected. This stage ensures that the number of shuffles of the training data (training sets) is enough to be representative of the entire training dataset and to prevent overfitting of the classification model.

2.6. Binary Classification

The selected features were recalculated based on their common region(s), and missing data were imputed for the entire dataset. The features were Z-score normalized before and after imputation. Then, a 10-fold cross-validation SVM classification was applied

and the averaged training and testing performances were calculated. In every binary classification (Control-vs.-AD, AD-vs.-AD-CVD, or AD-CVD-vs.-Control), the tilts for which their selected features yielded ≥75% averaged test accuracy were chosen as the most informative ones in relation to using the IH33 signal in that classification.

In order to find the most informative features among the top IH33 and FP_{ave} selected features across all the tilts, the IH33 features of the most informative tilt(s) were pooled with the top FP_{ave} selected features of our previous work [34]. Then, the above feature reduction, selection, and classification were applied on the entire pooled features. It is noteworthy that, at this stage, the features of the training sets were known; thus, no feature extraction was needed. The most informative selected features of each classifier were then used in a 5-fold (as the blind test set was smaller) cross-validation SVM classification for the blind testing dataset and the averaged performances were computed.

2.7. Diagnostic Hierarchy Algorithm

Given the three SVM binary classifiers and using the approximated posterior probabilities of an SVM model via the Platt scaling method [57], six probabilities were calculated for each participant. Every two of these probabilities identified the extent to which a participant belonged to either of the two groups out of the three populations, i.e., Control (C), AD, or AD-CVD. Additionally, the averaged sensitivity and specificity of the binary classifiers on the training data were incorporated as a weighting coefficient to the above probabilities. This helps in accounting for the binary classifier that had a higher classification result. Then, the weighted averages of the two probabilities for each group were calculated and used as a score that showed the degree of assignment of a participant to that group. Finally, the three scores for every participant (score of being identified as AD, AD-CVD, and C) were normalized to represent a probability measure. As an example, the following formulas show the calculation of the normalized score (probability measure) of a participant as a control subject:

$$Score_C = Average\{P_{C_{C-vs-AD}} \times W_{Cc-vs-AD} + P_{C_{AD-CVD-vs-C}} \times W_{CAD-CVD-vs-C}\} \quad (2)$$

$$Normalized\ Score_C = Score_C / (Score_C + Score_{AD} + Score_{AD-CVD}) \quad (3)$$

where $P_{C_{C-vs-AD}}$ and $P_{C_{AD-CVD-vs-C}}$ are the probabilities of a participant to be identified as a control in the "Control-vs.-AD" and "AD-CVD vs. Control" classifiers, respectively. In addition, $W_{Cc-vs-AD}$ is the averaged sensitivity of the "Control-vs.-AD" binary classifier, and $W_{CAD-CVD-vs-C}$ is the averaged specificity of the "AD-CVD vs. Control" binary classifier. The sensitivity and specificity of the binary classifiers were calculated as follows:

$$Sensitivity = \frac{TP}{TP + FN} \quad (4)$$

$$Specificity = \frac{TN}{TN + FP} \quad (5)$$

Moreover, the MoCA score was used (as in [31]) to increase the three-way classification accuracy by separating healthy cognitive aging from a spectrum of cognitively impaired participants (control versus patient). A recent meta-analysis revealed that a MoCA cutoff score of 23 lowers the false positive rate (i.e., falsely identifying a participant as a cognitively impaired individual) and shows an overall better diagnostic accuracy [58]. Consequently, if a participant's MoCA score was 23 or below, which implies the participant's cognitive impairment, the participant was classified to either the AD or AD-CVD group depending on which of the two normalized scores was higher. On the other hand, participants with MoCA scores above 23 were classified to one of the three groups (Control, AD, or AD-CVD), based on which of their computed normalized scores was the highest. Figure 3 shows the flow chart of the diagnostic hierarchy algorithm for the three-way classification. The final selected features and classification performances are reported in the Results section.

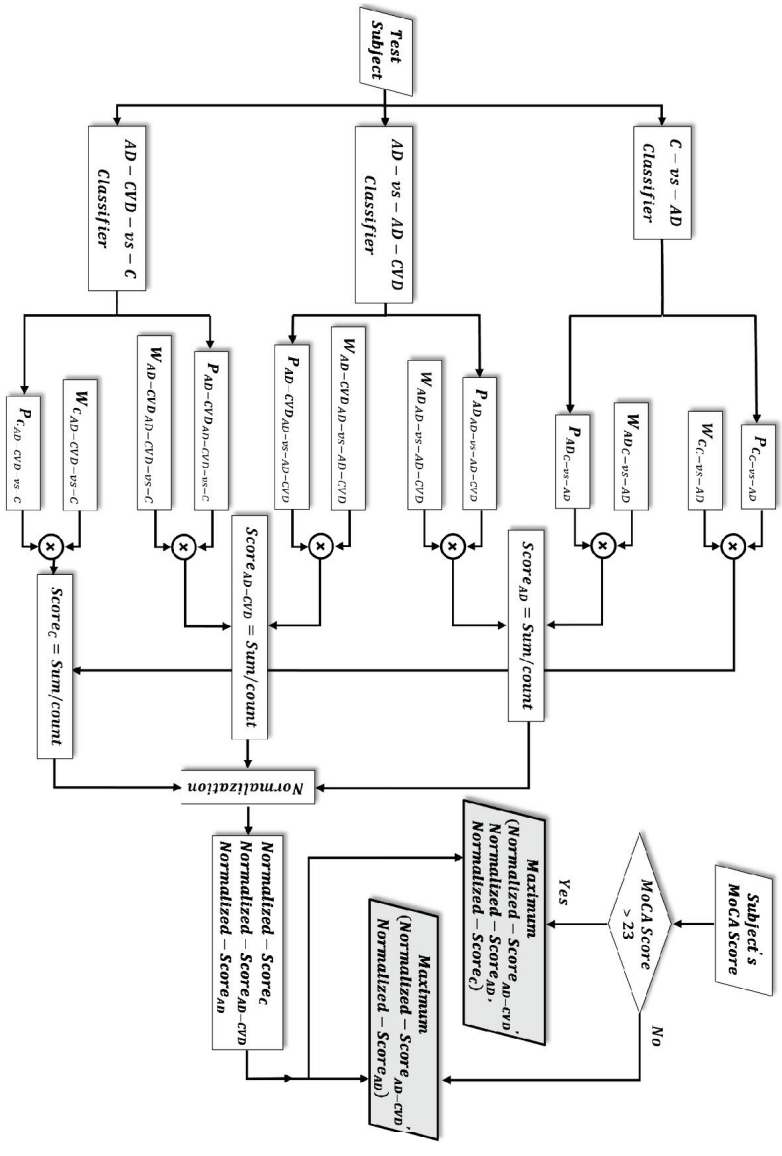

Figure 3. Flow chart of the three-way classification. Depending on the subject's Montreal Cognitive Assessment (MoCA) score, either of the two grey-color-filled parallelograms determines the classification result. The test subject is classified to the population group in which it achieved a higher/highest normalized score.

2.8. Statistical Analysis

One-way multivariate analysis of covariance (MANCOVA) was conducted on the final selected most informative features of the Control-vs.-AD, AD-CVD-vs.-Control, and AD-vs.-AD-CVD classifiers with sex and age as covariates. All of the signal processing steps were performed using the MATLAB (v2017a) environment except for the analyses of covariance, which were performed using SPSS v21 (IBM, New York, NY, USA).

3. Results

Table 2 lists the averaged test binary classification performances of the Control-vs.-AD, AD-vs.-AD-CVD, and AD-CVD-vs.-Control classifiers on the entire training dataset for every tilt. In each classification, the tilts are sorted based on the averaged classification accuracy. This table shows that back/forward, supine up/down, and up/down tilts in the AD-vs.-AD-CVD classifier, supine up/down and IT tilts in the AD-CVD-vs.-Control classifier, and supine up/down tilt in the Control-vs.-AD classifier are selected as the most informative tilts (≥75% accuracy) in the classification of their corresponding populations.

Table 2. Supervised support vector machine (SVM) binary classification averaged test results on the entire dataset.

Averaged Test Performances of the Binary Classifiers on Training Dataset											
AD-vs.-AD-CVD				**Control-vs.-AD**				**AD-CVD-vs.-Control**			
Tilt	**Sens (%)**	**Spec (%)**	**Acc (%)**	**Tilt**	**Sens (%)**	**Spec (%)**	**Acc (%)**	**Tilt**	**Sens (%)**	**Spec (%)**	**Acc (%)**
Back/forward [a]	95	60	80	Supine up/down [a]	86.7	80	82.3	Supine up/down [a]	60	90	80.3
Supine up/down [a]	70	80	76.7	Back/forward	75	70	73	IT [a]	55	88.3	77
Up/down [a]	80	70	75	Supine rotation	80	60	70.3	Rotation	45	85	72.1
IT	85	60	74.2	Up/down	86.7	45	69.7	Back/forward	30	88.3	68.3
CT	70	60	65.8	IT	76.7	55	68	Supine rotation	25	86.7	65.5
Supine rotation	80	40	62.5	CT	83.3	35	63.5	Up/down	10	85	59
Rotation	80	40	61.7	Rotation	75	25	54	CT	15	76.6	54.8

The results are sorted according to the highest average accuracy. [a] The tilts that achieved an accuracy ≥ 75% are marked as the most informative tilts. Sens: sensitivity, Spec: specificity, and Acc: accuracy.

Considering the IH33 selected features of the most informative tilts and pooling them with the most informative FP_{ave} selected features that were previously identified in [34], the final selected most informative features were found. A set of three FP_{ave} features that were selected across all the tilts for the AD-vs.-AD-CVD classifier in [34] showed 78% averaged test accuracy; thus, these features were pooled with the IH33 features in the AD-vs.-AD-CVD classifier. Table 3 presents the final selected most informative features for the three binary classifications. In this table, the selected features are listed based on the EVestG tilt, the type of signal (FP_{ave} or IH33), the EVestG segment, and the recorded ear side. The area under the curve (AUC) values associated to the receiver operating characteristic (ROC) curves of the 10-fold cross-validation for each feature was calculated and averaged. This denotes the relevance of each feature to the target class. As seen, the signal type of all of the final selected features was found to be the IH33 signal. Moreover, the majority of the final features (six out of nine) were selected from the supine up/down tilt recording.

Table 4 reports the averaged test performance of the binary classifiers on the blind testing dataset. The AUC values associated with the ROC curves of the 5-fold cross-validation for each feature were calculated and averaged. As seen, the averaged AUC calculated values for the blind testing dataset were close to the averaged AUC values for the training dataset. Moreover, among the three classifiers, AD-vs.-AD-CVD achieved the highest accuracy (80.9%).

Table 3. The final selected most informative features (F1, F2, and F3) for the three binary classifications.

Selected Most Informative Features of the Binary Classifiers				
	Tilt	**Signal Type**	**Segment_Side**	**AUC**
AD-vs.-AD-CVD	F1—Upright average	IH33	BGi_LR	0.64
	F2—Up/down	IH33	OnBB_R	0.77
	F3—Supine up/down	IH33	OnBB_R	0.79
Control-vs.-AD	F1—Supine average	IH33	BGi_L	0.62
	F2—Supine up/down	IH33	RTC_BGi_L	0.78
	F3—Supine up/down	IH33	RTC_BGi_LR	0.82
AD-CVD-vs.-Control	F1—Supine up/down	IH33	OnAA_L	0.51
	F2—Supine up/down	IH33	OnAA_R	0.78
	F3—Supine up/down	IH33	OnBB_R	0.51

The selected features are listed based on the EVestG tilt, the type of signal, i.e., averaged field potentials (FP_{ave}) or IH33, the EVestG segment, the recorded ear side, i.e., left (L), right (R), or summation of left and right (LR) sides, and the averaged area under the curve (AUC) values associated with the receiver operating characteristic (ROC) curves of 10-fold cross-validation.

Table 4. SVM binary classification averaged test results on the blind testing dataset.

Averaged Test Performances of the Binary Classifiers on the Blind Testing Dataset				
	Sens (%)	**Spec (%)**	**Acc (%)**	**AUC**
AD-vs.-AD-CVD	75.11	88.9	80.9	F1 = 0.66, F2 = 0.77, F3 = 0.79
Control-vs.-AD	87.6	66.4	74.9	F1 = 0.62, F2 = 0.8, F3 = 0.82
AD-CVD-vs.-Control	72.5	67	70.2	F1 = 0.5, F2 = 0.77, F3 = 0.51

Sens: sensitivity, Spec: specificity, and Acc: accuracy. F1, F2, and F3 are the selected features of each binary classifier according to Table 3.

Figures 4–6 demonstrate the IH33 signals of the final selected most informative features that achieved the highest averaged AUC for the training dataset in every binary classification. These signals are plotted separately for the training and blind testing datasets. The time bins that contributed to the calculation of the significant feature are mentioned and shown with a star in each Figure. The classification scatter plots of the features of Table 3 are also presented for training and blind testing.

As seen in the Figures, the averaged AD IH33 signal is shifted towards longer time intervals/lower frequencies, i.e., a larger population percentage of firing in lower frequencies as well as a smaller population percentage of firing in higher frequencies, compared to those of the control and AD-CVD IH33 signals. Conversely, the averaged AD-CVD IH33 signal is shifted towards shorter time intervals/higher frequencies, i.e., a larger population percentage of firing in higher frequencies as well as a smaller population percentage of firing in lower frequencies, compared to those of the control and AD IH33 signals.

Table 5 shows the three-way classification performance including the confusion matrix, one versus rest approach sensitivity and specificity (i.e., one population is assumed as the positive group and the other two populations are merged together as the negative group), and balanced accuracy for the training and blind testing datasets. Balanced accuracy is calculated as the arithmetic mean of the sensitivities or recalls for each class; thus, it naturally provides a higher weight to the classes with a smaller sample size, which can be more appropriate if the classes are not exactly balanced. Thus, balanced accuracies of 85.7%, and 79.6% were attained on the training and blind testing datasets, respectively.

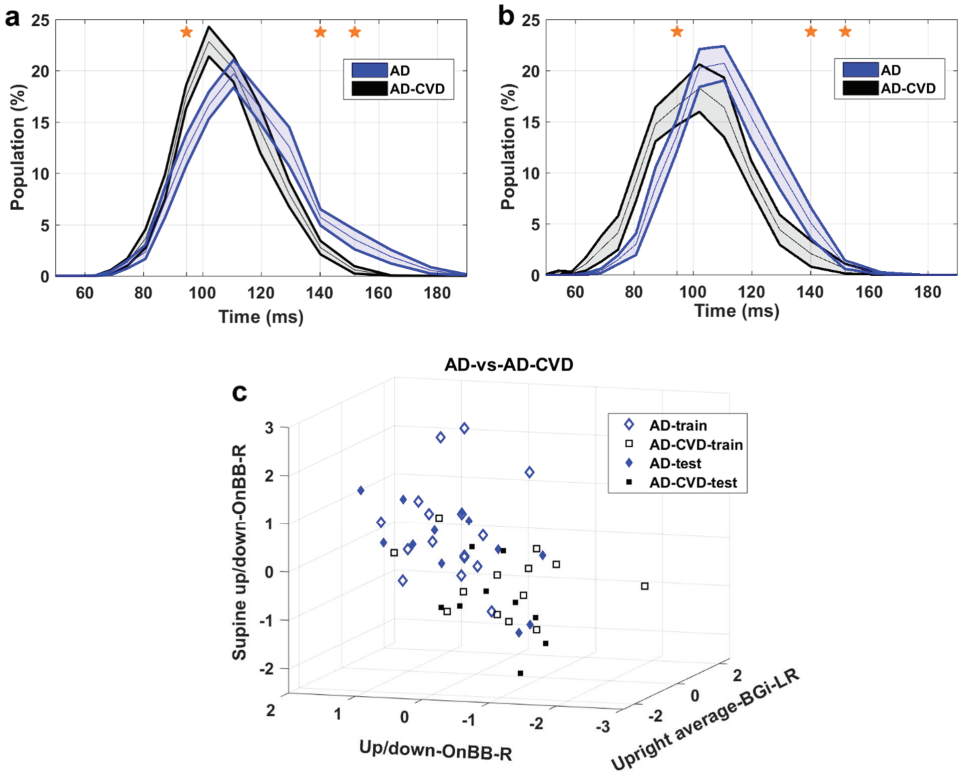

Figure 4. AD-vs.-AD-CVD classification. (**a**) IH33 signals of the final selected most informative feature of AD-vs.-AD-CVD classification that achieved the highest averaged AUC for the training dataset, i.e., supine up/down-OnBB-R, for training and (**b**) blind test datasets. Mean with standard error band is shown for ease of visualization. The middle point of time bins that contributed to the calculation of the feature are marked with stars and are as follows: 94.5, 140.2, 151.8 ms. (**c**) The AD-vs.-AD-CVD classification scatter plot of the features of Table 3 for training and blind testing datasets.

Table 5. Three-way classification averaged training and blind testing results.

Train, Test Dataset Classification Results		**True Class**					
Total Number = 54, 27		**AD**	**AD-CVD**	**Control**	**Sens vs. Rest (%)**	**Spec vs. Rest (%)**	**Balanced Accuracy (%)**
Predicted Class	AD	15, 10	2, 0	2, 0	93.8, 83.3	89.2, 100	85.7, 79.6
	AD-CVD	1, 2	11, 8	3, 2	84.6, 88.9	90, 77.8	
	Control	0, 0	0, 1	19, 4	79.2, 66.7	100, 95.2	

The confusion matrix, one versus rest approach sensitivity, specificity, and balanced accuracy for the training and blind testing datasets are listed. Sens: sensitivity and Spec: specificity.

Statistical Analysis

MANCOVA was applied on the combined selected features of the Control-vs.-AD, AD-CVD-vs.-Control, and AD-vs.-AD-CVD classifiers. A statistically significant difference was found between the two populations after accounting for sex and age; no significant effect was found for sex or age covariates (details are provided in the Supplementary File).

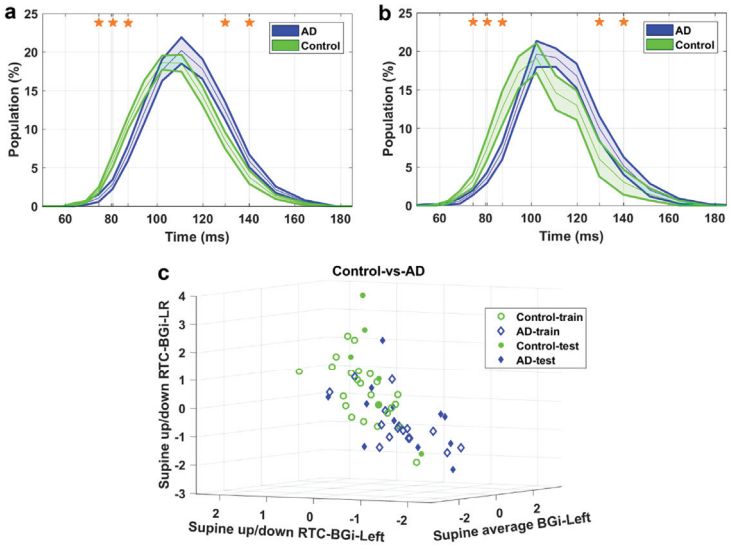

Figure 5. Control-vs.-AD classification. (**a**) IH33 signals of the final selected most informative feature of Control-vs.-AD classification that achieved the highest averaged AUC for the training dataset, i.e., supine up/down-RTC-BGi-LR, for training and (**b**) blind test datasets. Mean with standard error band is shown for ease of visualization. The middle point of time bins that contributed to the calculation of the feature are marked with stars and are as follows: 74.5, 80.6, 87.3, 129.6, and 140.2 ms. (**c**) The Control-vs.-AD classification scatter plot of the features of Table 3 for training and blind testing datasets.

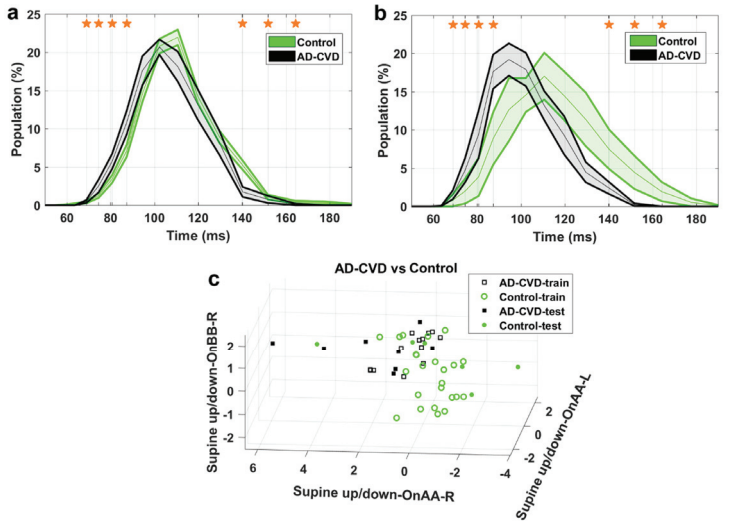

Figure 6. AD-CVD-vs.-Control classification. (**a**) IH33 signals of the final selected most informative feature of AD-CVD-vs.-Control classification that achieved the highest averaged AUC for the training dataset, i.e., supine up/down-OnAA-R, for training and (**b**) blind test datasets. Mean with standard error band is shown for ease of visualization. The middle point of time bins that contributed to the calculation of the feature are marked with stars and are as follows: 68.9, 74.5, 80.6, 87.3, 140.2, 151.8, and 164.3 ms. (**c**) The AD-CVD-vs.-Control classification scatter plot of the features of Table 3 for training and blind testing datasets.

4. Discussion

In this pilot study, we applied our developed automated algorithm [34] to extract unbiased features of EVestG IH33 signals in regard to the separation of pairs of AD, AD-CVD, and healthy control populations. We designed three binary classifiers for every EVestG tilt and compared the accuracies of classification across different EVestG tilts. According to Table 2, the supine up/down tilt was selected as one of the most informative stimuli (achieved an accuracy of $\geq$75% when applied alone) in all of the three binary classifiers, while the back/forward and up/down (sitting position) tilts, and the IT tilt were selected in the AD-vs.-AD-CVD and AD-CVD-vs.-C classifications, respectively. It is noteworthy to mention that although the IT tilt achieved $\geq$ 75% accuracy in AD-CVD-vs.-C classification, it was not very successful in the identification of AD-CVD participants (specificity = 55%). Among the EVestG tilts, the supine up/down tilt predominantly stimulates the utricular organ, and together with the sitting up/down tilt, which mainly stimulates the saccule, contains the lowest contribution of muscle artefacts, hemodynamic effects, and participant anxiety. Considering the closeness of the utricular maculae to the stapes and thus to the EVestG recording electrode, it is more likely that the EVestG response is mostly driven from the utricle [59]. Therefore, the selection of the supine up/down tilt for mutual separation of the three aforementioned groups can be considered physiologically and experimentally reasonable. According to epidemiological human studies, saccular and utricular impairments are associated with five- and four-fold increased odds of AD, respectively [60]. Human studies on measuring Cervical Vestibular Evoked Myogenic Potential and MRI analysis have suggested that decreased saccular function is significantly related to a lower average hippocampal volume [61,62]. These results may give a picture of the cognitive impairment impact of AD on the otolithic organ, particularly the saccule, thus justifying the selection of the up/down tilts for AD-vs.-AD-CVD classification. Finally, the back/forward tilt also showed a high AD-vs.-AD-CVD classification accuracy. Features of this tilt together with the supine up/down tilt were previously found to be discriminative in the prediction of the response to rTMS treatment for AD and AD-CVD participants [33]. Although the back/forward tilt stimulates almost the entire vestibular organ, it could contain blood pressure change and anxiety components, which both need to be carefully studied. It is noteworthy that the back/forward tilt features were not selected as the final selected most informative features in our study.

Using the combination of IH33 features from the selected most informative tilts and the previously selected FP_{ave} features [34], the final selected most informative EVestG features in the classification of pairs of AD, AD-CVD, and control populations were identified. According to Table 3, all of the selected features were found from IH33 signals, and as expected and hypothesized, they were from either the supine up/down or up/down tilts. It is worth noting that the discriminative features that were selected as being predictive of rTMS efficacy in our previous study were also found from IH33 signals. The final selected most informative feature with the highest averaged AUC from the training dataset (0.79) for separation of the AD and AD-CVD populations was found from the upward moving deceleration (OnBB) segment of the supine up/down tilt (Figure 4). Interestingly, the same feature was selected previously [31] but more intuitively for both classification and prediction of the response to treatment in AD and AD-CVD populations. Furthermore, the final selected most informative features of each classifier were used to classify the blind testing dataset. The moderate averaged performances in Table 4 show the robustness of the extracted features. According to Figures 4–6, the averaged AD IH33 signals corresponding to the final selected most informative features were shifted towards lower frequencies, i.e., a larger population percentage of firing in lower frequencies as well as a smaller population percentage of firing in higher frequencies, compared to those of the control and AD-CVD IH33 signals. On the other hand, the averaged AD-CVD IH33 signals corresponding to the final selected most informative features were shifted towards higher frequencies, i.e., a larger population percentage of firing in higher frequencies as well as a smaller population

percentage of firing in lower frequencies compared to those of the control and AD IH33 signals. This trend was consistent between the training and blind testing datasets.

Synaptic loss, which precedes neurodegeneration, is one of the pathological hallmarks of AD and the strongest predictor of cognitive decline [63,64]. Much evidence indicates that Aβ oligomers (AβO), rather than Aβ plaques, could mediate the neurotoxic effects of the Aβ pathway [63,65,66], as they build up earlier and are more potent than Aβ plaques in eliciting abnormalities in synaptic function and neural network activity [64,65]. Over the past few years, lines of evidence in animal models, and in in vitro and human studies have suggested that synaptic failure, particularly at the early stage of AD, is induced by neuronal hyperactivity rather than later stage hypoactivity [64,67–69]. They support the major role of AβO accumulation in neuronal hyperactivity observed at the onset of AD, in both cortical and subcortical brain regions, although other AD-peptides may also contribute [40,64,68,70].

In the past decades, studies have implicated the disruption of cholinergic and glutamatergic neurotransmission in instigating synaptic failure and AD pathology [23]. However, an increasing number of studies support the onset of AD being linked to the decrease in GABAergic inhibitory function as a result of the pathological elevation of AβO peptides [39,40]. This in turn can induce activation of the excitatory glutamatergic response and cause a vicious cycle of an excessive release of Aβ as a result of the disruption of the excitatory/inhibitory neuronal balance [40,64]. Given the GABAergic inhibitory role in regulating, synchronizing, and preventing excess neuronal signaling [23,71], it is not surprising that GABAergic-decreased inhibition increases the incidence of neuronal firing in local assemblies of interconnected neurons in the early stage of AD [23,39,63]. However, this enhanced activity occurs locally among the proportion of neurons that are more vulnerable and not the overall neuronal network [40,67]. Therefore, despite the increased local hyperactivity and due to the lack of unified synchrony of larger assemblies of interconnected neural circuits involving different brain regions, the pathologically elevated AβO in AD could result in network activity destabilization, reduced excitatory current, and synaptic depression [63]. As evidence, this localized neuronal hyperactivity causes gamma wave conductance disruption (lower power of gamma oscillatory activity) in the MCI and early stage AD pathology [39,64,72]. This may imply the lack of overall brain wave modulation of higher frequency firing during the onset of AD.

Studies have shown a similar yet lower degree of various GABAergic component alterations, including depression of GABA levels [39], increased GAD activity [37], synaptic function disruption at GABAergic terminals [37], and increased sensitivity of GABA receptors [73], indicating the lack of inhibitory responses in subcortical regions such as the thalamus, Locus Coeruleus (LC), cochlear, and vestibular nucleus compared to cortical regions during the AD pathology or aged brain. Notably, AβO in the LC neurons of AD patients showed a close association with impaired GABA A receptors, which result in the defacilitation of overall neural network activity due to local (at single cell levels) neuronal hyperexcitability [65]. Given the LC bidirectional links to the vestibular nucleus [74], and similar GABAergic alternations such as the increased sensitivity of GABAergic receptors in an aged vestibular nucleus complex [73], this may imply that AβO-induced GABAergic inhibitory disruption may reduce the facilitation of vestibular firing, particularly afferent discharges, at the vestibular periphery, thus resulting in the speculation about a lower frequency firing pattern for AD patients.

On the contrary, it has been shown in animal and human studies that, as a result of a decrease in the blood flow supply of the brain tissues, the neuronal inhibition and GABAergic activity significantly increases [43,44] and then decreases during the recovery process. Moreover, the increase in GABA levels is observed in patients with vascular risk factors (diabetic aged participants that were compared to controls) [75,76]. Similarly, GABA levels are shown to increase after inhibiting brain glycogen in Type 2 diabetic rats [77]. It is argued that the increased GABA activity could be assumed to be an underlying mechanism that reduces cell injury by antagonizing glutamate excitotoxicity, enhances the tolerance

of neurons to the ischemic and hypoxic condition, and has significant neuroprotective effects [45]. Given that the inhibition increases fast spike synchrony between excitatory neurons [42,46], and reduces the slow (long) timescale relationship among large population of neurons [47–49], it is probable that, as a result of a chronic CVD condition, the synchrony of the neuronal network in the transmission of faster firing increases and leads to a firing pattern that is shifted towards higher frequencies. Conforming to this could be the excitation of vestibular nuclei and vestibular afferents via the efferent feedback loop following hypotension [50].

Finally, a hierarchy diagnostic algorithm was developed for three-way classification by averaging the pairs of probabilities that identified a participant to belong to one of the three population groups. The averaged specificity or sensitivity of the classifiers over the training dataset were also used as weighting coefficients of the probabilities. Thus, three normalized linear weighted average scores were calculated for each participant. Then, the participant's final diagnosis was the group where he/she had the highest normalized score. This could be similar to the way the brain of a physician concludes a clinical diagnosis: by comparing the symptoms against each class of dementia (and healthy controls) and going with the one with the highest likelihood of probability.

As shown in our previous studies [31], the averaged IH33 signal of the control population sits in between the AD and AD-CVD ones (a graph of the IH33 signals for the three populations is added in the Supplementary File). This causes averaging of the probabilities that assign a participant to either the AD or AD-CVD group to sometimes be misleading. As an example, an AD participant can gain a low classification probability of being a control in the Control-vs.-AD classifier; however, due to the special placement of the IH33 signals of the three populations over the range of frequency (or time), the same participant may gain a high classification probability of being a control in the AD-CVD-vs.-Control classifier. Thus, the average probability of being a control may become large, which is not correct. We solved this issue by incorporating a cutoff MoCA score, as a preprocessing step before EVestG signal classifications, which separated the cognitively impaired participants (MoCA ≤ 23) from the healthy ones. The groupings of such participants were later identified by comparing only the AD and AD-CVD scores of the three-way classifier.

5. Conclusions

In this pilot study, we extracted the most informative features of the EVestG signals to classify pairs of AD, AD-CVD, and healthy control populations in an unbiased and automated manner. We also identified the EVestG tilts for which their extracted features were the best candidates for the above separations. Additionally, the robustness of the most informative features was tested via a blind testing dataset. Using the participants' MoCA score and the normalized linear weighted average score of the binary classifiers, we developed a novel diagnostic algorithm for a three-way classification that resulted in 85.7% and 79.6% accuracy in the training and blind testing datasets, respectively. The possible physiological changes support the selected EVestG features. Disruptions to inhibition associated with GABAergic activity might be responsible for the shift of AD/AD-CVD EVestG IH33 signals to lower/higher frequencies.

6. Limitations and the Future of the Study

One of the limitations of this study is the small sample size of the dataset. Given the difficulties of participant recruitment, particularly participants who are diagnosed at the early stage of AD or AD-CVD, and the chance of not being able to record some participants' EVestG signals due to excessive ear wax, a slow data collection process and small dataset were the result. Moreover, noise corrupted signals due to artefactual reasons, which could have led to missing data and a further reduction in the sample size. Considering the heterogeneity of biological data, a larger sample size could represent the entire population more accurately; hence, the reliability and credibility of the selected features could be enhanced as well. Additionally, a larger sample size may include patients who suffer from

AD mixed with other types of dementia, i.e., AD-non-specific, as not all mixed AD patients are AD-CVD. The hierarchical algorithm that is introduced in this study may have the potential to be generalized to separate AD-non-specific groups from the AD, AD-CVD, and control groups. The discriminative features can also be used in future studies to monitor and investigate the effects of interventions, and to predict the disease's progression.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina59122091/s1, Figure S1: IH33 signals of the average of left and right RTC BGi segments in Supine Up//down tilt (Supine Up/down-RTC-BGi-LR) for the three populations over the range of frequency or time.; Table S1: One-way MANCOVA on the selected features of C-vs.-AD, AD-CVD-vs.-C, and AD-vs.-AD-CVD classifiers controlling for age and sex. Each feature is named based on the IH33 that is extracted from in terms of the IH33's tilt name, segment (seg), and the ear side, left (L) or right (R). Refs [78–80] are in the file.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Biomedical Research Ethics Board of the University of Manitoba (reference numbers: HS13541(B2010:050), approval date: 17 January 2019).

Informed Consent Statement: Informed consent was obtained from all subjects (and their caregiver in cases where the caregiver was a legal representative acting on behalf of the participant) involved in the study. Written informed consent was obtained from the all participants (and their caregiver in cases where the caregiver was a legal representative acting on behalf of the participant) to publish this paper.

Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request. For any data sharing, one must contact NeuralDX Pty. Ltd. (Toorak, VIC, Australia).

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Abbreviations

Aβ	Amyloid-β
AβO	Amyloid-β oligomers
Acc	Accuracy
AD	Alzheimer's disease
AD-CVD	AD mixed with levels of cerebrovascular disease symptomology
AUC	Area under the curve
BGi	Background segment
C	Control
CT	Contralateral tilt
CVD	Cerebrovascular disease
EVestG	Electrovestibulography
FP	Field potential

FP_{ave}	Average of spontaneous and driven vestibular field potentials
GABA	Gamma-aminobutyric acid
HIS	Hachinski ischemic score
IH	Interval histogram
IH33	33-Interval histogram
IT	Ipsilateral tilt
L	left
LC	Locus Coeruleus
LR	Summation of left and right signals
L-R	Subtraction of left and right signals
μ	Mean
MADRS	Montgomery–Asberg Depression Rating Scale
MANCOVA	Multivariate analysis of covariance
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NEER	Neural Event Extraction Routine
NINDS-AIREN	National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences
OnAA	Acceleration segment
OnBB	Deceleration segment
R	right
ROC	Receiver operating characteristic
RTC	Return to center
SD	Standard deviation
Sens	Sensitivity
Spec	Specificity
SVM	Supervised support vector machine
VaD	Vascular dementia
VN	Vestibular nucleus

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A Perspective: Challenges in Dementia Research

Mark Stecker

Fresno Institute of Neuroscience, Fresno, CA 93720, USA; mark@finsneuro.org; Tel.: +1-516-478-8304

Abstract: Although dementia is a common and devastating disease that has been studied intensely for more than 100 years, no effective disease modifying treatment has been found. At this impasse, new approaches are important. The purpose of this paper is to provide, in the context of current research, one clinician's perspective regarding important challenges in the field in the form of specific challenges. These challenges not only illustrate the scope of the problems inherent in finding treatments for dementia, but can also be specific targets to foster discussion, criticism and new research. One common theme is the need to transform research activities from small projects in individual laboratories/clinics to larger multinational projects, in which each clinician and researcher works as an integral part. This transformation will require collaboration between researchers, large corporations, regulatory/governmental authorities and the general population, as well as significant financial investments. However, the costs of transforming the approach are small in comparison with the cost of dementia.

Keywords: dementia; Alzheimer's disease; big data; neurophysiology; imaging; biomarkers

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1. Introduction

A total of 115 years has passed since Alois Alzheimer [1] published his paper on dementia, in which he made the optimistic statement: "A histological examination will enable us to determine the characteristics of some of these cases. This process will gradually lead to a clinical distinction of specific illnesses". However, despite subsequent massive clinical and basic science research [2,3], it remains difficult to identify and diagnose dementia in the early stages, or to develop a disease modifying treatment.

Now is the time for novel approaches. Historically, new and exciting ideas have arisen out of attempts to answer seemingly simple challenges. For example, the X-prizes [4], Hilbert's 10 problems in mathematics [5], the structure of DNA [6] or the electromagnetic spectrum emitted by a heated object [7], have all generated completely novel and unexpectedly important developments.

The purpose of this paper is to propose, in the context of current knowledge, specific challenges regarding dementia that may stimulate controversy and specific research. Many elements of these challenges have already been addressed to some degree, but the full promise of each challenge cannot be met without integrating multiple techniques and ideas.

2. Specific Challenges

2.1. Challenge 1: Optimizing and Quantifying the Patient Evaluation

There are many types of dementia, which can have different etiologies, symptoms and prognosis [8,9]. The first step in analyzing dementia must be a widely available, comprehensive, yet concise assessment of each individual, which can be applied serially [10] in both cognitively healthy persons and patients with clear dementia. It must include multiple components including those listed below.

2.1.1. Quantification of Behavior

Improved Analysis of Standard Behavioral Testing

The evaluation for cognitive impairment begins at the behavioral level [11]. The problem is that cognitive tests are naturally dependent on many factors, such as age [12,13], race, gender, education, language [14], IQ and experience [15], as well as medical factors such as sleep [16,17], pain and many others. There are two solutions to this problem, one is to pick a test or set of tests and then study how its results change with all of these factors [18]. Although this a very reasonable approach, it is complex because the number of factors that influence test results, even in normal people, will be large and difficult to predict. This results in large test variances for individuals and reduces the precision of the assessment. A second solution is to start with a number of tests including quantitative psychophysical tests (that may be less dependent on education and language than traditional paper and pencil tests) [19,20] and use statistical techniques to find a limited combination of these test elements, which is minimally dependent on the factors that influence cognition in cognitively healthy people. This is not enough, however, because the ideal test should not only yield results that were similar in cognitively healthy people, but also be sensitive to the different phenotypes seen in cognitive disorders of differing etiology.

Data Mining/Extraction Techniques

Important techniques that might provide additional information not available in the standardized paper and pencil and psychophysical testing, are modern data mining techniques to extract features in a video [21] or audio recordings of individuals [22]. The use of data available in social media [23] could also provide important information.

Other Testing

Other important non-neuropsychological clinical tests that can provide insight into dementia involve eye movements [24,25], retinal function [26], gait [27], olfaction [28,29], taste [30] and hand movements [31].

2.1.2. General Medical Conditions

No assessment of dementia is complete without a knowledge of the patient's general medical conditions. This would have to include all elements of the traditional history and physical, as well as laboratory testing for common systemic conditions that could affect the brain such as vitamin B12, thyroid function, etc. The National Alzheimer's Coordinating Center's Uniform Data Set [32] contains additional data that is also important.

2.1.3. The Neurological Exam

A full description of the patient would also include the results of the general neurologic examination as it provides information on strength, sensation, gait, reflexes, and cranial nerves that are important. Many quantitative methods have been proposed to calculate this [33,34] and the selection of the optimal data variables is critical. At the present time, specific examinations are used for each disease. This approach is useful once the pathophysiology of a disease is clear but for dementia, a wider net must be cast.

2.1.4. Imaging

The results of brain imaging are critical to any full patient description. Clearly, MRI and/or CT images of the brain should be obtained if possible [35,36]. However, a comprehensive evaluation should include the possibility of obtaining perfusion imaging [37] as well as CT angiogram and MR angiogram images [38] and metabolic PET scans [39]. Amyloid and tau imaging [40] are also important, as is functional MRI [41,42]. In particular, functional imaging coupled with electrophysiology can provide information about the brain connectome [43]. The Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/, accessed on 24 September 2022) has made great progress in this direction, but this pioneering work is just a beginning, and must be extended.

2.1.5. Electrophysiology

Much information on the function of brain networks is available in neurophysiologic studies, such as EEG and evoked potentials in dementia [44–47] and should be included in the patient database when available

2.1.6. Serum/CSF Biomarkers

Various biomarkers [48] provide valuable information on diagnosing and understanding the mechanisms underlying dementia [49,50]. Some of these are neurofilaments [51], Aβ42 [52,53], tau [54,55], GAP-43 [56], neurogranin [57], trem2 [58], neuron-specific enolase [59], YKL-40 [60], and neuroregulin [61] among others. These also include exosomes and microRNA, which contain important information about the state and function of cells in the central nervous system [62–64].

2.1.7. Neuropathology/Histology/Electronmicroscopy

When available, understanding the microstructure of the brain and the individual neurons can provide vital information about the mechanisms of cognitive decline in dementia [65–67]. This includes standard histology and immunopathology [68,69]. However, electron microscopy provides crucial information regarding the state of subcellular organelles and structures [70,71].

2.1.8. Omics

Geneomic, proteomics, metabolomics and other similar approaches have been proposed as valuable markers in the study of dementia [72].

Genomics

Knowledge of the individual genome [73,74], as well as epigenetic markers of expression [75], are also critical in understanding dementia.

Proteomics

In-depth proteomic profiling to identify diagnostic and prognostic markers and gain understanding of complex pathophysiologic mechanisms [76].

Denomics

This is the study of the demographic factors that may influence health outcomes including diet [77], education, income, age, exercise and other activities. It also includes exposures to various environmental factors included in the exposome [78].

Metabolomics

These studies [79,80] can find patterns of metabolites in the blood that could correlate with dementia, and may thus provide insight into mechanisms.

2.1.9. Managing the Data

What is proposed above is an enormous amount of information, but starting with a database that is too limited is problematic:

1. As more is learned about the different dementias, it may be that factors initially thought of low importance could become increasingly significant.
2. More data will help find the most effective tools for diagnosing and distinguishing among the different dementias.
3. More detailed knowledge will help build model systems that better reflect each type of dementia.
4. Increases the chance of unique new discoveries.
5. Data must be collected longitudinally over time.

2.1.10. Making It Practical

It is easy to conceive of such a large database, but the key to this challenge is to bring together the elements to make it practical:

1. Funding.
2. Government and regulatory agency buy in.
3. "Assuring beneficence, justice and respect for all persons involved" [81].
4. Allowing individuals control over the use of private information.
5. Data storage, access and availability. It is important that elements of the database be available at multiple levels, allowing maximal researcher access at various levels without compromising private information. Allowing general access to elements of the database can allow crowd-sourcing [82] that can lead to new insights.
6. Data analysis. New statistical methods and computing methods will need to be developed to analyze the data, including machine learning [83–85], as well as other techniques [86,87].
7. Large patient number. Using a large data set with many dependent variables requires a sizeable number of patients in order to find patterns in the data.

2.2. Challenge 2: Quantifying Normal Aging

There are many biologic processes that result in a dementia phenotype. Some of these processes arise from causes outside of the neuronal/glial networks responsible for cognition, such as stroke, infections, trauma and metabolic disorders. Some processes causing progressive cognitive impairment are pathologic, but some may be inherent to the normal brain. Although it is easy to recognize pathologic brain function when it is severe, in order to identify the initial steps in the progression of dementia, it is critical to have very precise definitions of normal function at each age. A database such as the one described under Challenge 1 provides the basis for comparing changes during normal ageing and dementiaa, and allows us to ask more specific questions.

2.2.1. Changes over Time

In the absence of any pathology, what is the fate of the neuronal/glial networks over time? This needs to be determined from many viewpoints including: behavioral [88–91], imaging [92–95], exosomes [96], metabolomics [97] and molecular biologic [98].

1. What is the time course of this change? There may in fact be multiple time dependent changes in different variables. Which variables demonstrate the first changes?
2. What mechanisms underlie the changes in normal elderly patients?
3. Are any of these "normal aging" changes seen in humans, also seen in animals and isolated neurons? Are the time courses of the changes the same in each system?
4. Are there natural processes, exposures or genetic factors in humans or animals that ameliorate or accelerate these time dependent changes?
5. Beware overzealous extrapolation from animals to humans [3].

2.2.2. Model Systems

Eventually, progress toward understanding normal brain ageing and dementia will be facilitated by robust model systems. Model systems that explain only a very few of the changes will not be as valuable as systems that explain many different changes. Models can be based in animals (with caution) [99], in vitro systems [100], mathematical or computational [101,102]. These models will be critical to exploring and creating new ideas.

2.3. Challenge 3: Quantifying Pathologic Aging

The same techniques used to study and quantify normal aging can be applied to patients who have diagnoses of different types of dementia:

1. Use the existing data to refine the definitions of the various dementia types [103–108].

2. Follow-up longitudinal data over time to find the first difference noted between normal brain aging and pathological aging in patients eventually diagnosed with dementia [109–112]. This will form a more effective focus for disease modifying treatment than changes that occur late in the illness.
3. What are the characteristics of the nervous system that are different (see Challenge 2) at the onset [113] of pathological aging?
4. What is the detailed temporal relationship between amyloid and tau pathology, and the various biomarkers and behavioral changes in the database [114–116]?

2.4. Challenge 4: Building New Model Systems for Dementia

There has been much work on animal models [117–120], cellular models, [121–125] and computational/mathematical models [126–129] of dementia. However, none of these has captured all of the critical elements involved in the pathogenesis of the dementias and so cannot generate the sought-after answers. With the additional information obtained as part of these challenges, more effective models capturing more of the critical elements of dementia can be created, that will better serve the goal of understanding and treating dementia.

The complexity of the human brain is such that it may not be possible to immediately find a single model. Thus, it is necessary to have multiple overlapping models beginning at the smallest scale. There has been much work on the dynamics of protein folding and molecular dynamics [130–132] that has been stretched to the organelle level [133]. Beginning with this, models of the relevant aspects of single cell behavior [134,135] can be created and matched to cellular models. The interplay between predictions and observations at this level can help optimize modelling at this low level. Subsequently, modelling using organoids and tissue slices can be used and compared to mouse rat and primate models, all of which will be compared to humans in various ways.

This requires large scale collaborations between scientists with different backgrounds using different techniques.

2.5. Challenge 5: Search for Factors That Modify the Trajectory of Dementia Related Changes

The data generated by the previous challenges forms the substrate to generate hypotheses and test potential treatments for dementia. The model systems can be used to help choose the most appropriate molecules and doses, while predicting side effects of treatment before applying them to humans. Once potential therapies reach the level of human trials, the comprehensive data sets will be the key to understanding outcomes and refining future therapies. In addition, analysis of the demographic and exposure data in the context of multivariable outcomes will be key to using the natural experiments resulting from different genetic and environmental variables to look for potential therapies that can be tested. This requires large numbers of patients and modern computational techniques. Maximal data access that does not compromise individual privacy must be allowed to maximize finding important trends in such a large database.

3. Discussion

The costs of dementia at the personal and family level are incalculable, but the global financial costs are estimated to be on the order of USD 3 trillion [136] yearly. By comparison, the total yearly NIH budget at USD 45 billion dollars is only 1.5% of this number, and the operating expenses of a huge corporation such as Amazon are on the order of USD 100 billion each year, or 3% of the costs of dementia. Although the cost of solving the challenges proposed in this paper (Table 1) is huge, they can likely be met with resources of that magnitude, if they are well organized. Despite the cost, the reward is so large that such an investment is warranted.

Table 1. Summary of Challenges in Dementia.

Challenge	Details	Cost	Difficulty	Comment
Optimizing and Quantifying the Evaluation	Develop and maintain huge clinical databases with clinical, imaging, molecular and biochemical data for large numbers of patients.	++++	++++	Although difficult, this is the necessary pathway to progress in diagnosing, understanding the mechanisms of and treating dementia.
Quantifying Normal Aging	Without a comprehensive understanding of normal brain, aging it is impossible to identify the events that initiate the downward decline we see in dementia.	+++	+++	Once the first challenge has been met, this is much simpler but still requires substantial resources due to the need for long term studies.
Quantifying Pathologic Aging		+++	+++	
Building New Model Systems		++	++	The key is collaboration between teams of scientists with different backgrounds ranging from quantum and statistical physics, chemistry, biochemistry and systems biology to clinical care.
Search for factors that modify the trajectory of dementia related changes		++	++	Once the database is established appropriate computational resources need to be available to allow for analysis.

4. Conclusions

Finding a cure for dementia has so far proven intractable using current scientific models. It is now time to pursue a new model driven by large scale collaborations, not only between researchers and clinicians, but also including large corporations and world governments as partners. In addition, involving the general population in decisions about data use and crowd-sourcing analyses on big data will be critical elements of this new approach.

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Review

Alzheimer's Disease Treatment: The Search for a Breakthrough

Allison B. Reiss [1,*], Dalia Muhieddine [1], Berlin Jacob [1], Michael Mesbah [1], Aaron Pinkhasov [1], Irving H. Gomolin [1], Mark M. Stecker [2], Thomas Wisniewski [3] and Joshua De Leon [1]

[1] Department of Medicine and Biomedical Research Institute, NYU Long Island School of Medicine, Mineola, NY 11501, USA; dalia.mddn@gmail.com (D.M.); bjacob05@nyit.edu (B.J.); mmesbah26@gmail.com (M.M.); aron.pinkhasov@nyulangone.org (A.P.); irving.gomolin@nyulangone.org (I.H.G.); joshua.deleon@nyulangone.org (J.D.L.)
[2] Fresno Institute of Neuroscience, Fresno, CA 93730, USA; mmstecker@gmail.com
[3] Center for Cognitive Neurology, Departments of Neurology, Pathology and Psychiatry, NYU School of Medicine, New York, NY 10016, USA; thomas.wisniewski@nyulangone.org
* Correspondence: allison.reiss@nyulangone.org

Abstract: As the search for modalities to cure Alzheimer's disease (AD) has made slow progress, research has now turned to innovative pathways involving neural and peripheral inflammation and neuro-regeneration. Widely used AD treatments provide only symptomatic relief without changing the disease course. The recently FDA-approved anti-amyloid drugs, aducanumab and lecanemab, have demonstrated unclear real-world efficacy with a substantial side effect profile. Interest is growing in targeting the early stages of AD before irreversible pathologic changes so that cognitive function and neuronal viability can be preserved. Neuroinflammation is a fundamental feature of AD that involves complex relationships among cerebral immune cells and pro-inflammatory cytokines, which could be altered pharmacologically by AD therapy. Here, we provide an overview of the manipulations attempted in pre-clinical experiments. These include inhibition of microglial receptors, attenuation of inflammation and enhancement of toxin-clearing autophagy. In addition, modulation of the microbiome-brain-gut axis, dietary changes, and increased mental and physical exercise are under evaluation as ways to optimize brain health. As the scientific and medical communities work together, new solutions may be on the horizon to slow or halt AD progression.

Keywords: Alzheimer's disease; amyloid; inflammation; dementia; drug therapy; diet; lifestyle

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1. Introduction

Alzheimer's disease (AD) is a progressive, fatal neurodegenerative condition that presents clinically as impairment of cognitive function and memory along with changes in behavior and personality [1,2]. Neuronal loss and synaptic dysfunction are hallmarks of the disease. Detected microscopically within the brain are amyloid plaques formed by aggregation of amyloid β and neurofibrillary tangles composed of hyperphosphorylated tau protein [3,4]. Increasing global concern has led to the allocation of extensive resources to study AD pathophysiology, but our understanding of its causes remains rudimentary, and our treatments are inadequate [5,6].

Currently, fully approved AD treatments are limited to acetylcholinesterase inhibitors and N-methyl d-aspartate receptor antagonists. These agents address some AD symptoms but are not disease-modifying [7,8]. Recently, the FDA partially approved the anti-amyloid human immunoglobulin (Ig)G1 monoclonal antibodies aducanumab and lecanemab [9–12]. Aducanumab, the first new therapy for AD since 2003, was approved by the FDA via an accelerated approval process. The effectiveness of this drug has been called into question, particularly since the FDA's own Advisory Committee voted against its release [10,13]. It carries serious risks of amyloid-related imaging abnormalities (ARIA)—edema or hemorrhage [14,15]. Lecanemab in Phase III testing showed more clear cognitive benefits, slowing

cognitive decline by 27% on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale at 18 months [11,12]. These relatively modest clinical benefits are also associated with the potential for significant ARIA complications. Other drugs with a similar mode of action are in development [16,17]. However, the impact of this drug class on AD is not curative and, at best, may modestly slow progression. The need for a more significant leap forward remains.

This review will survey the newest approaches to AD therapy beyond amyloid and tau, hoping that one or more of these may lead to true advances in conquering this devastating disease.

2. Finding a Viable Approach

Studies in humans indicate that eliminating or clearing amyloid-β (Aβ) or tau does not halt or reverse AD [18–20]. This calls into question the assertion that the Aβ oligomer is the primary initiator of AD. Instead, Aβ and tau protein likely appear after the damage is too extensive for repair, or they are indications of a pathological process and not the cause.

The multifactorial etiology of AD likely involves impaired regulation of multiple signaling pathways, ultimately leading to neuronal and synaptic loss and hypoplasticity [21,22]. AD neuronal death can be attributed to mitochondrial dysfunction, DNA oxidative damage, chronic neuroinflammation and failure of cellular repair mechanisms [23,24]. Ultimately, the preservation of neuronal function and prevention of neuronal loss is the goal of any cognition-preserving AD treatment.

3. Inflammation in AD

3.1. Overview

Aβ plaques and neurofibrillary tangles of tau protein are hallmarks of AD and indicators of neurological pathology that manifest years or decades before an official AD diagnosis [25,26]. However, therapies directed at these deposits have not shown therapeutic results in humans, and only a few symptomatic treatments for some patients with AD are currently available [27–29]. There is no cure, but studies over the years have shown that there may be causative agents that act via the promotion of neuroinflammation, which may lead to Aβ and tau accumulation as well as neuronal destruction [30]. In the following subsections, we discuss several anti-inflammatory drugs being considered for repurposing in treating AD and newly developed agents that can interfere with destructive inflammatory pathways in the neuron (Table 1).

3.2. Neuroinflammation and Microglia

Neuroinflammation can be defined as a sustained immune response in the CNS. Acute inflammation can help defend against insults to the brain, such as toxins, infection, or injury [31,32]. However, in the chronic phase, there can be a cycle of increased inflammation and further damage due to excessive activation of immune cells such as microglia, which can migrate and release proinflammatory cytokines [33]. Historically, immune antigens found around amyloid plaques in AD have been reported in studies since the 1980s. The findings of cytokines and activated complement factors were reported in the 1990s. This opened the door to the hypothesis that immunological processes are involved in the pathology of degenerative CNS diseases such as AD, schizophrenia, and Parkinson's disease [34,35].

In AD, microglia and astrocytes are the resident immune cells activated in the parts of the brain affected by Aβ plaques and tau NFTs [36]. Microglia are cells of mesodermal origin, and the most abundant immune cells present in the brain. Normally in the resting state of a healthy brain, they maintain homeostasis of the neuronal environment, control the proliferation and differentiation of neurons, and perform immune surveillance [37,38]. However, Microglia are dynamic, even in the resting state, constantly moving their fine cellular processes to execute their functions of phagocytosing cellular debris and regulating neural plasticity and synaptic formation [39,40].

Table 1. Potential Therapeutics for the Management of Neuroinflammation in AD.

Targets	Drugs	Modulation of Neuroinflammation
COX-1 and COX-2 inhibitors	NSAIDs (diclofenac/misoprostol, nimesulide, naproxen, rofecoxib, ibuprofen, indomethacin, tarenflurbil, and celecoxib)	COX-2 overexpression is seen in activated microglia. Potential COX-2 inhibition might reduce neuroinflammatory mediators and prostaglandin release by these cells.
TNF-α inhibitors	Etanercept, infliximab, XPro1595	Activated microglia promote the TNF-α and TNF receptor 1 axis to induce a neuroinflammatory state.
TREM2 agonists	(AL002a)—TREM2 mouse IgG1 antibody agonist (AL002c)—mouse IgG1 anti-human TREM2 monoclonal antibody agonist	Genetic mutations in TREM2 receptors are associated with AD. Activation of TREM2 is neuroprotective.
CD33 inhibitors	AL003—antibody against CD33 receptor	Higher CD33 levels and subsequent activation of CD33+ microglia are associated with higher Aβ plaque burden.
Filamin A conformation restoration	PTI-125—a small molecule drug that interacts with Filamin A to reestablish its native state	Altered filamin A promotes the hyperphosphorylation of tau by activating the signaling of Aβ42 using the α7-nicotinic acetylcholine receptor

Abbreviations: COX—cyclooxygenase; NSAIDs—non-steroidal anti-inflammatory drugs; TNF—tumor necrosis factor; TREM2—Triggering Receptor Expressed on Myeloid Cells 2; IgG1—immunoglobulin G1; Aβ—amyloid β.

When microglia detect injury or disease to the CNS, they become activated and change from ramified to amoeboid morphology and a pro-inflammatory phenotype [41]. They change appearance through cellular enlargement and retraction of their processes. In addition to the physical changes, microglia mount a host defence by releasing inflammatory mediators such as cytokines, chemokines, free radicals, and reactive oxygen species, which, in cases of overactivation, can be toxic to the brain [42]. When not over-exuberant, microglia have been shown to gather pathological debris and have positive effects as they clear Aβ plaques, as demonstrated in multiple animal model systems [43]. They release both neurochemicals with neuroprotective effects and neurotoxic mediators [44]. Constantly activated microglia, over prolonged periods, will become less able to clear Aβ plaques and peripheral macrophages are then activated, which further exacerbate amyloid and tau pathology as they surround the damaged areas. In the process, pro-inflammatory products are additionally released, and oxidative damage ensues, creating a cycle of damage [45]. It has even been shown that the release of cytokines such as IL-1 exacerbates amyloid pathology while IL-6 stimulates the kinase CDK5, which is a main mechanism in the tau hyperphosphorylation mechanism [46,47]. These findings have inspired the idea that inflammation may be the link between these two novel pathways.

Traditionally, microglia have been categorized into classical (M1) and alternative (M2) phenotypes, with a range of intermediate phenotypes occurring [48]. M1 microglia release inflammatory mediators, produce ROS, and contribute to neuronal damage, whilst M2 microglia release anti-inflammatory mediators, promote inflammation resolution, and are neuroprotective [49]. These two opposing types play a role in neurodegenerative diseases, including AD, multiple sclerosis and Parkinson's disease and have led to the study of balancing M1 and M2 polarization for increasing neuroprotection [44,50]. Although the canonical M1/M2 paradigm may be helpful, it should be noted that refinements in defining microglial state can yield a more accurate profile, and transcriptomics are applied to account for subtleties in phenotype in normal and AD cells [51].

3.3. Anti-Inflammatory Drug Repurposing as an Approach to AD via Microglia

M1 inhibitive agents such as non-steroidal anti-inflammatory drugs (NSAIDs), which act by inhibiting cyclooxygenases (COX) 1 and 2, enzymes that catalyze the conversion of arachidonic acid to prostaglandins, have not shown benefit in treating AD [52]. COX-2 is over-expressed in activated microglia, and thus it was reasoned that COX-2 inhibition might reduce neuroinflammatory activity and prostaglandin release by these cells [53]. Initially, throughout the late 20th century, several case-control retrospective epidemiological studies showed that rheumatoid arthritis patients who were on chronic NSAIDS had decreased severity and progression of AD as compared to non-NSAID users [54,55]. However, human trials showed variable outcomes with no positive conclusion. A meta-analysis of seven studies which included the NSAIDs diclofenac/misoprostol, nimesulide, naproxen, rofecoxib, ibuprofen, indomethacin, tarenflurbil, and celecoxib, showed the clinical significance of NSAIDs treatment compared with placebo when patients were assessed by cognitive and memory exams. However, studies were limited by study size [56]. This discrepancy between epidemiological and prior research studies has partly been attributed to the time NSAIDs need to provide a protective and/or therapeutic effect. This hypothesis was explored by the Baltimore Longitudinal Study of Aging, which showed that the risk of AD was reduced after two years of NSAID use. However, no conclusions could be made on protective benefit in terms of cognitive decline or the specific NSAID that conferred the most benefit. In addition, long-term NSAID use is associated with risks of gastric ulceration, bleeding, and nephrotoxicity, which may not be suitable for many patients depending on their medical conditions [57]. The more recent INTREPAD study observed the effects of naproxen in people who had a strong family history of AD but without an official diagnosis. One hundred people were prescribed naproxen, and the remaining 100 a placebo, and the new Alzheimer Progression Score (APS) was used to predict the onset of the clinical disease over the coming decade or more. The results proved negative, with no evidence that the APS was reduced with naproxen [58].

Recent work also shows that more modern disease-modifying anti-rheumatic agents with anti-inflammatory properties do not reduce AD risk [59].

3.4. Repurposing Anti-TNF Agents

Pro-inflammatory markers released by activated microglia, such as tumor necrosis factor (TNF)-α, have also been used as a target for AD therapies [60,61]. TNF-α can interact with the 55-kDa TNF receptor 1 (TNFR1) to induce a neuroinflammatory state, or it can interact with the 75-kDa TNF receptor 2 (TNFR2) to produce a neuroprotective effect [62]. Given this duality, therapies currently underway include TNF-α blockade, inhibition of TNFR1 signaling or induction of TNFR2 signaling. Etanercept, an anti-TNF-α antibody that is a fusion protein between a human IgG1 Fc-tail and TNFR2, has been studied in murine models of AD with Aβ plaque formation and found to decrease TNF-α levels, reduce neuronal injury and improve cognitive measures [63,64]. In addition, intra-cerebral administration of the chimeric anti-TNF-α antibody infliximab to mice overexpressing APP reduced the formation of both Aβ- plaques and tau neurofibrillary tangle [65].

A second-generation biologic TNF-α inhibitor, XPro1595, is a PEG-ylated mutant form of TNF that complexes with TNF-α in a way that prevents it from binding to TNFR1 [66]. XPro1595 has been studied pre-clinically in AD mice and human clinical trials. For example, the XPro1595 treatment of 5XFAD Aβ-overexpressing mice decreased Aβ plaques and reduced immune cell activation [67]. XPro1595 clinical trials have also shown positive results regarding targeting inflammation. For example, a 12-week, phase 1b study, which included weekly injections of 0.03, 1.0 or 3.0 mg/kg XPro1595 in mild-to-moderate AD patients, showed a 40.6% reduction in arcuate fasciculus inflammation, an area of the brain responsible for intra-cerebral connections, short term memory and language [68].

3.5. Inciting the M2/TREM 2 Phenotype in Microglia

Another pathway researchers have taken is to study the activation of M2 microglia to amplify the neuroprotective effects. Genetic mutations in microglial and cytokine receptors also corroborate the neuroinflammatory link to AD [69]. The most significant lead in recent studies has found that heterozygous mutations in the M2 microglia regulator known as Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) increased the risk of AD significantly. Initially, TREM2 was studied after gene sequencing revealed that this receptor's homozygous loss of function mutation led to an autosomal recessive disease known as Nasu-Hakola disease, which involves early-onset dementia and bone pathology [70]. Given its link to progressive dementia, a study was conducted using genome, exome, and Sanger sequencing to analyze the genetic variability in TREM2 in 1092 patients with AD and 1107 controls. Results showed more variants on exon 2 of the TREM2 gene in AD patients, with rs75932628 (encoding R47H) found to be the most common variant. This R47H mutation showed a highly significant association with AD ($p < 0.001$) [71]. An agonist TREM2 mouse IgG1 antibody (AL002a) developed to activate TREM2 signaling in vivo was administered intracranially to 5XFAD Aβ-overexpressing mice. The AL002a caused activation and recruitment of microglia to amyloid plaques, decreased Aβ deposition and improved memory and cognition in these mice [72].

Similarly, AL002c, a mouse IgG1 anti-human TREM2 monoclonal antibody, was studied in 5XFAD mice carrying the common variant (CV) of TREM2 and in 5XFAD mice carrying the R47H loss-of-function Trem2 mutation. An injection of AL002a increased the phagocytic activity of the microglia and reduced Aβ plaque toxicity in both types of mice [73]. In addition, a Phase I clinical trial of AL002 (NCT03635047) found the antibody to be safe and tolerable in healthy adults with mild-to-moderate AD, and the levels of TREM2 in CSF were found to be decreased in a dose-dependent fashion after a single intravenous injection of AL002. These favorable results have led to a currently ongoing Phase 2 randomized, double-blind, placebo-controlled clinical trial which examines the role of AL002 use in patients diagnosed with the early stages of AD [74].

3.6. CD33

CD33, a member of the family of sialic acid-binding immunoglobulin-like lectins, is a transmembrane receptor expressed on microglia that affects microglial phagocytosis [75]. Genome-wide association studies have revealed an association between late-onset AD and polymorphisms in CD33 [76,77].

In the AD brain, CD33 levels and the number of CD33+ microglia are increased, and higher CD33 expression correlates positively with higher Aβ plaque load [78]. In CD33 knockout mice, Aβ plaque burden is reduced. In cell culture studies using the THP-1 human macrophage cell line, knockout of CD33 increased phagocytosis of aggregated Aβ but also increased the inflammatory phagocytic oxidative burst [79]. The AL003 antibody, which binds to CD33, was evaluated in a clinical trial, but although target engagement was confirmed, the antibody is no longer in the pipeline [80–82]. The future of CD33 targeting AD remains uncertain, but small molecule binding to CD33 may be an avenue of study [83].

3.7. PTI-125

PTI-125, a small molecule AD treatment, binds to an abnormal conformation of filamin A that is induced by Aβ42 and restores the conformation to its native state [84]. In humans, a Phase 2a safety, pharmacokinetics, and biomarker study in 13 AD patients showed that after 28 days of twice daily oral treatment, all patients had a biomarker response to the drug (CSF P-tau decreased 34%, $p < 0.0001$), which was well tolerated, with no drug-related adverse events [85]. However, there is controversy surrounding this drug. While studies are continuing, including an open-label extension study for long-term safety and tolerability, the issue of possible irregularities is not resolved [86].

3.8. Role of Peripheral Inflammation in AD

An integrative perspective in relation to AD pathogenesis, specifically exploring systemic metabolic factors such as diabetes and abnormalities in the gut microbiome, has been gaining attention and has raised important questions. One of the first epidemiological studies to demonstrate the association between type 2 diabetes (T2DM) and dementia was the Rotterdam Study. This population-based prospective cohort study started in 1990 and included diabetes as one of the multiple modifiable cardiovascular risk factors. Over 8000 participants were followed over decades, and it was found that in relation to dementia, T2DM had the second most population-attributable risk. This value measures the magnitude of the potential to prevent disease [87]. Other studies have solidified this relationship and shown that glucose utilization is reduced in the AD brain with hypometabolism in specific brain areas on fluorine 18 fluorodeoxyglucose positron emission tomography neuroimaging [88–91]. Multiple research reports have gone a step further by labeling AD as type 3 diabetes in which insulin resistance can occur systemically, including in the brain and lead to multiple, thus-far unidentified pathways of neurodegeneration [92,93]. It has been postulated that the low-grade inflammatory state seen in persons with T2DM leads to immune activation that affects the brain [94–96]. In diabetic rodent models, pro-inflammatory markers, such as IL-2, IL-6 and TNF-α, are increased in the brain [97–99].

T2DM can impair autophagy, a vital process needed for clearing toxic reactive oxygen species and other waste, and this may interfere with the clearance of both Aβ and tau [100–102]. T2DM is a metabolic disease characterized by dysfunctional insulin secretion and the development of insulin resistance. Insulin affects not only glucose levels in the blood but also neurogenesis and energy metabolism in the brain. It is postulated that diabetes-induced peripheral insulin resistance can promote central insulin resistance [103]. This possibility has prompted the development of brain-available forms of insulin as potential AD treatment. Insulin, with a molecular weight of 5808 Da, is too large to passively cross the (blood-brain barrier) BBB, which limits permeability to 400 Da or less. Thus, extra-neuronal forms have been studied, specifically intranasal insulin. This insulin has been shown to evade the BBB and reach the CNS within 1 h of usage via multiple mouse and human in vitro studies.

Furthermore, its safety profile is low risk because there is minimal systemic absorption and subsequent effects on cortisol and growth hormone if maintained underdosing 200 IU [104–106]. The positive impact of intranasal insulin was initially explored in individuals without cognitive impairment. An eight-week trial of 160 IU of intranasal insulin in 38 healthy young male and female participants versus placebo showed improved hippocampal declarative memory via delayed word recall testing. Immediate recall memory testing showed no improvement [107]. Several pilot studies have been performed in men and women with mild to moderate cognitive impairment in which insulin or a placebo was given [108,109]. Memory scores improved, cognitive ability was maintained, and brain volume of the parietal and hippocampal areas was preserved over four months with the treatment. A study looking at intranasal insulin in mild cognitive impairment (MCI) and early AD found that the apolipoprotein (apo)E genotype affected the results such that benefits were greater in those not carrying the apoE4 allele, a known risk factor for AD [110]. The administration of intranasal insulin, although not a cure, may benefit some MCI and AD patients, but more extensive studies of efficacy and mechanism are needed [111,112].

Metformin, which easily penetrates the BBB, is a hypoglycemic drug with neuroprotective properties in animal models [113]. In rats, it protects against an amyloid-induced decline in cognitive function by reducing oxidative stress and neuroinflammatory processes [114]. In addition, Metformin has favorable effects on insulin pathways, and it has shown some promise in human studies [115,116].

The gut has also been explored as a potential link to the progression of inflammation in the brain leading to AD. There is a relationship between the brain and gut, known as the "microbiome-gut-brain axis," in which the bacterial communities in the gut communicate with the CNS via molecules that act both directly and indirectly to influence behavior

(Figure 1) [117]. Communication is bidirectional; thus, the brain can also affect the gut by changing appetite and eating patterns. The gut microbiome consists of many bacterial species residing in the small and large intestines, engaged in a symbiotic relationship with the human body [118]. The gut microbiome is involved in the immune response of the intestines, protecting the host from detrimental bacterial overgrowth and carcinogens by releasing short-chain fatty acid metabolites. Common gut species such as Saccharomyces, Bacillus and Bifidobacterium have been shown to break down short-chain fatty acids and affect the synthesis of dopamine, acetylcholine, glutamate, and serotonin [119–121]. These neurotransmitters and signaling molecules produced by bacteria in the gut enter the bloodstream through the enterohepatic circulation and can penetrate the BBB resulting in beneficial or detrimental effects on neuronal health [122].

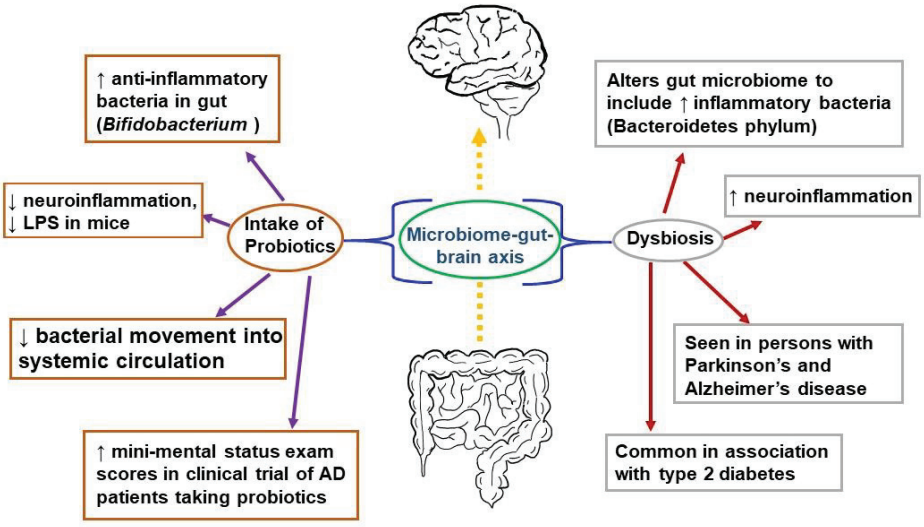

Figure 1. The microbiome-gut-brain axis is a potential pathological mechanism in AD. The gut microbiome comprises numerous bacterial species in a symbiotic relationship with the human organism. It helps protect the host from bacterial overgrowth and carcinogens via the secretion of short-chain fatty acid metabolites. Dysbiosis occurs when the gut microbiome is negatively altered and exhibits reduced species diversity. This, in turn, can promote the development of metabolic syndrome, the growth of inflammatory bacteria, and neuroinflammation. To combat dysbiosis, probiotics can support the growth of anti-inflammatory bacteria, decrease neuroinflammation, and improve mini-mental status scores among patients with AD.

An early study demonstrating a link between the gut microbiome and the brain was performed in germ-free mice characterized by a complete lack of exposure to microorganisms. These germ-free mice were found to have an amplified response to stress restored via recolonizing the mice with the gut microbiome species Bifidobacterium infantis [123]. They also showed a reduced brain-derived neurotrophic factor (BDNF) level in the cortex and hippocampus. Further, the transplantation of microbiota from mice exposed to chronic unpredictable stress into recipient mice not exposed to stress resulted in anxiety and depression-like behavior in the recipient mice [124]. In accordance with this outcome, when fecal matter from healthy mice was transferred into mice with Parkinson's disease-like syndrome, this afforded neuroprotection, especially against neuroinflammation [125]. Germ-free mice colonized with gut microbiota from human patients with multiple sclerosis exhibit multiple sclerosis-like autoimmune responses [126]. Fecal microbiota transplantation from an AD mouse model into wild-type mice resulted in memory dysfunction, reduced hippocampal neurogenesis, and increased hippocampal neuroinflammation in the

recipients [127]. These and many more studies have corroborated a connection between the brain and the gut.

Negative alteration of the gut microbiome, or dysbiosis, is seen in humans with AD, with a decrease in microbial diversity and, in some reports, an increase in Bacteroidetes species [128–130]. Bacteroidetes is an umbrella phylum of many different types of gram-negative bacteria found to incite a pro-inflammatory response from the gut, largely attributable to their outer membrane constituent lipopolysaccharide (LPS), a bacterial endotoxin [131]. Bacteroidetes species have been detected in high levels in Type II DM and Parkinson's patients [132]. Similarly, postmortem brain tissue from patients with AD found LPS and gram-negative bacterial DNA segments localized around amyloid plaques, which may indicate a link between the bacterial pro-inflammatory response and AD pathology [133].

In contrast, there are gut bacteria that may be beneficial to the CNS. The Bifidobacterium genus, gram-positive bacteria found widely in the gastrointestinal tract, have anti-inflammatory effects, and are used in probiotic products [134,135]. Murine studies using cognitively impaired mice injected with LPS showed that administering Bifidobacterium by oral gavage decreased LPS levels and improved cognitive function [136,137]. In human AD studies, which have been limited and with a small population size, there have also been some promising results. A double-blind, controlled clinical trial consisting of 30 AD patients randomized into a group of 30 taking a mix of probiotics (including Bifidobacterium) in milk and a group of 30 consuming milk without added probiotics showed a statistically significant improvement in mini-mental status exam scores in the group taking probiotics after 12 weeks [138]. Studies investigating the microbiome's association with AD are ongoing with the hope that specific strains of bacteria or combinations of strains may serve as a preventative measure in the clinical course of AD [139].

4. Delivery Systems to the Brain Crossing the BBB

Reaching the brain regions affected by AD is challenging, especially because the BBB, through low permeability and active efflux, blocks penetration into the CNS of many drugs and compounds [140]. Therefore, avoiding direct and invasive access to the CNS via methods such as intrathecal or intracerebroventricular injection is a high priority. Instead, it may be possible to use the circulatory system or the nose-to-brain route [141,142]. Lipophilic nanoparticles and biocompatible nanogels composed of hydrophilic polymers are a few technologies for delivery to the brain parenchyma [143]. Targeting the brain reduces the dosage needed and any accompanying toxicities by narrowing the distribution of the medication. In addition, encapsulation can prevent rapid metabolism and elimination and binding to plasma proteins [144].

Nanoparticles range in size from approximately 10 to 100 nm and can be organic or inorganic (often silicon or metallic) [145]. Organic nanoparticles consist of biomaterials such as liposomes, micelles, or polymers (natural or synthetic) that hold the pharmaceutical agent and can penetrate the BBB for site-targeted delivery in the case of the CNS. Designing a coated nanoparticle is a strategy that combines many advantages in traversing the BBB with minimal toxicity and immunogenicity, and good targeting. The technique involves coating the nanoparticle with a cell membrane-like phospholipid bilayer outer covering over a lipid-based or polymeric core that holds the drug [146,147]. Conjugation of ligands onto the nanoparticle surface can bring customized ligand-receptor binding and internalization of the particle in the desired cell type via receptor-mediated endocytosis [148]. Nanoparticles can also be used to carry oligonucleotides to employ antisense technology to alter gene expression [149].

Nanoparticles are a potential new tool for delivering AD therapy through the BBB and into brain regions where the benefit would be most tangible. However, there is much more work to be done to bring this technology into clinical use [150,151].

5. Stem Cells

Safely rejuvenating, rescuing, or replacing the neurons of the brain in AD is the rationale for the use of stem cells [152]. Stem cells can proliferate, self-renew, and differentiate into numerous subtypes characteristic of any of the three germ layers. These properties enable them to serve as suitable reservoirs for cell replacement therapies. Different sources of stem cells with varying capabilities have been identified [153,154]. The primary types of human pluripotent stem cells are (ESCs) and induced pluripotent stem cells (iPSCs) (Figure 2) [155]. Mesenchymal stem cells (MSCs) are multipotent and can transdifferentiate into ectodermal and mesodermal lineages, including neurons [156]. While ESCs are sourced from human embryos, MSCs are taken from adult tissue, while iPSCs represent a conversion of terminally differentiated somatic cells into an ESC-like state. MSCs and iPSCs avoid the ethical problems associated with ESCs [156–159].

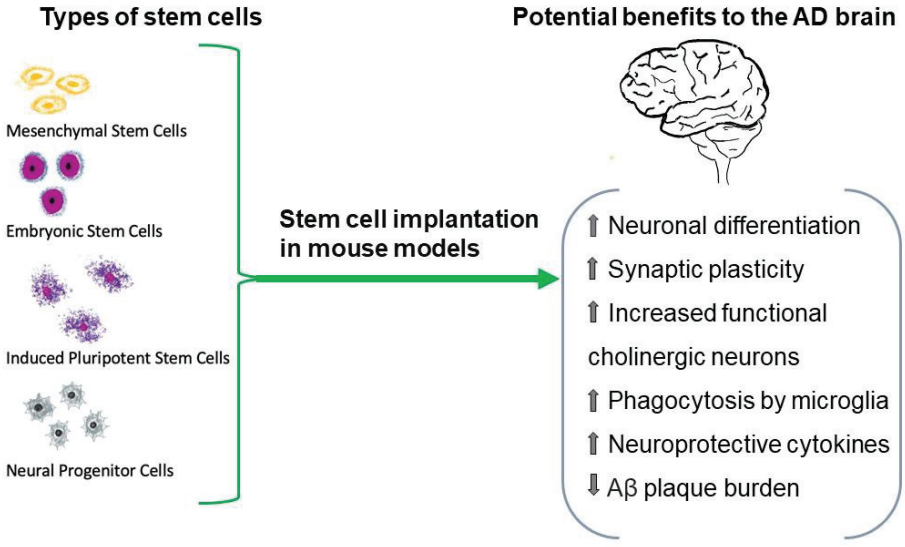

Figure 2. Stem cells are being explored as an avenue of AD treatment. Several sources of these pluripotent cells have been identified. Preclinical studies suggest that stem cells may be able to rejuvenate, rescue, and replace unhealthy neurons. In addition, transplantation of these cells into specific brain regions may yield benefits, as shown in this figure. However, more human clinical trials are needed for definitive answers.

In preclinical studies, ESCs could yield neural progenitor cells (NPCs) when programmed by different growth factors and elements in vitro [160]. In patients with AD, cholinergic neurons in the basal forebrain are lost, and their absence correlates with cognitive decline [161,162]. Bissonnette et al. transformed ESCs into basal forebrain cholinergic neurons and engrafted them onto cultured mouse entorhinal-hippocampal slices ex vivo and showed that these cholinergic neurons promoted functional synapse formation [163]. ESCs were used in vivo in the living mouse brain by Yue et al. [164]. This group produced basal forebrain cholinergic neuron progenitor cells from murine ESCs and transplanted them into the brains of transgenic AD mouse models. These engrafted cells could differentiate into functional cholinergic neurons in the forebrain and improve spatial learning and memory in the mice.

McGinley et al. performed intracranial transplantation of a human neural stem cell line derived from human fetal cortical tissue into an AD mouse model and found that the mice exhibited improved short-term non-associative memory [165,166]. Microscopic examination of the brain showed reduced amyloid burden and increased microglia in the

hippocampus and cortex. These benefits were seen even though immunohistochemical studies did not detect the human cells in the murine brain at 17 weeks post-transplant. The authors postulate that even transient exposure to the human ESC cell line was sufficient to confer positive effects.

Neural stem cells extracted from the hippocampus of 1-day old wild type mice were transplanted into the hippocampus of transgenic mice with tauopathy and AD-like traits, including memory impairment, and the mice receiving these stem cells exhibited improvement in short-term memory and decreased accumulation of tau neurofibrillary tangles [167]. A similar study used human ESCs transformed into medial ganglionic eminence (MGE)-progenitor cells, a type of cell that serves as a precursor to basal forebrain neurons. These MGE-like cells were transplanted into a murine model of learning and memory deficits induced by an immunotoxin, which resulted in the correction of memory loss [168].

Although ESCs show potential for treating AD in preclinical studies, their clinical application is limited by ethical issues, risk of teratoma formation, accumulation of mutations, abnormal immune responses, and rejection [169,170]. In addition, despite the advantages of the pluripotent state in ESCs, this property also represents a disadvantage because these cells can undergo genetic alterations leading to tumors or teratomas [171,172]. Therefore, human ESCs as the source of stem cells in treating AD are unlikely. Instead, mesenchymal, and hematopoietic stem cells have been the most widely used and investigated as potential therapeutics for AD [173–175].

MSCs are stromal cells derived from various adult sources (blood, adipose tissue, dental pulp) that can differentiate into multi-lineages [176]. These stem cells have a high expansion capacity, low immunogenicity, and low carcinogenic potential [177,178]. With regard to AD pathology in mice, MSCs have been shown to reduce Aβ plaque size, enhance Aβ clearance and reduce Aβ expression [179,180]. MSCs can also alter innate and adaptive immune responses by modulating neuroprotective cytokines such as interleukin (IL)-10 and downregulating pro-inflammatory cytokines such as TNF-α and IL-1β [181]. In addition, human MSCs in culture promote neurogenesis by releasing neurotrophic factors [182]. In preclinical studies, AD mice that received intracerebral transplantation of bone marrow-derived MSCs demonstrated lower Aβ accumulation and increased microglial phagocytic activity [183]. Several preclinical studies have also assessed the efficacy of umbilical cord-derived MSCs obtained from cord lining and Wharton's Jelly [184]. In mice, human umbilical cord-derived MSCs injected into the carotid artery can migrate into the brain parenchyma. An AD double transgenic mouse model of excessive amyloid deposition injected with these MSCs demonstrated reduced amyloid accumulation, increased microglial activation in the hippocampus and cortex, and better cognitive function during sensorimotor tests compared to AD mouse controls not receiving MSCs [185].

Despite progress in the field of stem cell technology, as demonstrated in preclinical studies using stem cells in animal models of AD, clinical trials assessing the efficacy of this therapeutic remain limited in number. There have been two clinical studies exploring the safety and efficacy of human umbilical cord-derived MSCs in AD patients. The NEUROSTEM-AD treatment, an open-label phase 1 trial (NCT01297218), reported that stereotactic delivery of human umbilical cord-derived MSCs into the hippocampus and precuneus was attainable, safe, and well-tolerated by 9 AD patients [186]. During the first 12-week and last 24-month follow-up periods, no significant adverse effects or dose-limiting toxicity were observed. Results from the trial did show a faster cognitive decline in patients than expected of typical AD progression. Researchers attributed this to the typically faster decline with early onset disease since seven out of the nine enrolled patients had early onset AD.

A second double-blinded, single-centre, open-label phase I/IIa clinical trial (NCT02054208) with 36 months of extended observation (NCT03172117) assessed the safety, dose-related toxicity, and efficacy of human umbilical cord-derived MSCs administered via three intracerebro-ventricular (ICV) infusions four weeks apart via an Ommaya reservoir ventricular access device [187,188]. The treatments were given in 2 stages. In the first stage of the

study, patients were placed in a low- or high-dose group. In the second stage, patients were randomized into a high-dose or placebo group. Patients developed a transient fever and elevation of cerebrospinal fluid (CSF) white blood cell count after each infusion that resolved rapidly. CSF total tau, p-tau, and Aβ42 were found to be decreased one-day post-infusion but returned to baseline at the 4-week follow-up. This was attributed to the short lifespan of MSCs. A follow-up study will examine neuropsychological scores, imaging, and profiles of biomarkers in these participants compared to the untreated control group.

Human iPSCs, often from fibroblasts, can generate neurons that can be used to study AD processes in human culture systems and cerebral organoids [189–191]. There is also the potential for precision medicine studies of unique properties of cells derived from specific patients for evaluation of AD mechanisms [192].

Clinical trials using iPSCs are still rare and not yet being applied in AD, although there are some studies on Parkinson's disease [193–196]. Progress in using stem cells in humans is slowed by the disadvantages, such as the need for immunosuppression and the risk of tumor formation with progenitor cells [165]. In addition, the complex anatomy and cellular environment of a patient with AD significantly differ from the homogeneous nature of transgenic animal models developed for the familial type of AD. The precise mechanism and effect of these therapeutics on patients is uncertain.

6. Deep Brain Stimulation

Deep Brain Stimulation (DBS) entails electrical brain stimulation using implanted electrodes, subcutaneous leads, and a pulse generator for neuromodulation [197]. This is an invasive modality requiring stereotactic surgical electrode implantation within the brain. The mechanism of action is not well-established, but it has been shown to activate or inhibit brain networks in a way that is postulated to reduce symptoms resulting from circuit issues of the human brain in AD and other disorders such as Parkinson's disease, essential tremor, primary dystonia, and obsessive-compulsive disorder [198–201].

In rodent models of AD, DBS has been shown to improve memory, decrease phosphorylated tau and amyloid plaque accumulation and promote cholinergic neurotransmission, hippocampal neurogenesis, and synaptic plasticity [202–204]. Within the past ten years, some preliminary clinical trials of DBS in AD demonstrated beneficial effects such as slower cognitive decline, decreased hippocampal atrophy, increased cerebral glucose metabolism and modulation of multi-network brain connectivity in patients suffering from the disease [205,206]. Various stimulation targets of the brain are engaged during DBS treatment in patients with AD. Human clinical trials have used DBS to stimulate the fornix, nucleus basalis of Meynert, and ventral capsule/striatum [205,207,208].

DBS, specifically the fornix, is being investigated as a treatment for patients with mild AD. Results from randomized clinical trials have demonstrated an improvement in cognitive function among some patients and no benefit in others [209]. The fornix, a part of the Papez circuit, is the principal inflow and outflow tract of the hippocampus and middle temporal lobe. Composed of an arcuate fiber bundle that extends from the hippocampus to the mammillary body, the fornix delivers input from the hippocampus to the anterior nucleus of the thalamus. It is responsible for encoding and integrating memory information [210,211]. When this structure is damaged, memory is severely impaired. A transition from mild cognitive impairment to AD is associated with fornix atrophy. Hamani et al. discovered unexpectedly that fornix stimulation could improve memory in a patient who received DBS to treat morbid obesity. Fornix DBS was able to increase recollection and evoke detailed autobiographical memories [212]. Studies in small numbers of subjects have shown that chronic fornix DBS can stabilize or attenuate the rate of memory decline, increase hippocampal volume, and promote cerebral glucose metabolism in AD patients [213,214]. In rodent AD models, chronic fornix DBS improved spatial learning memory and recognition memory, reduced amyloidosis and inflammation and decreased neuronal loss and changes in brain volume [215,216]. Ríos et al. investigated which sites and networks in the brain are the most optimal for DBS in patients with

AD. Researchers conducted a post-hoc analysis of data obtained from 46 patients from clinical trials associated with DBS to the fornix (NCT00658125, NCT01608061) [217]. Using structural and functional connectivity data from these trials, the authors reported a strong association with cognitive improvement when stimulated by the Papez and stria terminalis circuits. The most optimal site for stimulation existed at the interface of these two structures.

DBS may have a role in AD treatment, but it cannot be a curative procedure. It can only modulate symptoms. Furthermore, factors in DBS that still need elucidation include stimulation parameters and the exact mechanisms of DBS action in AD [210]. In addition to small sample sizes, a serious limitation of studies conducted thus far is the continued use by participants of acetylcholinesterase inhibitors while receiving DBS therapy. This is confounding because DBS may act, in part, by stimulating the release of acetylcholine [218,219]. DBS is also an invasive procedure with multiple risks, such as bleeding, infection, and other side effects associated with the surgical procedure and the risk of personality changes and depression [220–222].

We have now covered the pharmacologic and invasive brain treatments in use or development for AD (summarized in Table 2). In the following sections, we will explore the potential for lifestyle changes to affect cognitive function and their potential to modify AD risk and rate of progression.

Table 2. Experimental treatment approaches for Alzheimer's disease.

Category of Method	Specific Intervention	FDA Approved	Clinical Utility or Value	Side Effects	Potentially Disease-Modifying	References
Anti-amyloid	Aducanumab, lecanemab	Accelerated approval	Limited	Infusion reaction, headache, ARIA, brain swelling, brain hemorrhage	Yes	[9–13]
Treat CNS insulin resistance	Insulin, metformin	No	Unproven	Hypoglycemia with insulin, GI effects of metformin	Yes	[108–116]
Stem cells	ESCs, MSCs, iPSCs	No	Unproven	Risks from immunosuppression, tumor formation with ESCs, infection, bleeding	Yes	[161,183,186–188,192–194]
Deep brain stimulation	Delivery of electrical pulses to a defined area of the brain	No	No	Requires implant of the electrode, headache, infection, brain hemorrhage	No	[197–206,220–222]

CNS: the central nervous system; GI: gastrointestinal; ESCs: embryonic stem cells; MSCs: mesenchymal stem cells; iPSCs: induced pluripotent stem cells; ARIA: amyloid-related imaging abnormalities.

7. Diet as a Preventative Measure

Measures to delay or prevent the onset of AD have been pursued and tested since the disorder was identified in 1906. Some evidence supports lifestyle adjustments and changes in diet and physical activity level as a viable approach to reducing AD susceptibility [223–225]. Epidemiological studies suggest that limiting calories or carbohydrates, raising the intake of certain vitamins and antioxidants, or adjusting the ratio of saturated to unsaturated fats may lower AD risk. However, the true impact of these dietary adjustments is still unresolved, with conflicting data and failure to replicate the preclinical data obtained in animal models [226,227].

7.1. Overall Dietary Pattern

The Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH) diet are considered heart-healthy and good for the brain [228,229]. The Mediterranean diet includes vegetables, nuts, seeds, legumes, seafood, olive oil, moderate consumption of dairy and wine, and low meat consumption. The diet contains high omega-3, B vitamins, vitamin D, folic acid, and other necessary nutrients. Low red meat consumption may lead to iron

deficiency [230]. The DASH diet is similar but more restrictive in salt, alcohol, and chocolate consumption but allows for more meat. The MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) combines the DASH and Mediterranean diets [231].

Numerous studies show an association between these diets and a lower incidence of AD or MCI with the preservation of cognitive function [232–237]. For example, post-mortem examination of the brain in persons in the Rush Memory and Aging Project, a long-term study of older adults without dementia at enrollment that includes annual dietary assessments, found that those following the MIND or Mediterranean dietary pattern more rigorously over nearly ten years showed less AD brain pathology and lower amyloid load [238].

Adherence to these plant-forward diets may be especially beneficial when the diet is followed in early adulthood or middle age before cognitive symptoms manifest [239–241]. However, some studies show no effect of diet in middle age on dementia and/or AD risk later in life [242].

The DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE), an observational study conducted in Germany, assessed older persons at high risk for AD with extensive neuropsychological testing and a detailed food frequency questionnaire and found that the Mediterranean diet and the MIND diet were associated with better memory and language [243]. Ballarini et al. also used DELCODE data to show a positive association between adherence to a Mediterranean diet and memory performance, and they related these to structural brain images and CSF biomarkers to perform modeling that indicates that this diet may works by preserving brain volume and impacting CSF amyloid and tau biomarkers [244]. Finally, Gregory et al. used data from the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS) to evaluate the effect of the Mediterranean diet on persons living within and outside the Mediterranean region determined to be at risk for AD. They found that following the diet more stringently was associated with better scores on the Four Mountains test, a test of spatial memory, particularly in female participants and within the Mediterranean region [245].

A recent literature review showed an association between lower sodium intake and better cognitive function, but with a modest effect that needs further study and control for confounding variables [246]. In addition, the reports that were evaluated were too heterogeneous for a meta-analysis.

Conversely, a Western type of diet of highly processed foods rich in saturated fats, refined carbohydrates, and salt has been associated with more rapid cognitive decline [247–251]. In addition, the Western diet contributes to obesity and insulin resistance and promotes an inflammatory state, all of which may predispose to the development of AD [252–254]. Advanced glycation end products (AGEs) formed in the disrupted metabolic environment of poor glucose control may be one important link between Western diet-induced obesity and cognitive decline [255]. AGEs are present in the tau tangles and amyloid plaques in the AD brain and induce oxidative stress and immune activation in the CNS [256–258].

It is essential to recognize that studies involving many foods are especially problematic as different foods within each diet may have a different effect on dementia risk [259].

7.2. Calorie Restriction

Calorie restriction has been found to protect against cognitive decline, possibly because it results in decreased systemic inflammation and oxidative stress [260–262]. In animal models, calorie restriction is associated with increased longevity, delayed senescence, and neuroprotection [263–265]. In addition, it has been shown in humans that restricting calories can improve glucose and lipid metabolism, reduce blood pressure, and decrease biomarkers of inflammation, all of which may support brain health. However, the effects of AD in humans are not proven [266–269].

7.3. Vitamin D

Epidemiological observations have uncovered a neurosteroid hormone vitamin D deficiency in many patients with AD and impaired cognitive function [270,271]. The vitamin D receptor is present in the human brain in neuronal and glial cells, where its activation by vitamin D is important in brain development and function [272–274]. A prospective study of 1658 elderly persons without dementia followed for an average of 5.6 years found a substantial increase in the risk of developing AD and all-cause dementia with vitamin D deficiency [275]. Meng et al. performed a two-sample randomization analysis looking at associations between vitamins and AD and found low vitamin D levels causally associated with increased AD risk [276]. Multiple meta-analyses have also shown a link between low circulating levels of vitamin D and AD [277–279]. The association is particularly strong when vitamin D deficiency is profound, with levels below 10 ng/mL [280,281]. However, other studies have failed to find a clear benefit in AD risk reduction with vitamin D supplementation in older adults [282–284].

Several neuron-preserving effects of vitamin D have been shown in animal models, and these support the importance of achieving sufficient serum levels of this compound. Among these neuroprotective properties is the ability of vitamin D to reduce inflammation and oxidative stress and to regulate calcium homeostasis [285–288].

In murine models, vitamin D reduces Aβ plaque build-up and promotes degradation [289–291]. Furthermore, the prevention of Aβ accumulation is attributed to augmented expression levels of APP and BACE1 by vitamin D [292].

7.4. The B Vitamins: B6 (Pyridoxine), Folate (B9), B12 (Cobalamin)

The roles of folate, vitamin B6, and vitamin B12 have been scrutinized because these vitamins have links to CNS function, and deficiencies are common in older persons [293,294]. A de Wilde et al. meta-analysis found that vitamin B12 and folate availability in the brain and circulation is lower in AD patients than in controls [295].

These vitamins participate in the linked cycles of folate and methionine metabolic pathways with the consumption of homocysteine, a key step accomplished by cyclative methylation of homocysteine to methionine. In insufficient B6, B12 and/or folate, hyperhomocysteinemia occurs and may be associated with cognitive impairment in later life [296–300]. However, the efficacy of these vitamins in reducing elevated homocysteine and preventing or slowing AD progression is unclear. Results of multiple studies of AD and MCI patients supplemented with these B vitamins have been conflicting. Many have failed to demonstrate slowing of cognitive decline [301,302].

On the other hand, a randomized study of 240 MCI patients found that folate and vitamin B12 in combination reduced inflammatory markers and improved cognition after six months [303]. Another recent study of 120 AD patients, half randomized to receive B12, and folate and the other half randomized to receive a placebo over six months, found that supplementation with these vitamins improved cognitive performance [304]. However, these patients were not on a folate-fortified diet before enrollment, which may have allowed the needed contrast with newly added folate.

Sufficient levels of vitamin B6 are essential for CNS function because this vitamin is a coenzyme in numerous reactions involving amino acid production, a required cofactor for the synthesis of dopamine, and it plays a crucial role in the synthesis of γ-aminobutyric acid (GABA), the main CNS inhibitory neurotransmitter [305]. Vitamin B6 may thus counteract nerve damage by limiting excitotoxicity [306]. In addition, folate is essential in modulating homocysteine levels, and it reduces oxidative stress, but its ability to lower inflammatory cytokine levels is in dispute [307,308].

Vitamin B12 plays a role in the cellular metabolism of carbohydrates, proteins and lipids, and its deficiency has neurologic consequences that can include cognitive decline [309–311]. In addition, vitamin B12 has anti-oxidant properties postulated to be neuroprotective [312]. Politis et al. found an association between low serum B12 and higher peripheral blood mononuclear cell production of Il-6, an inflammatory cytokine [313].

Song et al. showed that high homocysteine and low B12 levels were linked to temporal lobe atrophy in AD subjects [314]. A case-control study from Shrestha and colleagues with a sample size of 90 found a significant association between vitamin B12 deficiency and AD after adjusting for age [315].

More research is required to determine whether the association between the B vitamins and cognition indicates a path to treatment. The studies thus far point to the importance of maintaining the level of these vitamins in the normal range in older persons and to the cooperative nature of their activity.

7.5. Antioxidants

An imbalance between the production of reactive oxygen species and the ability of the brain to generate an anti-oxidant defence is widely thought to contribute to AD pathophysiology [316,317]. In addition, oxidative stress can damage neurons through disruption of the mitochondrial respiratory chain, protein and lipid peroxidation, and induction of neuronal apoptosis [318,319]. Based on these accumulated findings, anti-oxidative stress therapy could be beneficial in preserving neurons in AD. However, this data is mixed, and the issue is unresolved [320,321]. Beydoun et al. used the Third National Health and Nutrition Examination Survey (NHANES III) to examine interactions between serum nutritional biomarkers of antioxidant status in relation to AD in a selection of adults over 45. Although incident all-cause dementia was inversely associated with serum lutein + zeaxanthin and β-cryptoxanthin levels, no significance was found with AD-specific dementia [322]. However, they did find an antagonistic interaction between vitamin E and lycopene in relation to AD incidence. Another study utilized The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study to examine diet and cognition longitudinally and found a link between vitamin E consumption and greater verbal memory performance [323]. In a multi-centre clinical trial that randomly assigned 78 AD subjects to 16 weeks of treatment with either vitamin E + vitamin C + α-lipoic acid or Coenzyme Q or placebo, results were not encouraging. Antioxidants did not improve CSF amyloid or tau biomarkers, and the cognitive decline accelerated in the vitamin E + vitamin C + α-lipoic acid group.

8. Mental and Physical Activity

8.1. Exercise and Physical Activity

Multiple studies have repeatedly demonstrated that increased physical and mental activity is associated with a decreased risk of AD [324].

Exercise and diet may forestall AD symptoms [225,325–327]. Exercise can attenuate some known AD risk factors, including hypertension, hyperglycemia, and obesity [328,329]. Exercise can also improve cerebral blood flow [330]. It is estimated that non-demented persons who engage in regular physical activity reduce their risk of cognitive decline by more than 25% compared to sedentary persons, and effects exceed 30% when the activity level is high [331,332]. In addition, physical activity may help to preserve executive function in persons with dementia [333]. Walking alone was recently shown in a pilot study to improve cognitive performance in a small sample of MCI patients [334].

Exercise can prevent or delay the loss of brain volume and improve the functional connectivity of brain regions [335,336]. In addition, exercise may reduce oxidative stress. However, studies in humans have not found exercise to consistently improve levels of BDNF, a neurotropic factor important in maintaining synaptic function and neuronal plasticity [337–341].

People over age 65 are often increasingly sedentary [342]. Numerous studies have indicated that certain measures of gait can predict future cognitive and functional decline [343]. Furthermore, cross-sectional, and longitudinal studies have associated gait abnormalities with imaging, biofluid, and genetic markers of AD across all stages [343]. Exercise for older persons may be difficult due to functional limitations, painful joints, fear of falling and other issues [344]. Considering these issues is important in removing barriers to optimize participation in physical activity by older adults [345].

8.2. Mental Exercise

Researchers have also questioned whether cognition-focused interventions can lower the risk of AD or at least help to maintain cognitive reserve [346,347]. Higher education level, which may covary with regular mental exercise, has also been associated with a reduced risk of dementia [348]. Many physicians recommend that individuals of all ages perform word searches, sudoku, crossword puzzles, and other word-matching games. In addition, computer programs and virtual reality experiences are designed to challenge the brain [349,350]. The benefits of mental exercise to the AD brain are uncertain, but cognitive stimulation may be helpful, particularly in MCI patients [351–354]. Studies are underway or planning to evaluate the combination of mental and physical challenges using virtual reality in persons with mild AD [355,356].

In summary, lifestyle adjustments may have value in delaying AD onset (Table 3). For example, maintaining overall good health by incorporating physical and mental activity combined with a nutritious diet can provide the brain with a nourishing and sustaining environment but is limited in how much it can alter the course of AD.

Table 3. Lifestyle modifications for prevention and treatment of Alzheimer's disease.

Lifestyle Change	Specific Intervention	Clinical Utility or Value	Side Effects	Potentially Disease-Modifying	References
Alter gut microbiome	Consumption of probiotics and prebiotics. Fecal transplant.	Unproven	Gas, bloating, constipation, nausea, allergic reactions.	Yes	[130,138,139]
Change overall diet	Mediterranean diet, DASH diet, MIND diet	It may preserve memory and lower dementia risk	A Mediterranean diet low in iron	Yes	[230–237,239–241]
Calorie restriction	Intermittent fasting	Unproven	Hunger, nutritional deficiencies	Maybe	[260–262,266–269]
Physical activity, exercise	Structured activity program, non-sedentary lifestyle	May preserve executive function	Risks from falls	Yes	[325–327,331–333,344]
Mental	Cognitive challenges, puzzles, memory tasks, matching tasks, and spatial recognition tasks.	Unproven	None	Maybe	[346–348]

CNS: the central nervous system; GI: gastrointestinal; ESCs: embryonic stem cells; MSCs: mesenchymal stem cells; iPSCs: induced pluripotent stem cells; ARIA: amyloid-related imaging abnormalities; DASH: Dietary Approach to Stop Hypertension; MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay.

9. The Future

Unraveling the intricacies of AD etiopathogenesis is an arduous but not insurmountable task that has been approached in multiple ways, as illustrated in this review. However, to find the breakthrough that is so urgently needed, the evidence supports a move away from simplistic attempts to lower amyloid or tau production and perhaps to move on to a more complex strategy that preserves neuron longevity, modulates autophagy, and maintains mitochondrial integrity and bioenergetic functions [357,358].

Valuable clues can be garnered from families with inherited forms of AD. There are ways that the human genetic makeup can forestall AD symptoms in the face of familial AD. Persons carrying a mutation in the presenilin one gene that causes a substitution of the 280 Glutamic acids by Alanine (*E280A*) in the encoded protein exhibit an autosomal dominant form of early onset AD with complete penetrance by the time the patients reach their early seventies in age [359,360]. In those harboring this mutation, the onset of dementia is delayed for those who also carry specific apoE alleles, including the apoe2 allele and the apoE3 Christchurch mutation [361,362]. Lopera et al. showed that heterozygosity for a rare variant (H3447R) in the gene for reelin, an extracellular matrix protein and a ligand that binds apoE, also delays AD symptoms in a person carrying the *E280A* mutation [363]. Insights such as these give hope that a mechanical model of AD can be built, and with

a better understanding, real headway can be made. In addition to natural mutations in humans, we can also learn from AD brain models constructed in cell culture that may mimic many properties of the human brain [364].

10. Conclusions

The incidence of AD has steadily increased in the past few decades, affecting up to 50% of people 85 years of age and older. Current therapies include acetylcholinesterase inhibitors, N-methyl d-aspartate receptor antagonists, and, more recently, anti-amyloid antibodies. However, the effectiveness of these therapeutic strategies is limited, none are curative, and they are variably palliative. This paper analyzes more novel potential strategies beyond the attenuation of amyloid and tau accumulation. Novel anti-neuroinflammatory drugs and repurposing of currently available anti-inflammatory drugs, such as TNF-α inhibitors, are just some strategies discussed in this paper. The potential effects on the brain of systemic processes involving glucose metabolisms and energy production, such as T2DM and metabolic syndrome, are explored, and the possible role of the microbiome-gut-brain axis in the pathogenesis of AD is covered. The effect of deficiencies in organic compounds and the role of modifiable factors like diet and exercise in the progression of cognitive decline are considered. Strategies aimed at safely replacing affected neurons via stem cells and effectively delivering these therapeutics via lipophilic and biocompatible nanoparticles are also discussed; Although preclinical animal work involving stem cell transplantation shows promise, clinical testing is the next step. The pressing need for effective medical treatment requires further research and a better understanding of the fundamental mechanisms involved in the AD process. Extensive effort and determination are essential in the search for a significant breakthrough.

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Review

Informal Caregiving and Alzheimer's Disease: The Psychological Effect

Emily Hellis [1] and Elizabeta B. Mukaetova-Ladinska [1,2,*]

[1] School of Psychology and Visual Science, University of Leicester, Leicester LE1 7RH, UK
[2] The Evington Centre, Leicester General Hospital, Gwendoline Road, Leicester LE5 4QF, UK
* Correspondence: eml12@le.ac.uk

Abstract: *Background and Objectives*: People with Alzheimer's disease and dementia in general benefit from home-based care as demonstrated via their better quality of life, increased lifespan, and delayed disease progression. Since currently nearly half of the dementia care is being provided by informal and unpaid caregiving, the health, wellbeing and quality of life of informal dementia caregivers is extremely important. *Materials and Methods*: We used a systematic review process with searches based upon the six elements from the "Quality of Life Scale for Informal Carers of Older Adults" with additional items on traditional and non-traditional caregiving ideologies, as well as caregivers' experiences. *Results*: We identified 19 studies with primary data. Informal caregivers of older adults with Alzheimer's Disease experience significant emotional strain, documented through increased levels of anxiety and depression, as well as increased caregiver burden and poorer quality of life, primarily due to caregiving ideologies, financial strain and a lack of support. *Conclusions*: Our findings suggest that caregiving should be a normative component of adult education to better prepare individuals with the mental and physical skills required for undertaking informal caregiving. They should also help inform policy makers to develop novel programs and services to both assist and reduce informal caregivers' strain, whilst considering their different social and cultural contexts.

Keywords: Alzheimer's disease; depression; anxiety; caregiver burden; traditional ideologies

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1. Introduction

Living in an ageing population has many benefits, both economically and socially, and yet it poses concerns for the healthcare system. In 2019, life expectancy was 79.4 years for males and 83.1 years for females. Due to the COVID-19 pandemic these estimates fell by 1.3 and 0.9 years, respectively [1]. Improvements in healthcare and the management of chronic conditions mean that people are living longer. However, as people age, they are often affected by one of more age-related diseases. This multi-morbidity means that older persons face a range of unique challenges leading to an increased need for care [2]. In addition to this, there is expected to be a 23.9% increase in people aged over 65 by 2039 [3]. With this comes the higher need for caregiving. It is, thus, appropriate to consider the impact caring for older persons has on the caregivers themselves and whether appropriate measures are in place to preserve their own health, wellbeing and quality of life (QoL).

Populations, projections and polling from Carers UK have estimated there to be ~9 million adults in the UK who are caregivers [4]. This does not take into consideration formal caregiving through the public and private sector. In 2016 the Office for Budget Responsibility investigated fiscal sustainability and public health spending, concluding that with the increasing health demands of our ageing population, the UK budget for healthcare would need a £13.3 billion increase within 5 years [5]. Demographic cost pressures in the years to come will push public spending ever upwards [6], thus finding a sustainable solution to the health and social care crisis remains a key challenge for generations to come. A greater reliance on informal caregiving may be considered as a potential source of relief

for these underfunded systems. However, this increased demand for care must not become detrimental to informal caregiver's wellbeing.

An informal caregiver may be identified as someone who provides some form of unpaid, ongoing assistance to a person with a chronic illness, age-related disease, or disability. This assistance is primarily with activities of daily living (ADLs): toileting, bathing, feeding, dressing and mobility assistance, and instrumental activities of daily living (IADls), such as financial assistance, transportation, shopping, cooking, cleaning and medication management [7]. Unsurprisingly, informal caregivers have been identified as key supportive figures in assisting older persons' self-management of age-related diseases [8].

Currently, some of the most prevalent age-related diseases are the Dementias. This refers to a group of diseases which lead to progressive cognitive impairments and interfere with ADLs [9]. The most common type of Dementia is Alzheimer's Disease (AD), a 'neurodegenerative disease with insidious onset and progressive impairment of behavioural and cognitive functions including memory, comprehension, language, attention, reasoning and judgement' [10], accompanied with disturbed perception and thought content, mood disorders and changes in behavior (i.e., aggression and wandering). Importantly, these behavioural and psychological symptoms are often associated with high levels of distress and anxiety for both the person with AD and their caregivers [11]. Therefore, it is not surprising that AD represents one of the main challenges for care providers of the elderly.

With the complexity of AD comes a high level of treatment and care which is extremely costly. Estimates per individual are set at around £32,350 per year with a total cost of £24.2 billion per year in the UK, £10.1 billion of which is attributable to informal caregiving and unpaid care [12]. With both medical professionals and scientists advocating for home-based care due to reported benefits for the individual with AD (increased lifespan and delayed disease progression [13]), the need to consider the informal caregiver's QoL and wellbeing is extremely important, especially when one considers the breadth of research documenting links between informal caregiving and mental ill health [7,14], as well as the increased need for informal caregiving.

The Quality of Life Scale for Informal Carers of Older Adults was developed by Maltby et al. [15] based upon items from the Adult Carers Quality of Life Questionnaire [16]. The additional items developed in this scale considered that currents themes within general literature on caregiving of older adults came from traditional and non-traditional caregiving ideologies, as well as caregivers' experiences. This was represented via six elements, five of which were based on Elwick's questionnaire as seen in Figure 1 below.

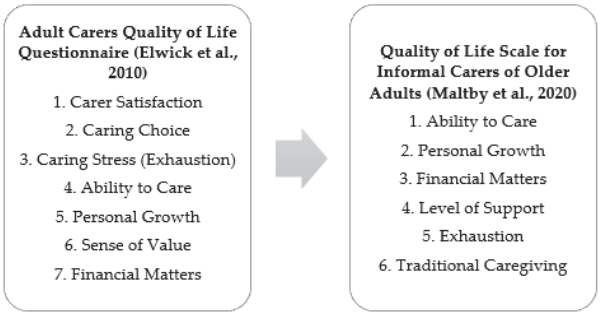

Figure 1. The development of the elements from the Quality of Life Scale for Informal Carers of Older Adults from the Adult Carers Quality of Life Questionnaire [15,16].

The sixth new element 'traditional caregiving role' reflects a positive attribute which added to the caregivers' QoL through feeling rewarded by their caregiving role and the relationship with those cared for. Thus, considering this additional element and the further five elements, it seems appropriate to consider these components as potential 'risk factors' affecting the QoL, health and wellbeing of informal caregivers of older in-

dividuals and those with AD. More specifically, due to their associations with mental ill health, these elements may be considered risk factors for Anxiety and Depression in these individuals [7,11,14].

In this review, we explore the association between Anxiety and Depression and the informal caregiving for people with AD as well as caregivers' QoL, using the elements set out in the Quality of Life Scale for Informal Carers of Older Adults [15] as a basis. Findings from this study will inform future research within this area with the discussion of current and potential support for informal caregivers of individuals with AD.

2. Materials and Methods

A systematic study selection process was used to assess and interpret current research within this domain. During the planning stage search terms were determined based upon the Quality of Life Scale for Informal Carers of Older Adults [15] (Table 1). Systematic literature searches with no limit to study design and published until 01.10.2022 were carried out across several databases including Google Scholar, PubMed, PsycINFO and ResearchGate (Figure 2).

Table 1. Search terms.

Participant Identification Terms	Caregiving Terms	Wellbeing Terms	Further Terms
Dementia	Caregiver	Stress	Ability to Care
Alzheimer's	Carer	Depression	Finance
Alzheimer's Disease	Informal Caregiver	Anxiety	Money
Elderly	Caregiving	Quality of Life	Personal Growth
Old Age	Support	Depressive Symptoms	Positive Experience
Older Age		Anxious Symptoms	Negative Experience
Cognitive Decline		Mental Health	Traditional Views
		Wellbeing	Non-traditional views
			Caregiving Views
			Ideologies

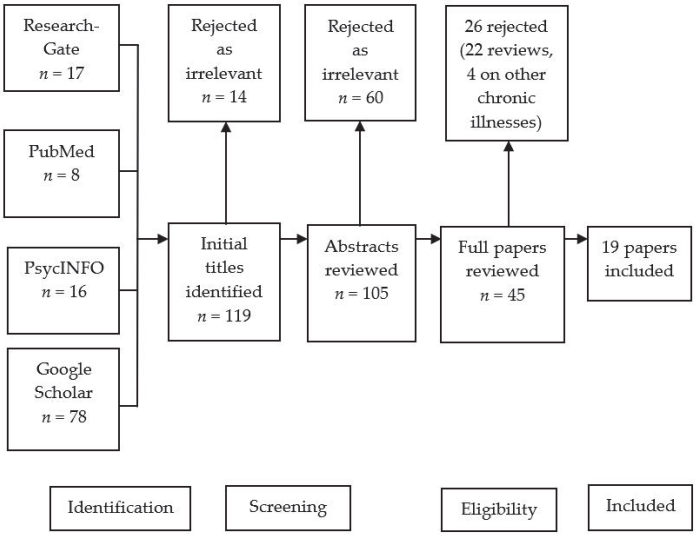

Figure 2. Systematic search process: PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram of article eligibility.

3. Results

Following on from Maltby et al.'s research [15], in order to better understand the psychological effects of informal caregiving for persons with AD, we explored further each element of the Quality of Life Scale for Carers of Older Adults. The results of these elements are summarised below (Table 2).

3.1. Traditional Caregiving Ideologies

A traditional caregiving ideology is one in which the needs of the person cared for are prioritised [17–21]. Caregiving is seen as an expectation, natural and virtuous, and often linked to high moral standards. A widely documented traditional ideology is Confucianism, a belief originating from Chinese culture which teaches individuals that they have a caregiving role within their family, with a focus on loyalty, interdependence and the maintenance of family harmony [22]. People are taught from a young age to respect their elders and that children are expected to care for older family members physically, financially and emotionally (filial responsibility) [17]. This has been found to hold true in more westernised society with later generation Chinese-American informal caregivers [17]. Due to this filial responsibility caregivers often have to make personal sacrifices to meet the individual caregiving needs of a person with AD. However, most caregivers report that they are willing to put the AD individuals' needs above their own [23]. Furthermore, these caregivers often felt more positive and had better health due to the fact they were fulfilling their filial responsibility.

Lower levels of depression were found in informal caregivers with traditional ideologies, as well as great self-efficacy and the ability to respond more appropriately to some of the challenging behaviours common in AD [24]. Similar notions were previously reported with caregivers appearing to have felt psychological rewards through caregiving [25,26], by fulfilling filial responsibilities they found it easier to cope with stressors associated with informal caregiving of a person with AD. Informal caregivers who cared for a spouse with AD held traditional ideologies which came from their marital vows 'in sickness and in health' [27]. This was often associated with positive attitudes and lower levels of depression.

Opposing research has described a varying perspective, linking traditional caregiving ideologies to the informal caregivers feeling that they 'have no choice' in carrying out caregiving responsibilities [28]. Informal caregivers have reported making sacrifices in their personal and professional lives, such as missing social events and cutting down paid work [29]. These have all been found to be factors involved in worsening of their levels of anxiety and depression, as well as a decreased QoL [30].

3.2. Non-Traditional Caregiving Ideologies (Exhaustion Factors)

Non-traditional caregiving ideologies differ in that the informal caregiving is unexpected and often reflects a deviation from the caregiver's life plan with no perceived reward [31]. Caregivers with non-traditional ideologies have reported feelings of having their lives temporarily stopped, they look at caregiving as an 'obligation' and mention 'looking forward' to when it was complete [27]. These non-traditional ideologies are often associated with higher caregiver burden, defined as 'the level of multifaceted strain perceived by the caregiver from caring for a family member and/or loved one over time' [30]. Caregiver burden was also associated with negative consequences, including a negative effect on the care provided, a decrease in QoL for the caregiver and the individual with AD, as well as deterioration in both physical and mental health. Higher levels of stress, anxiety and depression were also witnessed and have been directly related to the limited time informal caregivers give to themselves due to personal and professional sacrifices [32–35].

Table 2. Summary of included articles.

Authors	Method/Data Collection	Subjects	Country Setting	Findings
Miyawaki (2020) [17]	Structured interviews	*n* = 40 caregivers *Description*: 2nd, 2.5 and 3rd generation female Chinese-American caregivers caring after older relatives, some with dementia (NB. dementia type and number of carers for people with dementia not specified)	USA (Seattle and Houston)	Later generation caregivers had higher acculturation Filial responsibility remained high across generations Traditional caregiving was seen across all generations If the interviewed caregivers needed care in the future, their views upon this differed. Thus, caregivers from Seattle preferred the concept of longer-term care facilities whilst caregivers from Houston preferred being cared for by their children. This research emphasised the importance of caregiving attitudes and preferences being generationally and ethnically specific, and the importance of our understanding of this in a geographical context.
Sterritt and Pokorny (1998) [18]	Semi-structured interviews	*n* = 9 caregivers, with 3–8 years in caregiving; male and female African American Caregiver's of relatives with Alzheimer's Disease	South-Eastern USA	Found that caregiving is seen as a traditional family value Caregiving is thought of as an act of love Social support can be considered a mediator of caregiving burden Caregiving is considered to be a female role
Gray et al. (2009) [20]	Structured Interviews	*n* = 236 white, Hispanic, and Chinese-American women caring for relatives with either a diagnosis of Alzheimer's Disease (or other dementia)	USA (San Francisco Bay area)	Attitudes and beliefs regarding AD/Dementia seen in Hispanic and Chinese caregivers may delay help-seeking activities for people with AD/Dementia. Hispanic and Chinese subjects were more likely to believe it to be a normal part of ageing diagnosable via a blood test than their white counterparts. This was attributed to their traditional and cultural beliefs.
Jones et al. (2011) [23]	Scale development	Questionnaires completed by 593 individuals. Filial concepts from scales using African-, Asian-, Euro-, Latino-, and Native American subjects were examined.	USA (Southern California and Native Americans)	Filial values predicted caregiving activities and caregiver health Three filial concepts were identified: Responsibility, Respect, and Care. These reflect attitudes and beliefs inherent in the complex multidimensional construct of filial values. A positive relationship between adult children professed filial values and their actual filial conduct was found. There was a stronger association between responsibility and care in males than females. Asians and African Americans displayed more filial responsibility.

Table 2. *Cont.*

Authors	Method/Data Collection	Subjects	Country Setting	Findings
Holland et al. (2010) [24]	Interventional study	*n* = 47 Chinese American dementia caregivers	USA (San Francisco Bay area)	Caregivers were found to report significant levels of distress, depressive symptoms, and also showed indications of resiliency—High levels of self-efficacy, positive caregiving experiences, and problem solving. Stronger beliefs in Asian values were associated with more normal cortisol patterns, less depressive symptoms, and greater self-efficacy, highlighting the salience of culture in shaping the caregiving experience of Chinese Americans.
Zhan (2004) [25]	Interviews	*n* = 4 Chinese-American caregivers of family members with AD	USA	There were ethnocultural and structural barriers facing the subjects; stigmatism of AD in the Chinese community, lack of knowledge about AD, a lack of culturally and linguistically appropriate AD services. There were negative impacts on mental and physical health. Involvement in caregiving was associated with health in Chinese-American women.
Jones et al. (2001) [26]	Questionnaire based study	*n* = 50 Asian-American Women caregivers for aging parents (29 Chinese-American; 21 Filipino-American). All participants born outside of the USA.	USA	Caregiving role integration was positively associated with all three perceived health measures in the Filipino group, but not in the Chinese group. Caregiving role satisfaction was consistently high in both groups. Caregiving role satisfaction and psychological well-being were significantly correlated for the combined group and for the Filipino caregivers. Total caregiving role stress was significantly correlated with overall health and current health only in the combined group. Support that helps to decrease role stress and to increase role satisfaction may be more effective than efforts to decrease the extent of role involvement.
Lawrence et al. (2008) [27]	In-depth interviews	*n* = 32 male and female caregivers of people with dementia (PwD)	UK (four socially and ethnically diverse south London boroughs: Lambeth, Southwark, Lewisham and Croydon)	Caregivers were identified as holding "traditional" or "non-traditional" caregiving ideologies. Within traditional ideologies caregiving was seen as a natural and honourable concept, something that is expected to happen. The majority of the South Asian, half of the Black Caribbean and a minority of the White British participants were found to possess a traditional ideology.
van de Ree et al. (2018) [29]	Structured Interviews	*n* = 123 informal caregivers of older adults (*n* = 22, 17.9%. had dementia; subtype not specified)	Netherlands (North Brabant)	Partners of the older adults provided more informal care than any other relative relationship. Female caregivers were 3-fold more likely to experiences relational problems due to caregiving. Majority of caregivers reported physical, mental and relational strain due to the intense nature of caregiving, particularly in the first six months.

Table 2. *Cont.*

Authors	Method/Data Collection	Subjects	Country Setting	Findings
Kang et al. (2016) [35]	Questionnaire based study	*n* = 87 caregivers of PwD (subtype unspecified)	Korea (Busan)	Caregiver burden, knowledge of dementia and levels of education predicted the quality of care given. Caregivers' decreased QoLcame from caregiving burdens. Interventional and educational programmes aimed at reducing these burdens and increasing knowledge were deemed necessary to improve QoL and the quality of care given.
Shepherd-Banigan et al. (2020) [36]	Cross-sectional approach	*n* = 1509 familial caregivers of PwD within the Veteran Affairs (VA) programme (PwD = 44.9%)	USA (Nationwide)	Caregivers who care for veterans with trauma-based co-morbidities as well as cognitive decline reported high levels of depression, loneliness and financial strain even though they were part of the enhanced support system of the VA programme. Authors suggest a planned expansion of the programme to address these issues.
Harding et al. (2015) [37]	Secondary analysis	Data from 4 UK studies of informal caregivers of people with cancer (*n* = 105), dementia (*n* = 131; dementia subtype not specified) and acquired brain injury (*n* = 215)	UK (Sites not specified)	Caregivers' burden was highest in those caring for acquired brain injury (ABI) and was followed by dementia caregivers' burden. Total, subscale, and most individual elements of caregiver subjective burden differ between cancer, dementia, and ABI caregivers. However, concepts of duty, responsibility, and perception of financial situation were similar between the 3 groups. These should be considered when designing future intervention strategies to reduce caregivers' burden in these groups.
Ku et al. (2019) [38]	Longitudinal study using interviews	*n* = 231 caregivers of PwD in a dementia clinic in Southern Taiwan	Taiwan (Tainan)	Behavioural disturbance [measured by the Neuropsychiatric Inventory (NPI)] showed no impact on the cost of care but was a significant predictor for caregiver burden. Caregiver burden was also associated with a functional decline in ADLs. Financial stability was associated with lower caregiver burden. These findings denote that financial assistance for low-income caregivers and educational training for behavioural disturbances are required to reduce caregiver burden.
Kang (2021) [39]	Secondary analysis	*n* = 956 unpaid family caregivers (National Long Term Care Survey, USA)	USA	The caregivers' perceived burden was associated with financial strain, with variations due to familial relationships. The identification of these correlates can help with the development of effective interventions for caregivers' burden.
Semiatin and O'Connor (2012) [40]	Interviews	*n* = 57 family caregivers of people with Alzheimer's Disease	USA (Boston and Bedford)	Self-efficacy accounted for a significant percentage of the variance in positive aspects of caregiving after controlling for other factors commonly associated with positive aspects of caregiving including caregiver demographics, care recipient neuropsychiatric symptoms, and caregiver depression. High self-efficacy relates to caregivers' perception of positive aspects of the caregiving experience.
Pendergrass et al. (2019) [41]	Cross-sectional study	*n* = 734 informal caregivers of PwD and other chronic illnesses	Germany (Bavaria)	There was an association between a higher experience of benefits, care duration, increase in depressive symptoms, increased physical grievances and a higher level of burden.

Table 2. *Cont.*

Authors	Method/Data Collection	Subjects	Country Setting	Findings
Horrell et al. (2015) [42]	Qualitative	n = 60 informal caregivers	New Zealand	The authors studied how emotions underpin informal caregiving. A caregiver's choice of how they lived their lives was often influenced by their emotional attachment to the cared for, with higher attachment being associated with a decrease in wellbeing. The selflessness shown by the caregivers emphasised caregiving's relational nature and challenged the prevalent perspective of caregiver burden documented previously.
Abreu et al. (2018) [43]	Cross-sectional study	n = 54 informal caregivers of PwD (n = 28 Alzheimer's Disease, n = 12 vascular dementia, n = 9 mixed dementia, n = 2 Dementia with Lewy Bodies, n = 3 frontotemporal lobe dementia)	Portugal (Porto district)	Psychological distress was documented in half of the caregivers. Somatization, obsessive–compulsion, interpersonal sensitivity, anxiety, and paranoid ideation were seen in a large proportion of caregivers. The authors suggested placing focus on the alleviation of caregivers through education and additional support to help decrease their distress and burden
Laparidou et al. (2019) [44]	Qualitative	n = 35, 18 caregivers, 17 healthcare professionals	UK (Lincolnshire)	Primary stressors on caregivers came from lack of knowledge regarding Dementias and the challenge of diagnosis, often due to lack of understanding by healthcare-professionals. Secondary stressors were due the need for support and communication issues with healthcare professionals. The authors suggest that these stressors may be effecting the caregivers' wellbeing r and may lead to an unnecessary move to institutionalised care for the care-recipient.

These non-traditional ideologies are reflected across families, with relatives of informal caregivers often refusing to provide support [27]. Feelings of guilt among relatives of individuals with AD and uncertainty were often aroused [30]. Underpinning these non-traditional ideologies is the sense that provision of care should not be down to the family/friends but to healthcare professionals, with informal caregivers often reporting immense pressure from family/friends to place the individual with AD into a residential care setting [45]. This often led to feelings of isolation and loneliness, effecting their mental wellbeing.

3.3. Financial Status

One must also consider the financial implications of caring for an older person, particularly the financial implications associated with AD, as mentioned previously. Many informal caregivers must forgo their full or part-time employment to dedicate their full time and energy towards caring for the older adult with AD. Full-time informal caregivers receive little to no support from the government—Currently, carer's allowance stands at just £67.60 per week [46]. When one considers the financial savings mentioned earlier, with informal caregiving relieving the NHS of around £152 billion in care per year [47], it is devastating to think that the informal caregivers are provided with far less than a minimum wage job per week in order to provide this care, especially with the current cost

of living crisis. Therefore, it comes as no surprise that the financial strains associated with informal caregiving have been linked to mental ill health and physical ill health within these informal caregivers [36].

Financial stress and mental ill health (i.e., increase in depressive symptoms and anxiety) are associated [48]. The experience of financial burden has been reported as five times greater when the caregiver has difficulties in balancing their caring role and their professional work [37,38]. The biggest financial strain is experienced among younger informal caregivers, who also have an increase in depressive and anxious symptoms compared to their older counterparts [39]. However, a tighter family bond was linked to both less financial strain and a decrease in depressive and anxious symptoms.

3.4. Personal Growth

Little research has commented on the positive effects of informal caregiving. It is, therefore, appropriate to consider the role of personal growth in informal caregiving as per the Quality of Life Scale for Informal Carers of Older Adults [15] in order to assess the need for future research focusing on this concept. From the limited research focused on positive effects of caregiving and its effect on personal growth, it appears that these positive caregiving experiences may act as a buffer for the effect of physical demands and psychological distress that informal caregiving has on a caregiver [40]. As well as this, the sense of personal growth, that comes from the positive experience of caregiving, has provided them with the ability to view their role as a caregiver with a more balanced perspective, leading to fewer reports of anxious and depressive symptoms [49]. In contrast to this, statistically significant correlations between depressive symptoms and a sense of greater benefits and personal growth from caregiving, a seemingly counterintuitive notion [41], have been found. However, this research concluded that personal growth is still able to occur from informal caregiving whilst experiencing depressive symptoms due to the demands of caregiving and the decline in health of a relative, spouse or a friend.

3.5. Ability to Care and Level of Support

An individual's ability to care and the levels of support they receive from relatives and friends are appropriate to consider together. These themes are interchangeable, as documented by the findings that one's ability to care is very much dependent on the level of support one is receiving [42,50,51]. As such, both one's ability to care and the level of support one receives have both been associated with mental well-being within informal caregiving [43,44].

Informal caregiver's confidence in themselves and their ability to care have a significant negative correlation with reported stress and poorer mental wellbeing [52]. This highlights the importance of considering support needs for informal caregivers in order to prevent additional health problems and prevent the practice of informal caregiving from occurring. Thus, it is not surprising that both anxiety and depression are reported to be common in informal caregivers of older adults with chronic care needs, i.e., cancer [32,34] or dementia [40,47,49], and seems to be closely linked to the level of support received and ability to care, much like that seen in individuals with non-traditional caregiving ideologies whose families did not offer support.

4. Discussion

The purpose of this research was to explore the six elements set out by the Quality of Life Scale for Informal Carers of Older Adults and their association with poor psychological wellbeing in informal caregivers of Older Adults with AD. As shown by the results, poor financial status, non-traditional caregiving ideologies and lack of support have been linked to higher levels or anxiety and depression in informal caregivers. This was also seen across some research relating to traditional caregiving ideologies; however, these were also seen as a protective factor towards mental ill-health, similar to that seen for personal growth [22,28]. Although it appears that these elements are related to anxiety and depression in informal

caregivers of those with AD, this requires further research to establish the true relationship between these concepts.

4.1. Traditional Caregiving Ideologies

The lack of research surrounding high levels anxiety in informal caregivers of those with AD who hold traditional caregiving ideologies may be due to the positive outlook associated with traditional caregiving ideologies and fulfilling filial responsibilities [53]. As a result, traditional caregiving ideologies should perhaps be viewed as a protective factor for anxiety in informal caregivers of persons with AD as opposed to a risk factor.

Interestingly, however, previous research did find an association between higher levels of depression and traditional caregiving ideologies, suggesting that the significant burden, stress and time associated with providing informal care, particularly to those with AD, leads to increased level of depression [30]. A possible explanation for this is the individual feeling of being 'trapped' by the traditional ideologies caregivers have been brought up with. Additionally, caregivers may perceive that it is their duty and responsibility to provide this care, particularly if looking after a parent, as they feel they must care for their parent as their parent had once cared for them. With this comes a cost to their own health and wellbeing.

When searching for previous literature surrounding traditional caregiving ideologies and anxiety/depression, there was little discussion about support available for informal caregivers. Nevertheless, the informal caregiver's traditional ideologies in respect to caregiving will need to be considered when conceptualizing ways in which novel programs and services can be developed to assist informal caregivers. This is important since due to informal caregivers' traditional ideologies, they may be less likely to accept support from outside their family network, as they believe it is their filial responsibility to provide care. In addition to this, they may be less likely to seek professional help when experiencing depressive symptoms, as they may feel guilty that they are feeling emotionally strained from their informal caregiving, something which is expected and required of them by their families.

In conjunction with previous research, these findings provide guidance for future research in both quantitative and qualitative manner. Firstly, it would be of interest to use the Quality of Life Scale for Informal Carers of Older Adults [15] using subjects who are informal caregivers and measure levels of anxiety and depression using a tool such as the Hospital Anxiety and Depression Scale (HADs) [54] to determine an association between traditional caregiving ideologies and anxiety/depression levels. Secondly, it would be important to investigate how traditional views vary across different cultures and ethnicities, and whether it is these variations in traditional caregiving ideologies and teachings that cause the documented differences in psychological wellbeing in terms of anxiety and depression.

4.2. Non-Traditional Caregiving Ideologies (Exhaustion Factors)

In the Quality of Life Scale for Informal Carers of Older Adults [15] the non-traditional caregiving ideologies are measured as part of the 'exhaustion' variable. This variable is thought to encompass non-traditional ideologies in that an individual's fears about the informal caring role and deviation from their life expectations loads on exhaustion factors. As seen in previous studies, non-traditional caregiving ideologies are based upon a deviation from one's life plan and are often associated with caregiver burden and exhaustion [27–30]. It is, thus, not surprising that there is an association between holding non-traditional caregiving ideologies and an increase in caregiver burden, increased levels of anxiety and depression, feelings of isolation and guilt. All of these are contributing to a decreased QoL for both the informal caregiver and, as a result, the person with AD that is being cared for.

When looking at the statements in Maltby et al.'s (2020) questionnaire which measures these exhaustion factors/non-traditional caregiving ideologies [15], it is clear to see why previous research has documented a link between this element and anxiety and depression

in informal caregivers. Some of the statements include 'I am mentally exhausted by caring' and 'I feel I have less choice about my future due to caring', both of which can easily be related to feelings of anxiety and depression. It seems appropriate to consider what assistance can be put in place to enable informal caregivers to provide the care needed whilst not deviating too far from their life plan, as well as what support they require to help relieve feelings of stress, anxiety and depression.

4.3. Financial Status

Understandably finance underpins informal caregiving, from the amount of money it saves the NHS each year, to the amount it costs informal caregivers themselves, both in giving up professional employment and the costs associated with caring for a person with AD. Financial status was found to be a constant throughout, in terms of being a factor associated with poorer mental wellbeing and QoL [37,47]. In particular, younger informal caregivers were often the ones that reported the higher levels of anxiety and depression, but this greater prevalence was reflected across various age groups of informal caregivers of those with AD, suggesting that financial hardship should be considered as a risk factor for anxiety and depression in the informal caregiving population [47]. Since the experience of financial strains and financial burden has been associated with difficulties balancing a formal caring role, measures need to be put in place to help support informal caregivers.

Since the combination of financial strain and poorer mental wellbeing are leading to a decreased QoL for these informal caregivers, firstly it seems appropriate to tackle the concept of financial aid. With caregiver's allowance standing at £67.60 per week [36], and many informal carers forced to reduce hours or quite paid employment, more needs to be done to financially enable this caring to take place, especially when one considers the amount of savings informal care provides our public healthcare service. Secondly, with the increased financial strain among younger caregivers and resulting increased levels of anxiety and depression, it seems appropriate to consider the development of educational programs around financial management, as well as aid in finding employment with more flexible working hours. In addition to this, it would be appropriate to educate companies on the difficulties associated with informal care, which may lead to changing policy to better accommodate informal caregivers in the working environment.

4.4. Personal Growth

In informal caregivers of those with AD, personal growth appears to have a positive impact on anxiety and depression levels. Although research is limited, this is an extremely positive concept for informal caregiving. However, with some research indicating that depressive symptoms may still occur in line with feelings of personal growth in caregiving it is important to consider this further. For example, it is of psychological interest to further investigate specific caregiving experiences that are related to personal growth and a sense of achievement (for example, the impact of respite care where a volunteer or formal caregiver is assigned for a limited period of time to allow the informal caregiver time away from caring). By investigating this further, we will be able to inform policy ideas and help to facilitate more rewarding caregiving experiences for the informal caregiver and for the older adult being cared for. With this we will hope to increase the QoL of both the informal caregiver and the individual being cared for. In addition to this, the development of novel support programs and therapeutic interventions, which aim to educate and aid individuals with these more positive experiences of caregiving to help with personal growth, will be an appropriate support tool. Informal caregiving should not come at a cost to the physical and mental health of the caregiver, or their QoL, and these programs will enable a better QoL for informal caregivers.

4.5. Ability to Care and Level of Support

Informal caregivers have higher level of depressive symptoms, and they are associated with a lack of support and subsequent ability to care [42,50,51]. This lack of support was

often reported to be from relatives and has been shown to tie into caregiving ideologies, with those holding non-traditional ideologies providing the least support and often leading to feelings of guilt, anxiety and isolation, whilst families holding traditional ideologies were reported to offer the most support [51]. In addition to this, those brought up with traditional ideologies reported feeling more prepared for informal caregiving and as such showed a better ability to care and hence lower depressive symptoms [44].

With previous literature suggesting a link between lack of support and feelings of ability to care, anxiety and depression in informal caregivers [55], it is important to consider the next steps for this premise. We suggest that efforts should be made to make clear distinctions between the factors affecting the QoL of the informal caregiver as this may lead to different policy responses. For example, it may be more appropriate to provide respite for informal caregivers rather than looking at ways in which they can continuously perform their caregiving obligations. In line with this, the potential of the use of technology is a concept to consider. For instance, they can help aid the 24/7 caregiver hotlines to provide support when traditional resources are unavailable. Dementia patients often have disturbed sleep, which causes the caregiver to also be up at odd hours. Telephone, computer, or video supports can help caregivers through these difficult times. Substantial progress has been made recently to aid both formal and informal caregiving [56–60], thus this may be an avenue to contemplate with future research in combination with findings from this study. However, further research is needed on caregivers' views, with a solutions-based approach that will identify caregivers' problems and at the same time will provide possible solutions to address these based on the perceived needs of the caregiver.

5. Conclusions

Overall findings highlight a link between financial strain, anxiety and exhaustion for informal caregivers of older adults with AD. In addition, higher levels of depression are associated with financial strain, exhaustion and traditional caregiving ideologies. Non-traditional caregiving views feed into the concept of exhaustion and were measured as such in the Quality of Life Scale for Informal Carers of Older Adults. These findings suggest that caregiving should be a normative component of adult education, in order to better prepare individuals with the mental and physical skills required for undertaking informal caregiving. These findings will help inform policy makers to develop novel programmes and services to both assist and reduce informal caregivers' strain, taking into account their different social and cultural contexts.

Most of the studies included in the current study focused on Asian or Asian-American caregivers, arguing for the need for more studies to address broader range of cultural approaches to caregiving. We feel both a quantitative approach using the Quality of Life Scale for Informal Carers of Older Adults along with the HADs scale will be an appropriate next step for future research, followed by a qualitative approach interviewing informal caregivers of AD in order to gain a more in depth understanding.

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Review

How Telemedicine Can Improve the Quality of Care for Patients with Alzheimer's Disease and Related Dementias? A Narrative Review

Efthalia Angelopoulou [1], Nikolaos Papachristou [2,†], Anastasia Bougea [1,*,†], Evangelia Stanitsa [1], Dionysia Kontaxopoulou [1], Stella Fragkiadaki [1], Dimosthenis Pavlou [3], Christos Koros [1], Yıldız Değirmenci [4], John Papatriantafyllou [1], Eleftherios Thireos [5], Antonios Politis [1], Agis Tsouros [6], Panagiotis Bamidis [2], Leonidas Stefanis [1] and Sokratis Papageorgiou [1]

[1] Department of Neurology, Aiginition University Hospital, National and Kapodistrian University of Athens, 11528 Athens, Greece
[2] Medical Physics and Digital Innovation Lab, Aristotle University of Thessaloniki, 54636 Thessaloniki, Greece
[3] School of Topography and Geoinformatics, University of West Attica, 12243 Aigalew, Greece
[4] Neurology Department, Istanbul Medipol University Faculty of Medicine, 34214 Istanbul, Turkey
[5] Primary Health Center of Vari, National Health System of Greece, 16672 Athens, Greece
[6] Department of Global Health, Boston University School of Public Health, Boston, MA 02118, USA
* Correspondence: annita139@yahoo.gr
† These authors contributed equally to this work.

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Abstract: *Background and Objectives*: Dementia affects more than 55 million patients worldwide, with a significant societal, economic, and psychological impact. However, many patients with Alzheimer's disease (AD) and other related dementias have limited access to effective and individualized treatment. Care provision for dementia is often unequal, fragmented, and inefficient. The COVID-19 pandemic accelerated telemedicine use, which holds promising potential for addressing this important gap. In this narrative review, we aim to analyze and discuss how telemedicine can improve the quality of healthcare for AD and related dementias in a structured manner, based on the seven dimensions of healthcare quality defined by the World Health Organization (WHO), 2018: effectiveness, safety, people-centeredness, timeliness, equitability, integrated care, and efficiency. *Materials and Methods*: MEDLINE and Scopus databases were searched for peer-reviewed articles investigating the role of telemedicine in the quality of care for patients with dementia. A narrative synthesis was based on the seven WHO dimensions. *Results*: Most studies indicate that telemedicine is a valuable tool for AD and related dementias: it can improve effectiveness (better access to specialized care, accurate diagnosis, evidence-based treatment, avoidance of preventable hospitalizations), timeliness (reduction of waiting times and unnecessary transportation), patient-centeredness (personalized care for needs and values), safety (appropriate treatment, reduction of infection risk),integrated care (interdisciplinary approach through several dementia-related services), efficiency (mainly cost-effectiveness) and equitability (overcoming geographical barriers, cultural diversities). However, digital illiteracy, legal and organizational issues, as well as limited awareness, are significant potential barriers. *Conclusions*: Telemedicine may significantly improve all aspects of the quality of care for patients with dementia. However, future longitudinal studies with control groups including participants of a wide educational level spectrum will aid in our deeper understanding of the real impact of telemedicine in quality care for this population.

Keywords: Alzheimer's disease (AD); telemedicine; COVID-19; World Health Organization (WHO)

1. Introduction

Dementia is a clinical syndrome characterized by cognitive decline leading to impaired functional activities of daily life [1]. Alzheimer's disease (AD) is the most common cause

of dementia, followed by Lewy body dementia and Parkinson's disease, frontotemporal dementia, vascular dementia, and other rarer underlying conditions [1]. It is estimated that dementia affects more than 55 million patients worldwide, with a significant societal, economic, and psychological impact not only on the patients themselves but also on their family members, caregivers, and health system [2]. Due to the increased life expectancy and aging population, the prevalence of dementia is expected to grow continuously.

Unfortunately, there is still no universally approved disease-modifying efficient treatment for AD and other neurodegenerative causes of dementia [2]. However, great efforts have been made toward the development of effective ways of care for patients with cognitive impairment. Appropriate symptomatic treatment, management of behavioral symptoms, support and education of caregivers, engagement in social activities, counseling, home modifications, and the use of non-pharmacological treatments have been shown to improve quality of life [3].

Even though early diagnosis has been associated with improved quality of life and treatment, literature evidence shows that many patients with AD and other forms of dementia have not received a formal diagnosis yet [4]. Diagnosis is often even more delayed in patients with early disease onset (younger than 65 years of age) [5]. Despite the availability of resources and services, many patients have inadequate access to appropriate treatment, specialized care, and holistic support [4]. In comparison to other age-related disorders, the quality of healthcare for patients with AD and related dementias is poor [6]. Potential underlying reasons include time constraints in medical practice, the lack of specialized neurologists, psychiatrists, and geriatricians in rural areas, the lack of experience and education of primary care physicians, the fragmented health care services, stigma, and the limited integration of community resources in dementia care [6,7]. Furthermore, intrinsic factors related to dementia, including limited recognition of medical needs, difficulties in communicating health problems and navigating health systems, may also lead to additional challenges in reaching appropriate care [8]. High-quality healthcare is a fundamental goal of the healthcare system. However, the observed inequity in the receipt of care indicates that current healthcare services are rather inadequate to holistically and efficiently address the needs of the patients. For these reasons, the World Health Organization (WHO) recognizes dementia as a public health priority, and alternative approaches to dementia care are urgently needed [9].

Telemedicine, defined as the remote diagnosis and treatment of patients via information and communications technology, holds promising potential for addressing this important gap [10,11]. Even though telemedicine has been already used for decades, the COVID-19 pandemic highlighted the emerging need for remote care, especially for the vulnerable population with chronic diseases, including patients with cognitive impairment. Physical distancing for preventing infection risk, increased caregivers' burden, overload of the healthcare system, and suspension of medical visits for non-urgent chronic conditions have contributed to the acceleration of remote care.

The reliability of telemedicine in cognitive impairment for diagnosis and follow-up, as well as the facilitators and barriers of this type of service in dementia care, have already been discussed elsewhere [7,12–14]. However, there is no literature review analyzing the ways in which telemedicine could improve the quality of care for patients with dementia in a structured manner. The increasingly growing research in this field and the rapid adoption of telemedicine in clinical practice necessitate a comprehensive analysis of the role of telemedicine in quality of care based on a commonly used conceptual framework, as well as a critical consideration of potential related challenges.

Herein, we analyze recent evidence on how telemedicine can improve the quality of care for patients with AD and related dementias. For this purpose, our discussion is based on the seven dimensions of healthcare quality defined by WHO (2018): effectiveness, safety, people-centeredness, timeliness, equitability, integrated care, and efficiency [15]. Next, we discuss the potential challenges and opportunities of telemedicine, especially for

patients with dementia, aiming for a better understanding of its role in this specific disease population. Finally, we provide perspectives for its effective implementation in the future.

2. Materials and Methods

Although our aim was not to conduct a systematic review, we followed the basic principles of a systematic review but limited to published peer-reviewed academic literature and a narrative synthesis of findings, as previously described [16–18]. We searched MEDLINE and Scopus databases for peer-reviewed articles investigating the role of telemedicine in the quality of care for patients with dementia written in the English language, with no time restrictions. The search was conducted between March 2022 and August 2022. We used the terms "dementia", "Alzheimer's disease", "cognitive impairment", "cognitive decline", "memory impairment", "healthcare", "care", "quality of care", "telemedicine", "telecare", "teleneurology", "tele-neurology", "remote care", "telehealth", "access", "accessibility", "effective", "effectiveness", "patient-centered", "personalized", "individualized", "integrated", "safe", "safety", "equal", "equitability", "equity", "timely", "timeliness", "efficient", and "efficiency" in different combinations. Relevant articles were screened in the title and abstract, and relevant articles were read in their full form. We included articles mentioning the role of telemedicine in the quality of care of patients with AD or related forms of dementia in terms of effectiveness, safety, equitability, timeliness, patient-centeredness, efficiency, and integrated care. Studies without mentioning results, studies among patients under the age of 18 years old, or those investigating intellectual disability were excluded. Through the snowballing process, we also screened the bibliography of each selected article for potential additional studies to include most of the key recent evidence [19]. For the purpose of this review, we organized our narrative synthesis of the included studies by the thematic categories defined by WHO on healthcare quality (1) effectiveness, (2) safety, (3) patient-centeredness, (4) timeliness, (5) equitability, (6) integrated care, and (7) efficiency.

3. Results

3.1. Defining the Concept and Dimensions of Healthcare Quality

Until now, there has been no widely accepted definition of "quality of healthcare"; however, there is a commonly shared comprehension of the main aspects and aims of healthcare quality, which includes the delivery of effective and safe care for the improvement of patients' welfare [15].

In order to explore how a new healthcare delivery model could improve the quality of care, we should first understand the dimensions of healthcare quality in an organized and structured manner. According to the conceptual framework of the United States Institute of Medicine (IOM), the quality of healthcare is defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [20]. This definition is widely adopted among healthcare stakeholders and highlights the importance of contemporary evidence-based care provision for positive outcomes at an individual and population level. Furthermore, IOM describes the six main components of healthcare quality: effectiveness, safety, patient-centeredness, timeliness, efficiency, and equitability [20]. As mentioned in the IOM report, this useful framework enables us to conceptualize better the main dimensions of healthcare quality [20], and it is currently used in many countries other than the United States [15].

Similarly, as recently stated in the World Health Organization (WHO) Framework on Integrated People-centered Health Services—which was based on the IOM framework—"high-quality care" involves "care that is safe, effective, people-centered, timely, efficient, equitable and integrated" (Figure 1) [15].

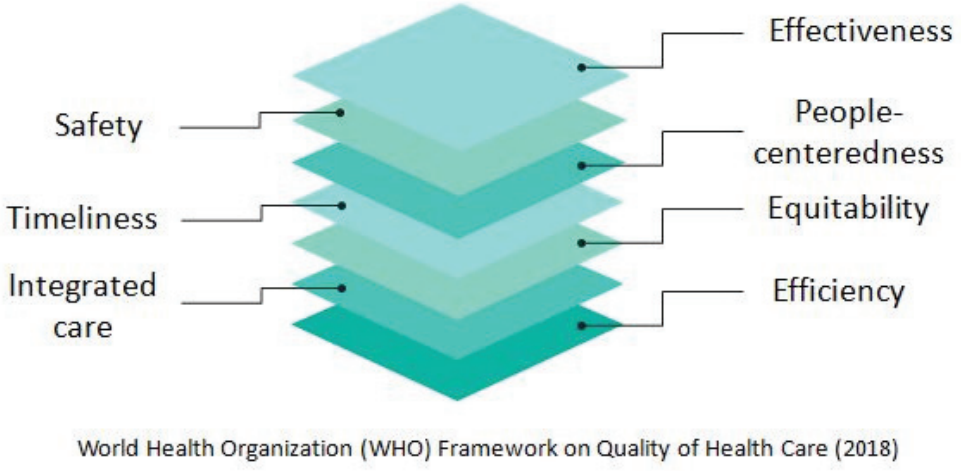

Figure 1. The seven dimensions of Quality of Health Care, according to World Health Organization Framework, 2018.

As explained by WHO, the effectiveness of care includes the provision of evidence-based health services to individuals who need them, and safety is defined by the avoidance of harm. People-centeredness means the delivery of care that respects and responds to personal needs, values, and preferences [15]. Timely healthcare provision implies the reduction of waiting times and delays that could be harmful not only for those who receive but also give care [15]. Equitable health services are those whose care quality is independent of age, race, ethnicity, geographical location, socioeconomic status, sex, gender, religion, and political or linguistic affiliation [15]. Integrated care is described as coordinated care across different levels and providers, allowing the availability of all appropriate health services throughout the life course [15]. Finally, efficiency in healthcare is defined as maximizing the benefit of available care resources and avoiding relevant waste [15].

In the following sections, we explore the potential of telemedicine to improve healthcare quality for patients with AD and other forms of dementia based on these seven dimensions of healthcare quality as described by WHO and further discuss future opportunities.

3.2. Definition and Primary Forms of Telemedicine

As mentioned above, telemedicine is defined as the remote diagnosis and treatment of patients using information and communication technology [10,11]. Even though the terms "telehealth" and "telemedicine" are used interchangeably in many cases, "telehealth" is a broader term incorporating additional remote non-clinical services, such as clinician training, medical education, and administrative meetings [21].

Essentially, there are three main types of telemedicine services: synchronous, asynchronous, and remote monitoring. Synchronous telemedicine involves the delivery of care in real-time, allowing for live interaction with the patient or the physician to provide expertise. A subtype of synchronous telemedicine visit involves the Facilitated Virtual Visit. An example of this type of visit is when the patient is at a site where diagnostic equipment is available (i.e., pulse oximeter, digital stethoscope) and the physician is at a remote site. At the patient's site, the telefacilitator (i.e., nurse) gathers objective medical measurements and transfers these data to the remote physician. Asynchronous telemedicine involves the "store-and-forward" technique, such as the transfer of prerecorded neuroimaging data for review by neuroradiologists [22]. Remote patient monitoring refers to the continuous assessment of a patient's clinical condition via direct video monitoring or review of various tests and images being collected remotely.

Telemedicine services are provided through a wide variety of applications, including telephone, video-conferencing, communication via e-mail, mobile applications, and the use of remote devices, such as wearable biosensors [23]. Wearable biosensors are multiplexed, smart devices that enable the non-invasive quantification of several dynamic biological signals in real time via optical, mechanical, and electrochemical modes of transduction. These approaches allow for integrated and multifaceted data acquisition and interpretation for personalized healthcare monitoring.

Teleconsultation refers to the cases when healthcare providers present a patient's case to medical experts in another remote location—usually at a hospital or specialized clinic—asking for expert consultation. In this case, the patients may or may not be present during the video conferencing. In other cases, telemedicine is provided by healthcare professionals directly to patients [21].

3.3. The Reliability of Telemedicine in AD and Related Dementias

Given that the evaluation of patients with AD and other types of dementia is majorly based on the medical history and clinical interviews with the patient and family members, telemedicine is a precious tool for these cases [7]. The diagnostic accuracy of dementia is comparable to traditional in-person examination [13]. Although several parts of the neurological examination, such as gait assessment, can be conducted remotely, other aspects of the exam, such as tone, deep tendon reflexes, and sensory and muscle strength examination, may be challenging to evaluate without a healthcare professional close to the patient. Neuropsychological testing is generally feasible and reliable through telemedicine. In particular, Mini-Mental State Examination (MMSE) can be reliably administered in patients with cognitive impairment [24]. Montreal Cognitive Assessment (MoCA) and a modified version for video-based conditions have been proven reliable if administered remotely in individuals with cognitive complaints or mild-to-severe AD, respectively [25,26]. Although no significant differences have been detected between in-person and video-based performance on MMSE and Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) of patients with AD during two-year period, individuals at advanced stages performed worse in some cases of video-based assessment [24]. The administration of other cognitive scales such as Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [27], language testing with Boston Naming Test and Letter and Category Fluency, memory testing with Hopkins Verbal Learning Test-Revised, attention and working memory testing with Digit Span forward and backward, as well as Clock Drawing Test and Visuospatial Memory Test can also be administrated reliably through telemedicine [12,28–30]. The assessment of AD staging with the Clinical Dementia Rating scale (CDR) [26] and depressive symptoms with the Geriatric Depression Scale (GDS) is also reliable [31]. Telephone-based instruments, such as Telephone Interview for Cognitive Status (TICS), are also helpful in assessing cognitive function remotely [32]. In addition, the use of automatic speech analysis for the diagnosis of dementia or other related digital tools may also help for the remote assessment of cognitive complaints [33].

3.4. Quality of Care for AD and Related Dementias and the Emerging Role of Telemedicine: Current Evidence

In this section, we summarize the importance of healthcare quality for patients with AD and other forms of dementia in each of the seven dimensions as defined by WHO (effectiveness, safety, people-centeredness, timeliness, equitability, integrated care, and efficiency, Table 1). We further discuss the emerging role of telemedicine in addressing the existing gaps (Table 2).

Table 1. Healthcare quality dimensions according to the World Health Organization (WHO), 2018, its definition, and examples of the value of each dimension of quality of care in Alzheimer's disease and related forms of dementia.

Health Care Quality Dimension	Definition	Examples of the Importance of High Quality of Care in Alzheimer's Disease and Related Dementias	References
Effectiveness	The provision of evidence-based health services to individuals who need them	Lack of education and training of primary care physicians in the diagnosis and treatment of dementia	[4,34]
		The differential diagnosis of dementia causes has important clinical impact	[35]
		The differential diagnosis between dementia mimics has important clinical impact	[36]
		Identification of atypical clinical presentations and rarer forms of dementia, especially at younger agesis challenging	[36]
		Detailed neuropsychological testing is often required for the accurate dementia diagnosis, especially at early stages	[37]
		The limited time of primary care physicians does not allow sufficient discussion, counseling, and personalized management plan	[34]
		Adherence to dementia guidelines and evidence-based recommendations is associated with better overall quality of care	[38]
		Adherence of primary care physicians to dementia guidelines and quality care indicators is inadequate	[38–40]
		Most patients with dementia have inadequate access to appropriate formal care services	[41]
		The participation of physicians in educational seminars on dementia care is associated with improved quality of life	[38]
Safety	The avoidance of harmto people for whom the care is intended.	Traveling to specialized physicians is challenging for dementia patients due to their cognitive and mobility issues	[7]
		COVID-19 poses high infection risks in traditional in-person clinical settings in the elderly	[33]
		During the COVID-19 pandemic, many older patients with dementia do not receive appropriate medical care	[42]
		Inappropriate and high prescription of antipsychotic drugs for patients with dementia is high	[43,44]
		Improper use of antipsychotics is associated with a higher risk of death and ischemic events in the elderly	[45]
		AD diagnosis is associated with higher COVID-19-associated mortality	[46]
People-centeredness	The delivery of care that respects and responds to personal needs, values, and preferences	Individualized interventions by primary care physicians in collaboration with dementia care managers are associated with lower caregiver stress and behavioral symptoms	[6,47,48]
		Personalized evaluation and management are associated with higher-quality dementia care	[34]
		Care models with shared decision making is associated with improved satisfaction	[49]

Table 1. *Cont.*

Health Care Quality Dimension	Definition	Examples of the Importance of High Quality of Care in Alzheimer's Disease and Related Dementias	References
		Patients' and family members' preferences, perceptions, and needs are an integral part of dementia care	[49]
Timeliness	The reduction of waiting times and delays that could be harmful not only for those who receive but also give care	Diagnostic sensitivity of dementia is correlated with the frequency of contact between patients and providers	[4]
		Regular monitoring contributes to a better quality of life	[38,43]
		Specialized neurologists and memory clinics are lacking in remote areas	[50]
		Earlier detection of cognitive decline is associated with better health outcomes	[49]
		AD prevalence is higher in rural areas	[51]
Equitability	The provision of care that is independent of age, race, ethnicity, geographical location, socioeconomic status, sex, gender, religion, political or linguistic affiliation	Limited recruitment of physicians at rural health centers	[22]
		Lack of transportation infrastructure and socioeconomic disparities limit the accessibility of patients living in rural areas	[52]
		Often long travel distances for appropriate access to specialized care	[53]
		Compared to non-Hispanic Whites, a greater percentage of non-Hispanic Blacks and Hispanics had a missed or delayed dementia diagnosis	[54]
Integrated care	Coordinated care across different levels and providers, allowing the availability of all appropriate health services throughout life course	Patients, caregivers, and family members often require referral for legal issues, advice on long-term facilities, improvement of home environment, psychological support, information about available services, support groups, educational resources, and administrative assistance	[34]
		Cooperation between different healthcare professionals for dementia care is limited, and community-based organizations are currently underutilized and inadequately incorporated into the healthcare system	[34,43]
		Social worker engagement improves the quality of care for dementia	[38]
		Transdisciplinary collaborative team care (physicians, neuropsychologists, social workers, registered nurses, and nurse practitioner managers) and linkages to appropriate community resources are associated with better quality of care, improved counseling, reduced caregivers' stress and patients' behavioral and depressive symptoms, and fewer hospitalizations and visits to the emergency departments	[38,55,56]

Table 1. *Cont.*

Health Care Quality Dimension	Definition	Examples of the Importance of High Quality of Care in Alzheimer's Disease and Related Dementias	References
		In integrated care, team members contribute with their expertise and clinical or management strengths for appropriate dementia care	[49]
		Fragmented care and difficult-to-navigate healthcare services are significant barriers to treatment	[57]
		The integration of community-based organizations (e.g., Alzheimer's Association) into the health systems improves quality of care for patients with dementia	[55]
		Participation of nurse practitioners in care is associated with higher healthcare quality for dementia patients, reduced risk of falls and incontinence, and better adherence to care recommendations	[58,59]
Efficiency	Maximizing the benefit of available care resources and avoiding relevant waste	Fewer emergency department visits and unnecessary hospitalizations may be associated with lower public healthcare costs	[22]
		Changes in routine and home environment may cause anxiety and exacerbate behavior symptoms in dementia patients	[60]
		Dementia care creates significant economic burden for patients, families, caregivers, and healthcare systems	[61]

Table 2. Healthcare quality dimensions according to the World Health Organization (WHO), 2018, and the role of telemedicine in each of them dementia care.

Health Care Quality Dimension	The Role of Telemedicine in Each of the Quality of Care Dimensions in Alzheimer's Disease and Other Related Dementias	References
Effectiveness	Telemedicine is effective in confirming or providing a diagnosis for cognitive impairment	[27,62]
	Alterations in drug prescriptions were recommended via telemedicine in more than 1/3 of patients (longitudianl study, 3-year follow-up period, 45 clinical video telehealth encounters)	[62]
	Rural community clinics can be effectively connected through teleconsultations with physicians specialized in dementia care in University Hospitals (longitudinal study, 188 patients with dementia, face-to-face versus telemedicine care)	[63]
	Telephone-based remote care is feasible for younger patients with dementia (retrospective study for a 2-year period, 1121 calls)	[64]
	Telemedicine provided by specialists is associated with 1.8 and 1.1 medication alterations for patients with dementia at initial assessments and follow-up visits, respectively, for 12-month period (longitudinal study, 199 clinical video telehealth patient encounters)	[65]
	Teleconsultation in dementia is associated with treatment modifications at approximately 10%, especially for those with AD or living with a relative (multicenter study, 874 patients)	[66]
	Telemedicine use is associated with longer treatment duration and compliance in dementia patients during a 5-year period (259 patients in-person, 168 patients via telemedicine)	[67]

Table 2. *Cont.*

Health Care Quality Dimension	The Role of Telemedicine in Each of the Quality of Care Dimensions in Alzheimer's Disease and Other Related Dementias	References
	Telemedicine is feasible for follow-up and ongoing care	[50,68]
	Fewer canceled medical visits and improved transitions between the follow-up clinic and primary care supported by a case manager or geriatric assessor via telemedicine (55 telemedicine sessions)	[68]
	Telemedicine via video-conferencing are associated with improved quality of life, better physical and mental health, less perceived burden, and higher self-efficacy, compared to only telephone-based visits among patients with neurodegenerative diseases	[42,69]
	Telemedicine via video-conferencing may improve the well-being and resilience of patients (self-efficacy, perceived burden) with neurocognitive disorders and caregivers and avert MoCA deterioration (60 older adults with neurocognitive disorder; supplementary telehealth via video conference vs. via telephone)	[60]
	Telemedicine is a valid triage tool for patients with frontotemporal dementia regarding clinical worsening (CDR-FTD scale), change in quality of life, and COVID-19 symptoms, with high satisfaction of the caregivers(26 telemedicine clinical interviews with caregivers, 4 with both patients and caregivers	[70]
	Telemedicine for acute illnesses is associated with less unnecessary visits to emergency departments among older adults with dementia in senior living communities (1 year of access to telemedicine is associated with a 24% reduction in emergency department visits)	[71]
	Emergency department use was reduced for ambulatory-care sensitive conditions after the introduction of telemedicine for older individuals in senior living communities (prospective cohort study at a primary care geriatrics practice)	[72]
	Videoconferenced geriatric medicine grand rounds on a weekly basis are feasible and beneficial for healthcare professionals in 9 urban and 14 remote rural areas (questionnaire: reason of attendance, evaluations of presentations)	[73]
Safety	Specialists could identify inappropriate drug use that might contribute to cognitive decline in almost half of the visits through telemedicine (interprofessional dementia assessment by a geriatrician, geropsychologist, geriatric psychiatrist or neurologist, and social worker using clinical videotelehealth technology)	[74]
	Telemedicine through video-conferencing is associated with better quality of life for patients with dementia compared to only telephone-based visits during the social isolation of the COVID-19 pandemic (60 older adults with neurocognitive disorder; supplementary telehealth via video-conference vs. via telephone)	[60]
	In case of home-based video-conferencing, telemedicine allows the physician to directly observe the home environment of the patient and suggest alterations such as individualized recommendations for the prevention of falls (feasibility study, 10 videoconferencing visits)	[75]
People-centeredness	Patients and caregivers accept telemedicine as a very convenient model of care. Patients with AD and their caregivers are very satisfied with telemedicine (overall satisfaction rates 88–98%)	[62,76–78]
	Telemedicine is preferred over in-person visits	[76,79]
	Similar satisfaction rates are observed between telemedicine and traditional in-person visits (230 participants recruited from outpatient dementia clinic)	[80]

Table 2. *Cont.*

Health Care Quality Dimension	The Role of Telemedicine in Each of the Quality of Care Dimensions in Alzheimer's Disease and Other Related Dementias	References
	Telemedicine allows for the identification of caregivers' needs (rural caregiving telemedicine program, 1-year questionnaire on risk factors, behavioral management, diagnosis, and medications)	[81]
	Semi-structured interviews for the experiences of patients and caregivers on telemedicine demonstrated that although proactive teleconsultations during the COVID-19 pandemic are effective, they should be focused on needs and practical recommendations (community-based patients living with dementia (30) and their carers (31))	[82]
	Telemedicine allows family members living away from the patient's home to attend the video-conference visit, allowing for shared decision making (older participants, 72.1% with cognitive impairment, 32 patient evaluations, 80 clinician feedback evaluations, satisfaction, care access during pandemic, and travel and time savings)	[83]
	Assistive technology use and telecare for individuals with dementia are not associated with prolonged time of independent living (randomized controlled trial, 495 participants)	[84]
Timeliness	Telemedicine allows for real-time medical reporting and sharing, thereby avoiding unnecessary delays (videoconferencing 28 patients from outpatient clinic)	[24]
	The use of wearable devices, remote monitoring sensors, or web-based platforms may facilitate early detection of medical emergencies and timely intervention	[33,85]
	Telemedicine reduces waiting times for appointments with specialized physicians, allowing earlier diagnosis and treatment of dementia-related various medical complaints(60 older adults with neurocognitive disorder; supplementary telehealth via video conference vs. via telephone)	[60]
Equitability	Telemedicine in rural areas is effective, with high satisfaction rates, allowing for better access to timely care, reduced cost, and avoidance of unnecessary transportation	[22,86,87]
	Telemedicine facilitates the elimination of geographical disparities, allowing patients with dementia from rural and urban areas to access specialized healthcare	[53,88]
	Digital literacy, lower education level, and worse cognitive function are associated with less engagement in remote interventions promoting lifestyle modifications among older adults	[89,90]
Integrated care	In a Tennessee-based program, specialists recommended referrals to social workers and the use of long-term care services in almost two-thirds of the telemedicine visits	[62,76]
	A Pittsburgh-based telemedicine program for dementia care, including a geriatrician, geriatric psychiatrist, psychologist, social worker, and nurse manager, is highly acceptable and successful fur rural areas (patient satisfaction survey, 156 clinic visits)	[74]
	Telemedicine may significantly enable interdisciplinary dementia care	[86,87,91–93]
	The use of a nurse practitioner-led mobile memory clinic incorporated in the general practice targeting patients with poor socioeconomic status and limited access to care is feasible and acceptable (1-year, 102 patients)	[94]
	Telemedicine can aid in the assessment and management of psychotic symptoms of patients with neurodegenerative disorders in long-term care facilities (multidisciplinary consensus panelist of best practices in telemedicine for patients with dementia-related psychosis or Parkinson's disease-related psychosis)	[95]

Table 2. *Cont.*

Health Care Quality Dimension	The Role of Telemedicine in Each of the Quality of Care Dimensions in Alzheimer's Disease and Other Related Dementias	References
	Telemedicine allows telerehabilitation for patients with AD dementia, frontotemporal dementia, and mild cognitive impairment	[96–99]
	Computerized cognitive training among patients with or at risk for dementia is effective	[100–102]
	Speech therapy is effective in primary progressive aphasia and alexia	[103,104]
	Virtual reality for patients with dementia is associated with reduced neuropsychiatric symptoms (i.e., depression and agitation, apathy) and quality of life	[105–107]
	Tele-exercise programs through video conferencing are feasible and acceptable among patients with AD and their caregivers	[108,109]
	Video-based caregiver support for stress, education, and training for behavioral symptoms are feasible and effective	[110–127]
	Remote telephone-based cognitive behavioral therapy to caregivers of patients with AD for the enhancement of physical or mental health is effective (273 family caregivers, 50-min sessions)	[128]
	Remote cognitive behavioral therapy to caregivers of patients with AD for insomnia treatment is also effective (four-session CBT-I protocol)	[129]
	Most caregivers are satisfied with the FamTechCare service, which allows for tailored expert feedback based on video recordings (multisite randomized controlled trial, satisfaction survey)	[130]
	Subjective burden levels of the caregivers have not been significantly affected by a telehealth-based intervention, while objective measures of activity and sleep showed a slight decline	[131]
	Assistive technology and telecare are not associated with reduced caregivers' burden (randomized-controlled trial)	[132]
Efficiency	Telemedicine reduces traveled distance and time spent traveling compared to in-person visits	[62,74,80]
	Telemedicine is beneficial for patients in advanced stages of dementia with mobility limitations, being bedridden or in a wheelchair, whose transportation is costly and time-consuming	[52,78]
	The avoidance of unnecessary transportations and the distance and time saved have significant effects on patients, caregivers, and family members that need to accompany them for medical visits(older participants, 72.1% with cognitive impairment, 32 patient evaluations, 80 clinician feedback evaluations, satisfaction, care access during pandemic, and travel and time savings)	[83]
	During the COVID-19 pandemic, e-mail-based care for patients with dementia is feasible and effective (retrospective analysis, 14-month period, 374 e-mails sent by 213 patients)	[133]
	Videoconferencing is cost-effective for dementia diagnosis, in case the specialist should drive for more than two hours in order to deliver in-person service (break-even analysis)	[134]
	The FamTechCare intervention aiming to provide dementia specialists feedback to caregivers based on video recordings is cost-effective, compared to telephone support interventions (clinical trial, cost-effectiveness analysis)	[135]
	A remote caregiver support intervention only resulted in short-term cost savings, which could not be maintained for one year (randomized controlled trial)	[136]

3.4.1. Effectiveness

Although the actual frequency of delayed or missed diagnosis of AD and related dementias remains unknown, it is estimated to be particularly high in primary care settings [4]. Many primary care physicians are not familiarized with the diagnostic criteria of dementia, and they lack appropriate education or expertise in assessing and treating patients with cognitive impairment [4,34]. Neurodegenerative causes of dementia should be differentiated from potentially reversible ones, including depression, infections, metabolic disorders, central nervous system tumors, autoimmune conditions, and functional cognitive disorders [35]. Dementia misdiagnosis may result in significant harm, so the correct discrimination of dementia mimics is very important [36]. Recognizing atypical clinical presentations and rarer dementia forms, especially at younger ages, such as frontotemporal dementia, is even more challenging [36]. The most commonly used cognitive tests lack sensitivity, and diagnosis may be missed for patients at early stages. Hence, detailed neuropsychological testing is often required [37].

Furthermore, the evaluation of patients with cognitive complaints requires significant time. Within the often-busy primary care settings, the physicians may not be able to sufficiently discuss with the family, provide counseling to caregivers, give referrals to the appropriate community-based organizations, and develop a personalized management plan [34]. Adherence to dementia guidelines and evidence-based recommendations has been associated with a better overall quality of care, patient health-related quality of life, and quality of caregiving [38]. However, several studies have demonstrated that the adherence of physicians to dementia guidelines and quality care indicators is inadequate in primary care settings concerning assessment, treatment, support, education, and safety [38–40]. As a result, most patients with dementia and their caregivers find it difficult to access formal care services, and when reached, this care is not the appropriate one [41]. In addition, the participation of physicians in education seminars about common issues in dementia care has been associated with improved quality of life of the patients [38].

In this context, telemedicine provides the opportunity for improved access to appropriate and specialized care. Telemedicine has been shown to be effective in confirming or providing a diagnosis in case of cognitive impairment [62,74,76,137–139], highlighting its significance, especially for remote, underserved areas. Regional community clinics in rural areas can be effectively connected through teleconsultations with physicians who are specialized in dementia care in University Hospitals. In this way, accurate diagnosis is facilitated, and an appropriate treatment plan is provided [63]. Telephone-based remote care is feasible for younger patients with dementia, too [64]. Telemedicine could also reduce the risk of behavioral and psychological symptoms of dementia related to the negative consequences of the COVID-19 pandemic [140]. Telemedicine provided by specialists has been associated with 1.8 and 1.1 medication changes on average for patients with dementia at initial assessments and follow-up visits, respectively, during a 12-month period [65]. In another study, alterations in drug prescriptions were recommended in more than one-third of the patients through telemedicine [62]. Telemedicine consultation in dementia care has also been associated with treatment modifications at approximately 10% in another study, especially for those with AD or living with a relative [66]. Telemedicine use has been associated with longer treatment duration and compliance in dementia patients [67]; it has also been proven a feasible method for follow-up and ongoing care [50,68]. Via telemedicine, the cancellations of medical visits are fewer, and the transitions between the follow-up clinic and primary care are also improved [68]. These results highlight the vital role of telemedicine in providing appropriate care by prescribing the proper medications for each patient and improving treatment compliance.

Through appropriate referrals by dementia specialists, telemedicine may also improve the patients' access to diagnostic work-up, thereby aiding in the correct diagnosis. For example, after a telemedicine assessment by dementia specialists, a lumbar puncture may be recommended and conducted at the peripheral hospital. Then, the cerebrospinal fluid sample could be transferred for biomarker analysis to the appropriate laboratories, whose

availability in remote areas is limited. In addition, images of Magnetic Resonance Imaging (MRI) can be transferred remotely to specialized neuroradiologists, allowing for a more accurate evaluation. Finally, after specialized assessment through telemedicine, genetic testing may be recommended, especially in early-onset, familial, or atypical cases, and blood samples could be transferred to the appropriate laboratories. These opportunities are especially important for residents living in remote areas with limited access to specialized care and guidance.

Overall, telemedicine visits through video-conferencing for patients with neurocognitive disorders have been associated with improved quality of life, better physical and mental health, less perceived burden, and higher self-efficacy [42,69]. Telemedicine via video-conferencing may also improve the well-being and resilience of patients with neurocognitive disorders and caregivers [60]. Furthermore, the addition of telemedicine has been associated with a delayed deterioration of MoCA scores compared to only telephone-based visits [42]. Even though research evidence on dementia subtypes other than AD is limited, it has been demonstrated that telemedicine is a valid triage tool for patients with frontotemporal dementia [70], highlighting its promising potential for other forms of dementia.

Importantly, dementia is associated with higher rates of hospital admissions attributed to ambulatory care-sensitive conditions, for which appropriate evaluation and early management in outpatient settings might have possibly prevented hospitalization [141]. Recent evidence shows that the number of plausibly avoidable hospital admissions of aged individuals with dementia is growing [142]. In rural areas, AD is associated with even higher preventable hospitalizations [143]. Usual underlying pathological conditions are pneumonia, congestive heart failure, and urinary tract infection, among others. Therefore, care for patients with dementia necessitates high-quality healthcare outpatient services for better outcomes and the prevention of avoidable visits to the emergency departments.

In this context, telemedicine has been shown to be a valuable tool for the avoidance of unnecessary visits to emergency departments [71]. Emergency department use has also decreased for ambulatory-care sensitive conditions after the introduction of telemedicine for older individuals in senior living communities in another study [72]. Hence, telemedicine may also aid in the reduction of potentially unnecessary emergency visits and hospitalizations, allowing for cost-effective care not only for the patients and their families but also for the health systems.

Concerning education, video-conferenced geriatric medicine grand rounds on a weekly basis are feasible, acceptable, and beneficial for healthcare professionals, who otherwise could not have access to those medical rounds [73]. This opportunity allows for the tele-education of primary care physicians on dementia care, which could subsequently benefit patients.

3.4.2. Safety

Regarding safety concerns, the cognitive and mobility impairment of patients with dementia poses several challenges during their traveling to specialized physicians for in-person visits [7]. Therefore, telemedicine is a valuable tool since it can reduce the risk of accidents during transportation [144].

Inappropriate and high prescriptions of antipsychotic drugs for behavioral symptoms, as well as inadequate review and monitoring of medications for patients with dementia, are high [43,44]. Improper use of antipsychotics has been associated with a higher risk of death and ischemic events, especially in the elderly [45]. In this regard, a study has demonstrated that specialists could identify inappropriate drug use that could potentially contribute to cognitive decline in almost half of the visits through telemedicine [74]. This evidence highlights the significant role of telemedicine in detecting treatment approaches that could potentially harm patients with dementia.

Furthermore, in the case of home-based video-conferencing, telemedicine gives physicians the opportunity to directly observe the home environment of the patient and suggest

alterations that could improve daily life and safety. For instance, physicians could make individualized recommendations for the prevention of falls [75]. In addition, social determinants of health, such as family dynamics and economic difficulties, can also be more effectively detected in video-based visits at home [22], allowing for a more holistic approach to dementia care.

COVID-19 poses high infection risks in traditional in-person clinical settings and affects elderly individuals disproportionately [33]. For this reason, during the COVID-19 pandemic, patients are generally encouraged to use telemedicine services for safer medical assessment and management when possible. This is particularly important for the vulnerable elderly population with chronic diseases, which are related to higher COVID-19-associated morbidity and mortality [33]. During the COVID-19 pandemic, older patients with dementia are also at higher risk of not receiving appropriate medical care [42]. AD diagnosis has been independently associated with higher COVID-19-associated mortality [46]. Therefore, the safer environment of telemedicine that protects against COVID-19 transmission and reduces exposure risk provides a valuable option for dementia care, also allowing the continuity of care that these individuals need. The avoidance of COVID-19-related hospitalizations also prevents secondary infections and other complications that have also been associated with increased mortality [145]. During the COVID-19 pandemic, non-urgent outpatient visits for chronic diseases were suspended, leading to a sense of abandonment because of a lack of physician–patient contact [52]. In this context, telemedicine through video-conferencing was associated with better quality of life for patients with dementia compared to only telephone-based visits during the social isolation of the COVID-19 pandemic, highlighting its role in minimizing the potential adverse effects of social distancing measures [60].

3.4.3. People-Centeredness

As demonstrated by the results of the UCLA Alzheimer's and Dementia Care (ADC) Program, the individualized evaluation of the specific needs of patients and their families, as well as the adoption of a personalized management plan, are associated with higher-quality dementia care, regarding screening, assessment, and counseling [34]. Care models using shared decision making between patients, family members, and caregivers have also been associated with higher satisfaction from patients and caregivers [49]. In addition, individualized pharmacological and non-pharmacological interventions by primary care physicians in collaboration with dementia care managers have been associated with lower caregiver stress and behavioral symptoms, as well as possibly fewer inpatient hospitalizations [6,47,48].

Patients' and family members' preferences, perceptions, and needs are an important integral part of dementia care. In this regard, patients and caregivers generally accept telemedicine, and they perceive it as a very convenient model of care. Patients with AD and their caregivers are very satisfied with telemedicine, with overall satisfaction rates ranging between 88–98% [62,76–78]. Similar satisfaction rates have been observed between telemedicine and traditional in-person visits in one study [80]. However, telemedicine was preferred over in-person in other studies [76,79]. Importantly, in most studies, response rates on satisfaction surveys are generally low, suggesting that selection bias may lead to an overestimation of participants' satisfaction [7].

Telemedicine allows the personalized assessment of individuals with cognitive impairment and may aid in developing and establishing an individualized treatment plan. Compared to primary care settings, telemedicine gives more time for discussion with patients, caregivers, and family members regarding their beliefs and needs [81]. A recent study investigating the experiences of patients with dementia and their caregivers in remote healthcare via semi-structured interviews demonstrated that proactive teleconsultations during the COVID-19 pandemic were effective. However, this study demonstrated that these teleconsultations should be more focused on real needs, practical recommendations,

and ways to replace non-verbal prompts, especially for the description of new health problems [82].

Telemedicine also gives the opportunity to family members living away from the patient's home to attend the video-conference visit, allowing for shared decision making a personalized treatment plan [83].

The use of smart home systems and remote monitoring devices allows older adults with cognitive impairment to live in their preferred environment, which may also delay their placement in nursing homes. In this way, patients' and family members' preferences are respected, and independent living with a sense of safety is facilitated [146]. On the other hand, another study indicated that the use of assistive technology and telecare for individuals with dementia was not associated with prolonged time of independent living [84]. Further studies are needed considering also dementia stage as an important factor that could influence the effects of assistive digital technologies.

3.4.4. Timeliness

Specialized neurologists and memory clinics are often unavailable in remote and rural areas [50]. On the contrary, AD prevalence has been shown to be higher in rural regions [51]. Telemedicine reduces waiting times for appointments with specialized physicians, thereby contributing to earlier diagnosis and timely treatment of dementia-related various medical complaints [60].

Earlier recognition of cognitive decline is associated with improved health outcomes [49]. A systematic review demonstrated that the diagnostic sensitivity of dementia is associated with the frequency of contact between patients and providers [4]. Regular monitoring contributes to a better quality of life [38,43], highlighting the importance of timeliness in a better quality of care. Via telemedicine, patients with dementia have the opportunity to receive regular follow-ups without the need to cancel scheduled visits for reasons related to travel restrictions.

Telemedicine also gives the opportunity for real-time medical reporting and sharing, thereby avoiding unnecessary delays that could affect the quality of care [24]. Furthermore, sharing brain imaging data or laboratory results in an asynchronous manner accelerates the assessment process and facilitates the prompt recognition of other medical conditions [33]. The use of wearable devices, remote monitoring sensors, or web-based platforms may also be beneficial tools for the early detection of potential medical emergencies and timely intervention [33,85].

3.4.5. Equitability

Equitability in quality and access are integral parts of healthcare delivery. Health inequality is defined as "differences in the distribution of health status and achievement of health outcomes that exist among specific groups due to genetic or other factors that cannot be prevented or modified" [147]. Factors contributing to inequity are associated with differences in availability, cost, and access to information for various population groups [148]. The "European Dementia Monitor" Project indicated important differences in organizational, financial, and practical aspects across European countries regarding accessibility to dementia care and treatment, resulting in inequity [148]. Race, ethnicity, age, gender, educational level, and geographical area may contribute to health inequalities [147]. It has been demonstrated that the area of residence plays a vital role in accessibility [148]. Patients in rural areas often have to travel long distances to obtain appropriate access to specialized care [53]. The lack of transportation infrastructure and socioeconomic disparities may also limit the accessibility of patients in rural areas [52]. It is also difficult to recruit and retain physicians at rural health centers or hospitals [22]. Concerning race and ethnicity, compared to non-Hispanic Whites, a greater percentage of non-Hispanic Blacks and Hispanics had a delayed or missed diagnosis of dementia [54]. Potential reasons for this situation include disparities in health insurance coverage, different proximity to

health services, racism, mistrust of the health system, and limited diversity in the healthcare personnel [54].

Telemedicine facilitates the elimination of geographical disparities since it gives equal opportunities for patients with dementia from rural and urban areas to access specialized healthcare [53,88], given the geographic misdistribution of medical specialties, including neurologists, telemedicine aids in eliminating this gap. Several studies have shown that telemedicine in rural areas is effective, with high satisfaction rates, allowing for better access to timely care, reduced cost, and avoidance of unnecessary transportation [22,53,149]. Telehealth also gives the opportunity to inhabitants of underserved and remote areas to be educated about health issues [22], including dementia prevention and care. Furthermore, telemedicine, offered by healthcare professionals trained in recognition of cultural diversities and needs of each person, can provide care to individuals living in underrepresented ethnic and racial communities, thereby contributing to the limitation of gaps in equitability.

On the other hand, inadequate experience with technology and digital literacy, lower education level, as well as a worse cognitive function have been associated with less engagement in remote interventions promoting lifestyle modifications among older adults [89,90]. Further attempts to train patients in the use of digital technologies are required to address healthcare inequalities related to the use of telemedicine interventions, especially among older individuals [150].

3.4.6. Integrated Care

Apart from their purely medical needs, patients with dementia, caregivers, and family members often require psychological support, referral for legal issues, advice on the selection of the appropriate long-term facilities, and discussion about solutions to improve the home environment to facilitate their living and reduce the risk of falls. In addition, patients and family members need information about available social services, daycare centers, activities, support groups, and educational resources, as well as administrative assistance during the application for long-term services or nursing homes [34]. In addition, fragmented care and difficult-to-navigate healthcare services are significant barriers to effective treatment [57]. Hence, dementia care requires a holistic and multidisciplinary approach, which should involve the integration of several different stakeholders and organizations.

The integration of community-based organizations (e.g., Alzheimer's Association) into the health systems has been shown to improve quality care for patients with dementia [55]. Transdisciplinary team care from physicians, neuropsychologists, social workers, registered nurses, and nurse practitioner managers has been associated with better quality of care, improved driving counseling, better caregivers' counseling, reduced levels of caregivers' stress, fewer patients' behavioral and depressive symptoms, as well as fewer hospitalizations and visits to the emergency departments [38,55,56]. Linkages to appropriate community resources have been shown to be beneficial. The participation of nurse practitioners in care has also been associated with higher healthcare quality for dementia patients, reduced risk of falls and incontinence, as well as better adherence to care recommendations [58,59]. Social worker engagement with home assessments may also improve the quality of dementia care [38]. In integrated care models, team members contribute with their expertise and clinical or management strengths in a collaborative manner to provide the most appropriate dementia care approach [49]. However, in general, the cooperation between different healthcare professionals for the care of each patient with dementia is still limited, and community-based organizations are currently inadequately incorporated into the healthcare system [34,43].

In this regard, research has shown that telemedicine may significantly enable interdisciplinary dementia care [86,87,91–93]. In particular, a Pittsburgh-based telemedicine program for dementia care, including a geriatrician, geriatric psychiatrist, psychologist, social worker, and nurse manager, was highly acceptable and successful fur rural areas [74]. In a Tennessee-based program, specialists recommended referrals to social workers [76], as well as the use of long-term care services in almost two-thirds of the telemedicine visits [62].

This evidence suggests that telemedicine offers a significant opportunity for appropriate referrals to other services and useful consultation regarding decisions for long-term care. A study among patients with poor socioeconomic status and limited access to care has shown that the incorporation of a nurse practitioner-led mobile memory clinic into the general practice was feasible and acceptable [94]. Telemedicine can also aid in the assessment and management of psychotic symptoms of patients with neurodegenerative disorders in long-term care facilities [95]. In addition, specialists at different organizations and regions can easily connect to a telemedicine video conference and offer their expertise in a feasible and effective way, thereby contributing to the provision of integrated and holistic care.

Apart from direct physician–patient care, telemedicine also allows telerehabilitation for patients with AD dementia, frontotemporal dementia, and mild cognitive impairment [96–99]. Computerized cognitive training among patients with or at risk for dementia has been shown to be effective [100–102]. In particular, speech therapy has been proven effective in primary progressive aphasia [103] and alexia [104]. Virtual reality for patients with dementia has been associated with reduced neuropsychiatric symptoms such as depression and agitation [105], apathy [106], as well as improved quality of life [107]. Tele-exercise programs through video conferencing have been proven feasible and acceptable [108], as well as possibly effective in enhancing physical activity in patients with AD and their caregivers [109]. Therefore, telerehabilitation services may be integrated into dementia care and can be beneficial for patients in remote areas where these in-person facilities are lacking.

Furthermore, several studies have indicated that video-based caregiver support for stress, education, and training in managing patients' behavioral symptoms is feasible and effective [110–127]. Remote cognitive behavioral therapy for the care givers of patients with AD for the enhancement of their physical or mental health [128] and for insomnia treatment [129] can also be effective. Most caregivers are satisfied with the FamTechCare service, which provides tailored expert feedback based on video recordings [130]. Telemedicine can also effectively educate caregivers about dementia management [52]. On the other hand, the subjective burden levels of the caregivers have not been significantly affected by a telehealth-based intervention in another study [131]. Furthermore, assistive technology and telecare were not associated with reduced caregivers' burden [132]. Therefore, telemedicine allows for a more holistic approach to dementia care by integrating various services, healthcare professionals, and facilities in a feasible way. However, the partially contradictory results highlight the need for further studies that could aid in our deeper understanding of the long-term effects of remote care in patients with dementia and caregivers.

3.4.7. Efficiency

Telemedicine has been shown to be very convenient for patients and their family members. Compared to traditional in-person visits, telemedicine can provide more flexibility regarding the time of the visit and limit potential alterations in the patients' daily routine [7]. On the other hand, routine changes and removal from the familial home environment may cause distress and exacerbate behavior symptoms in dementia patients [60]. In this regard, telemedicine provides an efficient solution, allowing the assessment of the patient at home or the community clinic [78].

Telemedicine can significantly reduce traveled distance and time spent traveling compared to in-person visits [62,74,80]. During the COVID-19 pandemic, e-mail-based care for patients with dementia was proven feasible and effective [133]. The avoidance of unnecessary transportation, as well as the distance and time saved, benefit not only the patients but also their caregivers or family members that need to accompany them for the medical visits [83]. Importantly, telemedicine is beneficial for patients in advanced stages of dementia with mobility limitations, being bedridden or in a wheelchair, whose transportation is costly, stressful, laborious, and time-consuming [52,78]. Furthermore, telemedicine may reduce waiting time for appointments with specialists in the waiting room, resulting in higher convenience and less frustration [22].

Dementia care creates a significant economic burden for patients, families, caregivers, and healthcare systems [61]. Therefore, health policy planning and the development of cost-effective novel approaches are required. Telemedicine has also been shown to reduce the cost of medical visits [83]. The avoidance of unnecessary transportation and the reduction of travel time result in lower costs. In addition, there are free communication platforms available that can be utilized for telemedicine purposes after careful consideration of patients' data safety [33]. The reduction of emergency department visits and unnecessary hospitalizations may also be associated with lower public healthcare costs [22]. Another study showed that videoconferencing was cost-effective for dementia diagnosis, in case the specialist should drive for more than two hours in order to deliver in-person service [134]. The FamTechCare intervention aims to provide dementia specialists feedback to caregivers based on video recordings and is cost-effective compared to telephone support interventions [135]. However, another study demonstrated that a remote caregiver support intervention only resulted in short-term cost savings, which could not be maintained for one year [136]. Therefore, in many cases, telemedicine use is associated with lower costs for the patients, family members, and the health system, as well as higher resource savings, allowing for more cost-effective and efficient care.

4. Discussion

Collectively, a growing body of evidence suggests that telemedicine may be a reliable and valuable tool for the care of patients with dementia. Regarding effectiveness, telemedicine can improve the accessibility to specialized care, especially for patients living in remote and underserved areas. Dementia specialists can reliably and effectively evaluate patients, neuropsychological testing can be provided, appropriate treatment recommendations can be suggested, and unnecessary emergency visits and hospitalizations may sometimes be prevented. Through telemedicine, patients can receive earlier diagnosis since travel and waiting time for the evaluation by a dementia specialist can be reduced. Telemedicine can also offer personalized care for patients' and families' needs and preferences, as well as cultural and ethnic/racial diversities, thereby contributing to patient-centeredness and equitability. The interconnection with community resources, the multidisciplinary team approach, the use of telerehabilitation services, and support and education for caregivers may also allow for improved integrated care. Throughtelemedicine, the infection risk is limited, which is a crucial safety issue, especially during the COVID-19 pandemic. Increased user convenience and reduced cost are some additional benefits in terms of efficiency.

However, it is essential to note that the number of visits, the stages of dementia of the participants, and the structure and elements of telemedicine visits across the established programs for dementia are highly variable [6]. For example, some programs provide video-based telemedicine care at home, while others at regional health centers or community clinics. Some programs include in-person visits for initial assessment, neuropsychological testing, or obtainment of vital signs, while others do not. Technical assistance is not available in all such telemedicine programs. In some cases, telemedicine is used only for initial evaluation, while in other cases, this model of care is applied for follow-up of diagnosed patients [7]. Moreover, a healthcare facilitator, a nurse, or a local physician, whose contribution is important for the remote assessment, was not always present during the telemedicine visits in the abovementioned studies. In addition, a control group (i.e., being evaluated in face-to-face visits) was not always used in the abovementioned studies. In many studies, the reasons for not participating in telemedicine visits have not been examined, potentially resulting in selection bias. Further, inter-rater variability is also an important factor to consider when comparing face-to-face and telemedicine visits in case the rater or physician is not the same in both situations. Therefore, comparisons between existing telemedicine models of care are hard to make, and conclusions regarding the reliability of the examination or improvement of care should be drawn with caution.

The development of more appropriate methodological approaches to evaluate reliability, effectiveness, and efficiency is also needed.

Furthermore, most studies in telemedicine for dementia care are cross-sectional. Longitudinal studies are needed to investigate both the short-term and long-term effects of telemedicine on patients' and caregivers' outcomes compared to in-person visits [7]. Further, studies after the COVID-19 pandemic are also needed since the COVID-19 pandemic was characterized by specific conditions and challenges that may not be applicable to the period after the pandemic. Additionally, most studies have been conducted among well-educated individuals of high socioeconomic status. This limitation limits the generalizability of results to patients of lower socioeconomic backgrounds or educational levels [70]. Future research is needed in this direction, including participants from a wide range of socioeconomic statuses and levels of education. Furthermore, the low response rates regarding satisfaction among participants require caution since non-responding may be associated with lower satisfaction levels [70].

Although emerging literature evidence, including clinical trials, has demonstrated the value and promising potential of telemedicine services in dementia care, their implementation in daily clinical practice, dissemination, and effective incorporation into the health systems are still limited. For this purpose, alterations in healthcare policies are required. Funding opportunities and research grants for pilot activities in telemedicine are sometimes utilized, but the sustainability of these initiatives without continuous public support is often limited. Organizational, administrative, and technical challenges usually fall on the shoulders of primary care physicians, long-term care facilities, or caregivers without adequate support from the public health system [95]. Higher government investments and more active engagement by healthcare stakeholders, healthcare professionals, patients, and caregivers are required in this direction [33].

Regulatory issues and the absence of national legislation and reimbursement for telemedicine services in many countries is another important barrier that may prevent physicians from offering care remotely to their patients [151]. The lack of legal regulations regarding data privacy issues may also hinder the adoption of telemedicine by patients [52]. In the United States of America, licensure requirements may limit the provision of telemedicine dementia care across different states [7]. A study in Brazil indicated that physicians needed regulations to offer teleconsultations [152]. Online prescription, coverage, credentialing, medical malpractice, privacy, security, and fraud are some of the regulatory issues that need to be handled for the effective use of telemedicine services [22].

Currently, in most medical schools and residency neurology programs, physicians have no official training in telemedicine. The limited education of healthcare professionals in telemedicine serves as another obstacle to its broader application in the health systems. However, in this regard, the American Academy of Neurology has provided a published framework for developing a telemedicine educational curriculum for neurology residents [153].

Using a novel telemedicine care model may also initially receive significant resistance from patients, families, and caregivers, especially older individuals. Some studies have shown that patients perceive in-person care by primary care providers better than telemedicine visits [154]. Since primary care providers can largely influence their patients, they can discuss with them the benefits and restrictions of telemedicine, answer potential queries, discuss privacy concerns, and explain that telemedicine will not replace in-person care or limit their continuous contact with primary care providers, but rather provide an additional opportunity, thereby encouraging its future use [154]. Furthermore, blended approaches bringing together remote and in-person activities have been recommended as potential facilitators [33]. Another potential barrier to telemedicine is the fact that many individuals are unaware of the availability of telemedicine as an option, as well as the limited understanding among patients and family members about how to access telemedicine services [22,155]. Finally, ageism and stigma may also result in the de-prioritization of older individuals in telemedicine visits [156].

Access to the appropriate technological equipment, digital literacy, and the availability of an internet connection are also important issues to consider, especially in remote rural areas [157]. In the United States of America, it has been estimated that more than half of older individuals were not ready for video-based visits during the COVID-19 pandemic, mainly due to inexperience with technology [158]. The use of technical jargon for digital terms is also an obstacle, especially for the elderly [33]. The wide variability of the available telemedicine platforms may hinder the acceptability and eagerness of being trained to use them [33]. For older patients, in particular, it has been proposed that providing written detailed instructions on how to use telemedicine services may help in this direction [158]. Training older individuals in digital tools may also be beneficial [33], and the use of understandable terms is also very important [33]. Caregivers also suggest that one technological barrier is that older patients with dementia have limited ability to manage the equipment and engage in remote programs without assistance [159]. Cognitive impairment is associated with loweruse of technology in older individuals [160].

Low income and educational levels have been associated with inadequate access to digital technologies; hence, technical assistance should be provided, especially in these cases [161]. Furthermore, the younger caregivers' age has been associated with higher rates of the feasibility of telemedicine visits for patients with dementia [162], suggesting that the experience of the caregivers with technology plays an important role. Some potential solutions include providing technological equipment, such as tablets or laptops, as well as ensuring free internet access to all [33].

Older patients often have significant concerns regarding privacy and confidentiality, and the use of secure software is very important. It should be clearly explained to patients to show their medical data are securely transferred and shared, as well as who has access to them [33]. Until now, older individuals' views and perspectives have not been adequately included in the design of telemedicine interventions [163]. However, the development of age-friendly telemedicine services adapted to the needs of older patients is of paramount importance [33]. Patients' preferences, prior experiences, and perspectives that may affect technology acceptability have not been studied among individuals with cognitive impairment yet [70]. Future studies are needed in this direction since these factors may significantly affect the feasibility and acceptance of telemedicine services. In this context, a personalized assessment of the users' needs before the telemedicine visits could allow for adaptations regarding equipment, hearing, or visual impairment [70].

Apart from the patients, physicians may be skeptical about the use of telemedicine, and there is evidence showing that they may be less satisfied with telemedicine compared to patients [7]. Some healthcare providers are also not adequately familiarized with telemedicine platforms [33]. Primary care physicians are satisfied with telemedicine services for dementia [164,165]. However, there is also evidence showing that healthcare professionals may not recognize the benefits of telemedicine for older patients with complex conditions, including cognitive impairment, based on the assumption that these patients may not be able to understand the instructions and effectively participate in the remote visits [166,167]. Discussions with healthcare professionals about their concerns and the exploration of potential solutions to mitigate these concerns have been recommended [33]. The adherence of general practitioners to teleconsultations' recommendations for older individuals in nursing homes has been associated with depressive symptoms [168], suggesting that the psychological effects of telemedicine on general practitioners should also be considered and further investigated.

Interrupted or delayed internet connection may also create difficulties. It can also interfere with neurological examination, especially regarding the evaluation of movement disorders, such as bradykinesia and tremor, which are sometimes important for the differential diagnosis of dementia subtypes. The availability of an IT technician, the adoption of a timely and simple backup process in case of connectivity failure, and the use of the same platform for all remote consultations are practical solutions [33,169].

Hearing loss in older ages is prevalent in up to 90% of patients with dementia and often remains untreated [13]. Hearing difficulties may challenge cognitive assessment [13]. Visual impairment is also very frequent among patients with dementia, and it is estimated to affect up to 30% of this population [13]. Hearing and visual impairment restrict the use of telemedicine since it may hinder effective physician–patient communication, and the patients may have difficulties hearing or seeing the instructions or the stimuli of the neuropsychological tests via video [33,170]. However, attempts for technological adaptations to visual or hearing impairment in the telemedicine environment are limited [13].

Although the validity of several neuropsychological tests has already been investigated in telemedicine settings, more work is needed for specific tests for various dementia forms and different disease stages.

Apart from the care of patients with cognitive impairment, telemedicine may also facilitate prevention strategies, raising awareness about AD and other forms of dementia, cognitive screening, and the increased participation of patients in clinical trials, especially for screening and recruitment [52]. This is especially important for patients in remote areas with limited opportunities to engage in clinical trials, which are usually conducted in university hospitals and big cities.

"Even though this was not a systematic review, our aim was to provide, for the first time, an initial map of the potential role of telemedicine in the improvement of quality of healthcare for patients with dementia, based on the WHO dimensions. For this purpose, we critically discuss available literature evidence, highlighting gaps and potential challenges for future research in this field".

5. Conclusions

In summary, telemedicine is a reliable and valuable tool for the care of individuals with cognitive impairment in AD or related forms of dementia. It has the capacity to improve effectiveness, timeliness, patient-centeredness, integrated care, efficiency, and equitability. It gives the opportunity for increased access to specialized healthcare, especially for patients living in underserved remote areas. This opportunity allows for earlier diagnosis, appropriate treatment, and fewer visits to the emergency departments and hospitalizations. Moreover, telemedicine allows for a multidisciplinary treatment approach and can improve personalized care by focusing on patients' and families' needs, preferences, and cultural, ethnic, and racial diversities. It is associated with high satisfaction rates and increased convenience for users. It can also provide support for caregivers, connection with community resources, education of the patients, caregivers, and primary care physicians, as well as increased access of patients to clinical trials. Furthermore, telemedicine may result in reduced cost and unnecessary transportation and lower infection risk.

However, significant challenges include legislative and regulatory aspects, resistance from patients, caregivers, and physicians, ageism and stigma, limited education of physicians in telemedicine, digital illiteracy, technological equipment or internet connection issues, hearing or visual impairment, limited awareness regarding the availability of telemedicine services, and lack of sustained support from the public sector.

In this context, further attempts are needed to investigate and overcome relative barriers to the implementation of telemedicine in daily clinical practice. Nevertheless, telemedicine provides a very useful way to address the emerging need for better quality of care for patients with dementia worldwide, and the public sector should invest more resources in its successful integration into the health systems.

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Review

Plants, Plants, and More Plants: Plant-Derived Nutrients and Their Protective Roles in Cognitive Function, Alzheimer's Disease, and Other Dementias

Helen Ding, Allison B. Reiss, Aaron Pinkhasov and Lora J. Kasselman *

NYU Long Island School of Medicine, Mineola, NY 11501, USA; helen.ding@nyulangone.org (H.D.); allison.reiss@nyulangone.org (A.B.R.); aron.pinkhasov@nyulangone.org (A.P.)
* Correspondence: lora.kasselman@nyulangone.org

Abstract: *Background and Objectives:* Alzheimer's disease (AD) is the most common form of dementia, with the risk of developing it attributed to non-modifiable and modifiable factors. Currently, there is no cure for AD. A plant-based diet may protect against cognitive decline, due to the effects of plant-based nutrients such as vitamins, antioxidants, and fiber. The aim of the review is to summarize current literature on plant-based nutrients and their impact on cognition. *Materials and Methods:* A search was conducted on PubMed for clinical and murine studies, using combinations of the following words: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E, "beta carotene", "antioxidants", "fiber", "vitamin K", "Mediterranean diet", "vitamin D", and "mushrooms". *Results and Conclusions:* A diet rich in vitamin B and antioxidants can benefit the cognitive functions of individuals as shown in randomized clinical trials. Vitamin K is associated with improved cognition, although large randomized controlled trials need to be done. Fiber has been shown to prevent cognitive decline in animal studies. Vitamin D may contribute to cognitive health via anti-inflammatory processes. Several medical organizations have recommended a plant-based diet for optimizing cognitive health and potentially helping to prevent dementia.

Keywords: Alzheimer's disease; plant-based diet; B vitamins; antioxidants; vitamin K; fiber; cognition

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and accounts for 60–80% of all dementia cases [1]. AD impacts more than 40 million people worldwide, and the prevalence of AD doubles every five years after age 65 [2,3]. While there is a normal age-related decline in memory that does not impact activities of daily living, an accelerated decline that interferes with a person's quality of living is seen in Alzheimer's disease [4]. Alzheimer's disease is often preceded by a period of mild cognitive impairment (MCI) [5]. MCI is defined as cognition that is no longer normal relative to age expectations but does not interfere with activities of daily living, and it is reported that MCI affects more than 40% of the population over age 60 [6]. AD poses a significant burden to patients, namely the number of healthy years lost due to being in a state of disability as well as premature mortality [7]. AD also poses a burden to caregivers, with increased caregiver burden associated with severity of AD [8].

The onset of AD is predicted by multiple risk factors. Some non-modifiable factors include age, gender, and genetic susceptibility such as apolipoprotein E status [9]. The cause of AD is likely multifactorial and the current understanding of the pathophysiology underlying MCI and AD is still incomplete. The most widely studied theory of AD pathogenesis is the accumulation of neurotoxic extracellular beta-amyloid plaques, which are insoluble protein aggregates that are pathological hallmarks of AD [10]. While the pathogenesis of AD is still not fully understood, the main hypothesis is that beta-amyloid

plaques interact with microglia in a way that results in pro-inflammatory cytokines and reactive oxygen species, which contribute to neuronal damage [11]. Furthermore, continuously elevated levels of beta-amyloid cause activation of the innate immune system via microglia activation, which leads to an inflammatory cascade that may contribute to AD pathogenesis [12].

The failure of anti-amyloid therapies to change the course of AD in human trials has caused a shift in thinking about the etiopathogenesis of the disease [13–15]. Inflammation and oxidative stress may result in synaptic and neuronal loss via mechanisms independent of amyloid formation [16,17]. High levels of inflammatory markers are often present in AD patients, and these same markers are associated with cognitive decline [18]. In addition to increased inflammation, which may be toxic long-term, AD has been associated with mitochondrial dysfunction, with changes in mitochondrial processing resulting in increased oxidative stress [19]. Neurons are highly dependent on mitochondria, as they have a high metabolic demand. High levels of reactive oxygen species (ROS) can build-up as a result of mitochondrial dysfunction or an insufficient amount of antioxidants, which leads to oxidative stress [20]. Furthermore, increased ROS levels result in increased inflammatory markers, demonstrating the connection between oxidative stress and inflammation [21].

In addition to beta-amyloid proteins, the microtubule-associated protein tau has been heavily studied in its relation to Alzheimer's disease [22,23]. Tau proteins in AD are hyperphosphorylated, causing the proteins to stick together in neurofibrillary tangles inside neurons [24]. These tangles then interfere with chemical and electrical signaling between neurons, and disruption of this process can lead to dysfunctional synapses and neuronal death [25]. Mouse models of AD have also linked tau to beta-amyloid build-up, hypothesizing that abnormalities of tau phosphorylation contribute to the toxicity of beta-amyloid [26]. Beta-amyloid's effects on neurotransmitter levels is well-documented in current literature, with studies showing beta-amyloid enhancing glutamate uptake and inhibiting acetylcholine release [27–29].

Current pharmacological interventions for Alzheimer's disease aim to correct the neurotransmitter imbalances that likely result from tau protein build up and neuronal dysfunction [30]. Current FDA approved drugs to treat cognitive symptoms of AD are acetylcholinesterase inhibitors (AChEI) and a glutamate regulator, memantine. Acetylcholinesterase inhibitors increase levels of acetylcholine, a neurotransmitter important in memory, attention, and learning [30]. Memantine decreases levels of glutamate, which is thought to be involved in neurotoxicity seen in AD [4,31]. These two classes of drugs are only effective in treating AD symptoms, but do not prevent or cure it. Furthermore, AChEI drugs have shown low efficacy in improving cognition of patients with AD, and they are associated with multiple adverse effects, like diarrhea, nausea, vomiting, bradycardia, and syncope [32]. Given the arguable efficacy of AChEIs and their side effects, the risk-benefit relationship of the drug is unclear. Studies on memantine have unclear results, with some clinical trials demonstrating meager evidence of its treatment in AD [33,34]. The complexity of AD etiopathology makes it difficult to prevent and cure the disease. Furthermore, current medications attack downstream phenomena, like neurotransmitter imbalances, that do not directly address the build-up of beta-amyloid and tau proteins, oxidative stress, or inflammation that are hypothesized to drive AD progression [4,18,21,35]

Although there is no cure for Alzheimer's disease, individuals can reduce their risk for developing AD by targeting modifiable risk factors. There are several modifiable risk factors for AD, such as diabetes, obesity, smoking, and hypertension. Additionally, modifiable risk factors like physical activity and healthy diet decrease the risk of developing AD [36]. Recent research has supported a diet rich in fruits and vegetables to be associated with prevention and delay of cognitive impairment [37]. Plant-based diets have been shown to be rich in antioxidants, vitamins, and fiber. Antioxidants and vitamins protect against neuronal degeneration via their anti-inflammatory effects and prevention of oxidative stress. Specific plant-derived nutrients are associated with decreased MCI, namely vitamins B, K, C, E and beta-carotene, the latter three being antioxidants [38,39]. The current hypothesis on fiber's

role in cognitive impairment focuses on the gut–brain axis, with fiber promoting certain bacteria in the gut microbiome that influence brain health and neuroinflammation [40].

In this review paper, we will examine the evidence of plant-derived vitamins B, K, C, E, beta-carotene, and fiber and their roles in preventing or delaying cognitive decline, as seen in dementias like Alzheimer's disease. Though technically not a plant, mushrooms will be briefly reviewed with respect to vitamin D and its role in cognitive health. This review is not exhaustive of all the benefits that these nutrients offer. Given the high prevalence of MCI in the elderly population and the safety and cost effectiveness of diet-change, we hope that this paper will be an extension of the current evidence supporting plant-based nutrition as a tool to reduce the risk of Alzheimer's disease [41–43].

2. Materials and Methods

A search was conducted on PubMed for epidemiological, clinical, and animal studies using the following keywords with the Booleans "AND" and "OR" in different combinations: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E, "beta carotene", "antioxidants", "fiber", "vitamin K", "Mediterranean diet", "vitamin D", and "mushrooms". Only human studies were reviewed in the discussions of vitamin B, antioxidants, and vitamin K interventions, although murine models were used in the discussion of mechanism. Both human and murine models were reviewed in the discussion of fiber. Publications in languages other than English were excluded. This review prioritized larger and more recent publications.

3. Results

3.1. Vitamin B

The B vitamins are made up of eight water-soluble vitamins (B1, B2, B3, B5, B6, B7, B9, B12) that act as coenzymes in many catabolic and anabolic reactions. The B vitamins' role in the brain includes synthesis of neurochemicals and production of methyl groups, which are necessary for DNA/RNA formation and repair [44]. Human epidemiologic studies have focused on the cognitive health benefits of vitamin B in the context of homocysteine metabolism [45]. Homocysteine is a risk factor for both cardiovascular disease and brain atrophy, and plasma homocysteine levels have been shown to be lowered with administration of vitamin B6, folate (vitamin B9), and vitamin B12 [45–47]. Vitamin B12 plays a role in the transformation of homocysteine to the amino acid methionine, and B6 and folic acid are necessary cofactors in that reaction [48].

3.1.1. Dietary Sources of Vitamin B

Most of the current literature on vitamin B and cognitive function focuses on vitamins B6, folic acid, and B12. As such, this review will focus specifically on these three subtypes, of which B6 is most bioavailable from plants. High levels of these B vitamin types have been related to higher cognitive performance, due to their homocysteine lowering effects [49]. Each of these types of B vitamins have different dietary sources, both plant and non-plant based.

The usual dietary sources of vitamin B12 are from animal products, such as meat, milk, fish, and eggs [50,51]. Vitamin B12 is synthesized by certain bacteria and archaea that are present in the gut of animals, but not in plants. After animals like cattle acquire B12 in their gut, the vitamin accumulates in tissue, which makes meat one of the best sources of B12 [52]. While vitamin B12 has been proposed to play an important role in Alzheimer's disease prevention, it is not plant-derived and as such would not be increased in a plant-based diet [53]. However, because current studies examine B12, B9, and B6 together, we still are discussing the role of B12 on cognitive function.

Folate is the natural form of vitamin B9, and folic acid is the synthetic form of folate that is found in fortified foods, like rice, pasta, and cereals. Natural folate is found in plant-based foods, particularly tropical fruits like mango and kiwi and green leafy vegetables, however folate has a lower bioavailability than synthetic folic acid [54,55]. The limited

bioavailability of folate is due to luminal factors like its destruction in the gastrointestinal tract and its absorption variability [56]. On the other hand, these factors do not impact the absorption of synthetic folic acid. Folic acid fortified foods have been shown to be up to two times more bioavailable than naturally occurring folate [56]. The various factors that impact naturally occurring folate absorption makes its bioavailability variable, and much of the dietary folate is from fortified non-plant foods [57].

Vitamin B6 is widely present in many foods, including meat, fish, beans, grains, fruits, and vegetables [58]. Its absorption in the intestine is via passive diffusion, which makes it rapidly absorbable [59]. A major source of vitamin B6 is through plants, specifically in chickpeas, potatoes, bananas, and squash [60]. Due to B6′s high bioavailability from plants, it is the B vitamin subtype that would be most implicated in a plant-based diet. Although B12 is solely derived from animal products, B9 can be found in some plant-based foods, such as beans and avocado. These foods also contain B6, although B6 is more rapidly absorbable than B9.

3.1.2. Vitamin B Interventions and Current Research

Of all the B vitamins, B6 is the most bioavailable subtype from plant foods. However, there is currently a lack of research focusing solely on B6′s role in cognition. Current research lumps B12, B9, and B6 together as they are cofactors in the metabolism of homocysteine, which has neurotoxic effects. As such, the studies in this section will not delineate between the various B vitamin subtypes.

Vitamin B6 is an important co-factor in the breakdown of homocysteine [61]. Elevated levels of homocysteine are a strong modifiable risk factor for vascular dementia and Alzheimer's disease [62,63]. High homocysteine levels are also associated with cognitive decline, brain atrophy, and neurofibrillary tangles [62]. A 2016 clinical trial by Cheng et al. found that supplementation of vitamin B improved cognitive function in patients with hyperhomocysteinemia [64]. This clinical trial found that daily vitamin B supplementation of 800 μg of folate, 10 mg of B6 and 25 μg of B12 resulted in improved cognitive function and reduced homocysteine levels after 14 weeks. Similarly, de Jager et al. found that patients with MCI had significant improvements in global cognition, episodic memory, semantic memory, and reduction in total homocysteine, with vitamin B treatment [65].

Another randomized control trial found no effect of vitamin B supplementation (2.5 mg folic acid, 0.4 mg B12, 25 mg of B6) on beta amyloid protein levels [66]. Total serum homocysteine correlated with plasma beta amyloid levels, and while participants in this study had significantly decreased homocysteine, there was interestingly no change in plasma levels of beta amyloid. This perhaps indicates that homocysteine and beta amyloid levels, while both related to cognitive decline, are regulated by independent measures. This RCT did not measure global cognition and memory [66]. Further studies examining homocysteine and amyloid-beta in patients with Alzheimer's disease are necessary to clarify their relationship to the disease progression.

A 2010 randomized controlled trial found that vitamin B6, B12, and folic acid supplementation decreased the rate of brain atrophy, a characteristic finding in individuals with MCI who later develop Alzheimer's disease [45].

A 2022 meta-analysis with a total of 95 studies and 46,175 participants found that B vitamins can slow cognitive decline, as measured by score changes in the Mini-Mental State Examination (MMSE) [67]. The interventional period had a significant impact, with B vitamin supplementation greater than 12 months resulting in significant MMSE changes but not so in intervention periods less than 12 months. Additionally, baseline cognitive status had an impact, as only the non-dementia population had slowed cognitive decline from vitamin B supplementation. This last point is contrary to the finding in the previously cited study performed by de Jager et al., which saw a significant benefit of vitamin B treatment in patients with MCI. A separate 2019 meta-analysis of 31 RCTs found no cognitive benefit from the homocysteine lowering effects of B vitamins [68]. Both meta-analyses focused solely on the MMSE as a way to quantitatively measure cognitive function. This ultimately

restricted them to examining only this one measurement tool. While encouraging that some studies did find vitamin B supplementation to slow cognitive decline, more trials are needed with a wider range of assessment tools to gain a more comprehensive view of the impact of vitamin B on cognition.

Current research on vitamin B supplementation and cognition has varied in the population sampled, cognition assessment tool, duration of intervention, and type of supplementation, providing only modest evidence to support the use of vitamin B supplementation in cognitive health or dementia. Additionally, there is still some question about the causality between homocysteine and cognitive levels. It is unclear whether increased total homocysteine levels cause cognitive impairment or if high serum homocysteine is a consequence of triggers that result from cognitive decline, such as poor diet and vitamin deficiencies [69].

Though the evidence is mixed on vitamin B supplementation and cognitive health, inadequate intake of dietary vitamin B is associated with accelerated cognitive decline [70]. Indeed, one community-based multi-center cohort study found that higher intake of vitamin B, including from dietary sources, correlates with higher cognitive function later in life [71], indicating an important protective role for plant-derived intake of vitamin B.

3.1.3. Vitamin B Mechanism

The benefits of vitamin B on cognitive function is related to the effects on homocysteine. The mechanism by which homocysteine detrimentally impacts brain health is still not fully known. However, it has been hypothesized that increased homocysteine levels result in oxidative stress, increased DNA breakage, decreased methylation of DNA, and dysregulation of its repair [72,73]. These neurotoxic effects are likely what lead to the accumulation of the beta-amyloid proteins and brain tissue atrophy seen in Alzheimer's disease. Homocysteine can be metabolized via two pathways, either degraded irreversibly or re-methylated to methionine [74]. Homocysteine's remethylation to S-adenosylmethionine is dependent on vitamins B12, B6 and folic acid [74]. Deficiencies in these B vitamins would prevent the metabolism of homocysteine, resulting in increased levels of homocysteine in the brain.

One consequence of this "homocysteine hypothesis" is that research has directed its focus on B12, folic acid B6, and not as much attention has been given to the other B vitamins. The impacts of the other B vitamins on cognitive function are, as a result, not as well understood. Additionally, it is difficult to determine the extent to which B6 specifically plays a role in cognitive health, as most clinical trials use a combined treatment of B12, folic acid, and B6.

Beyond its role as a necessary cofactor for the metabolism of homocysteine, B6 is also a cofactor in the synthesis of neurotransmitters [44]. Vitamin B6 has also been shown to have an impact on immune function. B6 levels have been inversely associated with systemic markers of inflammation, which is pertinent to note as inflammation contributes to pathologic states like cognitive decline and dementia [75,76]. Ultimately, further research exploring the mechanism of dietary B6 on brain health is necessary to better understand how this plant-derived vitamin can play a role in preventing cognitive decline.

3.2. Antioxidants: Vitamin C, Vitamin E, Beta-Carotene

Oxidative stress is one of the main factors implicated in neurodegenerative conditions like Alzheimer's disease [77]. Oxidative stress is defined as an imbalance between antioxidants and oxidants, with too much of the latter. The brain is particularly vulnerable to reactive oxygen species, due to its composition of easily oxidizable lipids and high oxygen consumption [77,78]. Mechanistically, reactive oxygen species may augment the production of beta amyloid proteins and the phosphorylation and polymerization of tau proteins, two proteins implicated in Alzheimer's disease pathology [79,80]. There is current evidence that oxidative stress can be decreased with the consumption of plant-based foods which are high in antioxidants, such as fruit and vegetables [81,82]. Measurements of antioxidant (vi-

tamins C, E, and beta-carotene) levels are higher in individuals on plant-rich diets, perhaps indicating dietary antioxidants as a promising prevention tool for Alzheimer's disease [83].

3.2.1. Dietary Sources of Antioxidants: Vitamins C, E, Beta-Carotene

Dietary sources of vitamin C and beta-carotene are from fruits and vegetables, and the main sources of vitamin E are through vegetable oils and nuts [9]. Since humans are unable to synthesize these antioxidants, they are fully obtained through dietary intake.

Vitamin C

The best food sources of vitamin C include citrus, kiwi, mango, peppers, tomatoes, and green leafy vegetables [84]. Vitamin C is a water-soluble vitamin, and around 90% of vitamin C daily intake in the general population is from diet, with 5–9 servings of fruit and vegetables estimated to equal 200 mg of vitamin C [84]. Vitamin C is absorbed mostly in the small intestine, through simple diffusion and active transport. In moderate intakes of 30–180 mg/day, vitamin C is absorbed at almost 90% [85].

Vitamin E

Vitamin E is found in fat-containing foods, and this fat-soluble property of vitamin E allows it to be stored in fatty tissue so it does not need to be consumed daily. The richest sources of vitamin E are from vegetable oils, although nuts, seeds, and green leafy vegetables also contain high amounts [86]. The benefits of vitamin E are dependent on other vitamins, such as vitamin C. There is a cooperative interaction between these two vitamins, with a combination of vitamin E and vitamin C having a stronger antioxidant effect than either alone [87]. The cooperativity between vitamin E and C may be due to the fact that vitamin C repairs vitamin E radicals, which are formed when vitamin E scavenges oxygen radicals [88].

Beta-carotene

Beta-carotene is a fat-soluble vitamin and is the most abundant precursor to vitamin A [89]. Dietary sources of beta-carotene include naturally orange and yellow foods such as carrot, tomato, pumpkin, and papaya [90,91]. The absorption of beta-carotene from plant sources is variable, ranging from 7 to 65% [92]. Dietary fat is one of the major factors that affects beta-carotene absorption, as beta-carotene itself is fat-soluble. A clinical trial showed that uptake of beta-carotene from raw vegetables in salads was significantly increased with the addition of dressings containing higher amounts of fat [93].

3.2.2. Antioxidants Interventions and Current Research

Current studies on supplemented vitamin E, C, and beta-carotene have conflicting results, indicating modest support for the use of supplementation in cognitive health. The Cache County Study, was a cross-sectional and prospective study of 5092 elderly participants, found that a combined use of vitamin E and C was associated with reduced Alzheimer's disease prevalence [94]. Similarly, the Rotterdam Study, a prospective study of 5393 participants free of dementia, concluded that high dietary intake of vitamin C and E may lower the risk of AD [95]. On the other hand, a prospective study from the Washington Heights-Inwood Columbia Aging Project did not find a decreased risk of Alzheimer's disease from vitamin C and E intake [96]. These differences in findings may also be due to chance, as the populations in the three studies were similar. The discrepancy points to the need for randomized trials examining the prevention of dementia with antioxidants.

Interestingly, a randomized clinical trial of 78 subjects found that supplementation of vitamin C, E and alpha lipoic acid led to decreased MMSE scores, even with decreased oxidative stress biomarkers in the CSF [97]. An RCT by Lloret et al. had a similar finding, where vitamin E was detrimental to cognition in some patients [98]. However, both these studies had a small sample size (n = 78, 57), and this finding has not been confirmed in larger RCTs. A study of 613 patients demonstrated that in patients with mild to moderate Alzheimer's disease, vitamin E supplementation compared to the placebo resulted in slower

cognitive decline [99]. This suggests that vitamin E may have a benefit in slowing disease progression in individuals with Alzheimer's disease. Additional clinical trials focused on dietary intervention and not supplementation may provide additional evidence of vitamin E's role in slowing cognitive decline in dementia.

A study by Grodstein et al. found that beta-carotene supplementation had no significant impact on cognition in the short term, but was associated with better verbal memory and overall better global cognitive scores in the long-term [100]. A cross-sectional study found that plasma vitamin C and beta-carotene were significantly lower in individuals with dementia as compared to the control group [101]. While promising that studies have found a positive association between supplemental vitamin C and beta-carotene and cognitive function, the evidence is not strong so more longitudinal studies with larger sample sizes are needed to confirm these effects.

Though the evidence is mixed on antioxidant supplementation and cognitive health, several cross-sectional and cohort studies looking at dietary antioxidant intake and cognition found associations between high food-based intake and better cognitive performance, though other dietary studies did not find similar results [102–106]. However, this may indicate that consuming dietary antioxidants, found in plant-based foods, may support cognitive health.

3.2.3. Antioxidants Mechanism

Antioxidants inhibit cellular damage by donating an electron to reactive oxygen species, effectively neutralizing them and reducing their ability to create damage [107]. The vitamin antioxidants include vitamin E, vitamin C, and beta-carotene [108]. As the body cannot manufacture these antioxidants, it is important to have a diet rich in these nutrients.

Vitamin C is a reducing agent and can neutralize ROS such as hydrogen peroxide, making it neuroprotective against oxidative damage [109]. Imbalance in vitamin C has been linked to neurodegeneration [110]. In addition to its ability to reduce free radicals, vitamin C acts as a first-line antioxidant by promoting regeneration of other antioxidants such as glutathione and vitamin E [111]. The neuroprotective effects of vitamin C are also due to its mitigation of neuroinflammation and suppression of beta-amyloid proteins [112]. In murine models, administration of vitamin C reduced pro-inflammatory cytokines TGF-alpha and IL-1beta as well as ROS [113]. High doses of vitamin C have also been shown to reduce the amount of amyloid plaques in murine models of Alzheimer's disease [114].

Vitamin E is the major lipid-soluble component of the cell antioxidant defense system [86]. Vitamin E is made up of eight tocopherols and tocotrienols, which are fat-soluble antioxidants. Of these eight, the most highly studied is alpha-tocopherol due to its bioavailability [115]. Vitamin E is located primarily in the cell and organelle membranes and acts as the first line of defense against lipid peroxidation, the process where free radicals degrade the lipid membrane [86,116]. In Alzheimer's disease, beta amyloid proteins induce oxidative stress which results in protein oxidation and lipid peroxidation, which negatively affects cell signaling and cell membranes [117,118]. Vitamin E can block the production of oxidative species, which decreases the amount of toxicity induced from beta amyloid proteins. Murine models have shown an association between vitamin E deficiency and expression of genes involved in regulation of beta amyloid proteins [119]. Furthermore, tocopherol and tocotrienols have been shown to have an inhibitory effect on enzymes that contribute to neuroinflammation in Alzheimer's disease [120].

Beta-carotene acts synergistically with other carotenoids in cell and organelle membranes to inhibit lipid peroxidation. One study observed a synergistic cooperativity between beta-carotene and vitamin C in a mechanism similar to that of vitamins B and C, with vitamin C repairing the beta-carotene radical [121]. The benefits of beta-carotene may also be due to its inhibition of acetylcholinesterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine. Acetylcholine has many functions in the central nervous system, including alertness, learning and memory, and wakefulness [122]. Lower cholinergic function is involved in severity of cognitive dysfunction, and studies have

shown that acetylcholinesterase inhibiting drugs treat cognitive symptoms of Alzheimer's disease [123]. Beta-carotene was found to inhibit AChE in murine models of Alzheimer's disease, indicating its ability to potentially attenuate cognitive deficits via its antioxidant effects and inhibition of acetylcholinesterase [38].

3.3. Vitamin K

Recently, there has been an increased body of evidence that suggests vitamin K has a role in brain physiology [124]. Vitamin K is a fat soluble vitamin that, in addition to its role in blood coagulation, is involved in the metabolism of sphingolipids, a class of lipids involved in the proliferation of brain cells and neuron myelination [124,125]. In addition to its role in brain cell development, vitamin K has been proposed to exert an anti-inflammatory and anti-apoptotic effect in the nervous system [126]. There are two main forms of vitamin K: vitamin K1 (phylloquinone) and vitamin K2 (menaquinone), with the main source of vitamin K1 from green, leafy vegetables and vitamin K2 from animal-based foods, fermented foods and synthesis by gut microbiota. Given that vitamin K2 is from animal sources and that very little is still known about it, we will primarily be examining research on vitamin K1.

3.3.1. Dietary Sources of Vitamin K

Phylloquinone (vitamin K1) is the major dietary source of vitamin K. It is obtained mainly from leafy green plants like spinach and collards. Darker green colored leafy vegetables have higher concentrations of phylloquinone than paler green vegetables, like iceberg lettuce. Green, leafy vegetables contribute approximately 60% of phylloquinone intake [127]. Other plant sources of vitamin K1 include plant oils like soybean, olive, and canola [128].

Menaquinones (vitamin K2) are the product of bacterial fermentation or from the conversation from dietary phylloquinone [129]. Natto, a Japanese soybean dish that is fermented with *bacillus subtilis*, is one of the plant foods highest in vitamin K2 [130]. There is still very little known about the contribution of dietary menaquinones to overall vitamin K levels.

3.3.2. Vitamin K Interventions/Current Research

Studies have shown associations between reduced vitamin K levels and poor cognitive function, however there is still yet to be randomized controlled trials exploring the benefits of vitamin K supplementation on brain health. Multiple small epidemiological studies have examined the relationship between vitamin K, as estimated by food questionnaires, direct measurement of serum vitamin K by high-performance liquid chromatography, and indirect measurements of vitamin K via dephosphorylated uncarboxylated Matrix Gla protein. These epidemiological studies add to evidence that vitamin K may play a promising role in cognitive health [131].

One of the larger cohort studies of 500 participants found that both dietary and serum phylloquinone were strong independent predictors of good cognitive function [132]. These results are in line with murine studies, which have shown vitamin K to have a positive effect on cognition and memory [133,134]. Randomized controlled trials are needed to further explore the relationship between low levels of vitamin K and cognitive decline, but this preliminary evidence supports the potentially protective effect of consuming vitamin K-rich foods on cognitive health.

3.3.3. Vitamin K Mechanism

In recent years, research has shown that vitamin K has an anti-apoptotic and anti-inflammatory effect, specifically mediated by the activation of growth arrest specific gene 6 (Gas-6) and Protein S [135]. Gas-6 is a vitamin K-dependent protein that has a key role in the development of the nervous system and has anti-apoptotic and myelinating activity in neuronal and glial cells [135]. Murine studies have shown Gas-6 to protect hippocampal

neurons from apoptosis [136]. Gas-6 has also been found to decrease beta-amyloid induced apoptosis by inhibiting the voltage-gated calcium influx that results in neurotoxicity [137]. Given that beta-amyloid accumulation is a characteristic feature of Alzheimer's disease, this suggests that vitamin K-dependent Gas-6 may be directly protective for Alzheimer's disease [137].

Protein S is another vitamin K-dependent protein, and in recent years it has been shown to confer neuronal protection during ischemic injury [138]. Ischemic brain injury has been associated with increased deposition of folding proteins, like the amyloid proteins implicated in Alzheimer's disease, and some research has even proposed that post-ischemic brain injury may result in Alzheimer's disease due to the generation of reactive oxygen species [139]. While Protein S does not seem to have the directly protective mechanisms that Gas-6 does, it is likely still beneficial due to its neuroprotective effects.

Currently, clinical studies investigating the role of vitamin K2 and Alzheimer's disease are lacking. However, in mouse studies, vitamin K2 levels were shown to suppress ROS and decrease the upregulation of proinflammatory cytokines induced by lipopolysaccharides [140]. This suggests that K2 may have some role in reducing neuroinflammation and neurodegeneration. Recent research has focused on the role of the gut microbiome in brain health, with dysbiosis of the gut microbiome linked to poor cognitive health [141,142]. This bidirectional communication between the brain and gut is also known as the "gut–brain-axis". Dysbiosis has been shown to negatively impact vitamin K production [141]. Given the link between the gut microbiome and Alzheimer's disease pathogenesis, it is important to further explore the connection between dysbiosis, vitamin K2 and Alzheimer's disease.

3.4. Vitamin D

Vitamin D is a fat-soluble vitamin that plays an essential role in calcium homeostasis and bone growth [143]. In addition to its role in bone growth, vitamin D has vital roles in neurodevelopment [144]. Vitamin D can cross the blood–brain barrier, and calcitriol, the active form of vitamin D, binds to vitamin D receptors (VDR) which are found throughout the brain [145,146]. The presence of high VDR in the human brain during development may indicate vitamin D's role in neurodevelopment [146]. Vitamin D is primarily synthesized in our skin, in the presence of sunshine. However, for many populations, the main source of vitamin D is through food, such as fatty fish, egg yolks, mushrooms, and foods fortified with vitamin D, and supplements [147]. In this review, we will primarily focus on mushrooms, which are not plants but fungi with a plant-like form [148].

3.4.1. Dietary Sources of Vitamin D

A large number of studies have shown that many countries have suboptimal vitamin D levels, mainly due to lack of sunshine. The main dietary source of vitamin D is from fatty fish, like tuna, mackerel and salmon. Mushrooms that are sun-dried and UV radiation-exposed are also a good source of vitamin D, particularly for vegetarians [149]. While technically a fungus, mushrooms are commonly considered a vegetable in the culinary setting [148]. When exposed to sunlight, the ergosterol that makes up the cell walls of mushrooms is converted into vitamin D [149]. Fresh mushrooms exposed to UV radiation have shown to have high bioavailability of vitamin D, with a 100 g serving of mushrooms providing more than half of daily requirements of vitamin D [150].

3.4.2. Vitamin D Interventions/Current Research

In a large meta-analysis of 1658 adults without dementia, vitamin D deficiency was shown to be associated with a significant risk of developing dementia [151]. Similarly, in a case–control study, participants with MCI and AD had significantly lower levels of vitamin D compared to healthy participants [152]. These findings are promising as they show that vitamin D may play a role in non-skeletal health.

However, despite these findings, the causal relationship between vitamin D and dementia cannot be confirmed as interventional studies have shown mixed results. A small

double-blind placebo-controlled clinical trial showed that a twelve-month supplementation with vitamin D led to improved cognitive function, however a larger double-blind placebo-controlled clinical trial showed that three year supplementation of vitamin D did not improve cognition [153]. Ultimately, while deficient levels of vitamin D are linked to cognitive dysfunction, there is not enough evidence to recommend supplementation of vitamin D to prevent cognitive impairments. More studies, particularly food studies, are needed to examine the relationship between vitamin D and cognitive health.

3.4.3. Vitamin D Mechanism

The effects of vitamin D are via the binding of vitamin D to an intracellular vitamin D receptor (VDR), which results in the inhibition or transcription of vitamin D-dependent genes [154]. VDR has been shown to be in the brains of humans, rats, mice, and zebrafish [155–157]. Given the temporal nature of VDR expression in both mouse and rat brains, it is hypothesized that vitamin D may be important in the differentiation of various cell types in neurodevelopment [144]. Furthermore, rat models have shown that rats born to vitamin D deficient mothers exhibit gross brain morphology and a reduction in nerve growth factor [158].

Vitamin D also may decrease neuroinflammation, due to its antioxidant potential. A rat study showed that vitamin D can increase the levels of glutathione and inhibit inducible nitric oxide synthase (iNOS), both of which reduce the toxicity to neurons [159]. iNOS produces nitric oxide, which is damaging to neurons and oligodendrocytes [160]. By inhibiting iNOS, vitamin D may prevent neuronal damage.

3.5. Fiber

Dietary fiber is made up of non-digestible carbohydrates that come from plant foods. Fiber intake has been shown to be associated with lower cholesterol, lower risk of heart disease, enhanced glycemic control, and better gastrointestinal function [161]. There are two main categories of fiber: soluble and insoluble. The main sources of soluble fiber are from fruits and vegetables, and the main sources of insoluble fibers are from whole-grains. Most high-fiber foods have a combination of soluble and insoluble fibers [162]. It is suggested that adults should eat between 20 to 35 g of dietary fiber daily [163].

3.5.1. Fiber and Its Impact on the Gut Microbiome

Dietary fiber is not broken down by human digestive enzymes but is fermented by gut bacteria, giving rise to short-chain fatty acid (SCFA) metabolites. Acetate, propionate, and butyrate are the primary SCFA products [164]. Recent research has shown SCFAs to have anti-inflammatory effects via modulation of the production of pro-inflammatory cytokines [165,166]. In addition to fiber having immune-modulating effects by production of SCFAs, certain fibers stimulate the immune system directly by interacting with immune cells [167].

Dietary fiber can also influence the composition of bacteria in our gut. Some dietary fiber is classified as prebiotic, which means it is a selective food source for beneficial gut bacteria which stimulates the favorable growth of good gut bacteria, like *bifidobacteria* and *lactobacilli*, while reducing the growth of pathogenic bacteria, like *clostridium* [168,169].

Recently, there has been growing interest in the gut–brain axis. The gut–brain axis is the bidirectional communication between the central and enteric nervous system. Studies have explored the impact of the gut microbiome on cognitive functions. There is emerging showing that the gut microbiota influences levels of anxiety, depression, and autistic behavior [170,171]. Dysbiosis, or an imbalance of the gut microbiome, has also been associated with mood disorders [172]. Studies on germ-free mice have shown how the composition of gut bacteria impacts the expression of neurotransmitters in both the central and enteric nervous system, stress and anxiety, and memory [173,174]. While the importance of dietary fiber on microbiome health has been established, there is still research that needs to be done on the connection between fiber and cognition, likely with the gut–brain axis as a

conduit. Additional research on the connection between dietary fiber and cognition may elucidate how plant-based diets rich in fiber may play a role in preventing the progression of Alzheimer's disease.

3.5.2. Mechanism of Fiber's Impact on Cognitive Function

While the importance of dietary fiber on gastrointestinal health and metabolism is well established, there is still research that needs to be done examining the impact of fiber on brain processes. The gut–brain axis has emerged as a key communicator between nutrition and the brain. Both microbiota-dependent and microbiota-independent effects of dietary fiber on cognition have been hypothesized.

Independent of the gut microbes, dietary fiber can promote the tight junction protein assembly in the gut, thereby promoting intestinal integrity [175]. A tight gut lining is important as loss of this integrity allows for harmful molecules like lipopolysaccharides (LPS) to enter the bloodstream, which can trigger systemic inflammation and neuroinflammation [176]. Furthermore, widespread inflammation can lead to the breakdown of the blood–brain barrier, which plays a key role in neurodegenerative disorders like Alzheimer's disease [177].

There are multiple microbiota-dependent pathways by which fiber may influence cognition. One way that fiber may communicate with the brain is by production of SCFAs. SCFAs positively impact the intestinal barrier and modulate the immune system in the gut. Outside the gut, SCFAs may also increase the integrity of the blood–brain barrier [178]. Additionally, prebiotic fiber results in the growth of beneficial gut bacteria like *Bifidobacterium* and *Lactobacillus*, which may influence cognition. Animal studies have shown correlations between certain good gut bacterial species and levels of brain-derived neurotrophic factor (BDNF), a key molecule in memory formation [179]. The production of neurotransmitters can also be influenced by bacterial species like *Lactobacillus* [180]. It is likely that there are multiple microbiota-dependent impacts of dietary fiber on cognition via anti-inflammatory effects of SCFAs and the growth of beneficial bacterial species.

Lastly, dietary fiber may benefit cognition by way of the vagus nerve. The vagus nerve may be activated by certain microbe species and SCFAs [181]. Vagal stimulation is beneficial to cognition as it stimulates BDNF expression and may be associated with improved memory, as shown in one human study [182,183].

3.5.3. Fiber Interventions and Current Research

The importance of a healthy diet and mental health has long been appreciated, with large cohort studies showing an association between a healthy diet and better mental health as well as improved executive functioning [184–186]. For example, the Mediterranean diet, which is rich in fiber, has been associated with reduced cognitive decline [187,188]. On the other hand, poor diets with increased intakes of processed foods have been associated with decreased executive functioning [189]. While there is growing knowledge on the impact of diet and cognition, it is unknown how much of these benefits can be associated specifically with dietary fiber.

Currently, most studies on fiber and cognition use animal models. As such, we will mainly be analyzing what we know from murine models. A study by Matt et al. found that both butyrate and dietary soluble fibers were associated with improved neuroinflammation. The study found that mice that were fed a high fiber diet had a changed microbiome and increased production of total SCFA production, particularly butyrate. The mice on the high fiber diet also had decreased expression of pro-inflammatory genes and less inflammatory microglial phenotypes [190]. The results of this study confirmed the results of previous murine studies, where butyrate, a SCFA increased in high-fiber diets, attenuated pro-inflammatory cytokines in microglia [191,192].

Murine models have also focused on the role of fiber in the gut–brain axis. A study by Shi et al. showed that fiber-deprived diets resulted in dysbiosis, which was significantly associated with cognitive deficits, reduced SCFA, and damaged hippocampal proteins [191].

Furthermore, microbiome changes were observed before cognitive impairment in mice with fiber deprived diets, perhaps indicating a causal impact of the gut microbiome on cognitive changes. Another study found that beta-glucan, a soluble fiber found in oats and barley, prevented cognitive impairment induced by a high-fat, fiber-deficient diet (HFFD) [193]. The HFFD resulted in microbiota changes, and even after a short-term beta-glucan supplementation of 7 days, there were microbiota changes before cognitive improvement, similar to the study by Shi et al.

Human studies have found positive associations between dietary fiber and cognition. One study analyzed data from the US National Health and Nutrition Examination Survey (NHANES) between 2011 and 2014, with a cohort of 1070 older adults, and found dietary fiber positively associated with some components of cognitive function, like word recall, word learning, attention, and language [194]. A smaller cross-sectional study of 65 children showed that dietary fiber was correlated with cognitive performance [194]. Similar results were found in a study with elderly subjects, aged 65 and older [193].

One small randomized control trial of 18 healthy female participants showed moderate increases in cognitive performance and increases of the beneficial microbe *Ruminoclostridium* with a four week supplementation of polydextrose, a dietary fiber [195,196]. This could indicate fiber's role in modulation of cognition via the gut–brain axis. One clear limitation to this RCT is small sample size. While promising to see positive results in this study, more and larger clinical trials are needed to better interpret the connection between fiber and cognition. Additionally, larger studies with participants exhibiting cognitive decline are needed to investigate the benefits of fiber in dementia, like Alzheimer's disease.

3.6. Discussion

Alzheimer's disease is the most common form of dementia that is associated with high mortality and morbidity. Several non-modifiable risk factors contribute to the risk of developing Alzheimer's disease, including older age, genetic polymorphisms, and family history. Multiple non-modifiable risk factors include hypertension, obesity, diabetes, and hypercholesterolemia.

Recently, there has been increased research on the role of dietary and lifestyle factors, such as plant-based diets, and Alzheimer's disease. Diet seems to play a role in cognition, which suggests that prevention strategies may be possible for Alzheimer's disease. However, there are still discrepancies between study results, and the lack of long-term clinical trials means definitive conclusions cannot be made. Conflicting results between studies may be due to various factors, such as differences in stage of disease, nutrient measurement techniques, age, and cognition measurement tools, though interestingly one study comparing people consuming animal products to those following vegetarian diets found an increased likelihood for dementia in the meat-eating population, indicating a potentially protective role for plant-based food in the diet [197]. More long-term, large-scale interventions are needed to shed light on the role of plant-derived nutrients and Alzheimer's disease, to help elucidate the complex pathogenesis of Alzheimer's disease and to explore how dietary changes can prevent and even treat disease.

The national USDA guidelines for a healthy plate of food recommends at least 1/2 plant foods (fruits and/or non-starchy vegetables) [198]. Furthermore, multiple national organizations promote plant-based diets. The American Medical Association (AMA), the oldest and largest American physician advocacy group, recently passed a resolution for hospitals to provide plant-based meals and to remove processed meats [199]. This resolution is backed by numerous studies that show the ability of plant-based diets to prevent and even reverse chronic conditions. Both the Alzheimer's Association and the Physicians Committee for Responsible Medicine recommend vegetables, fruits, and whole grains in the prevention of Alzheimer's disease [200,201]. More specifically, the National Institute on Aging states that the MIND (Mediterranean—DASH Intervention for Neurodegenerative Delay) diet may reduce risk of Alzheimer's disease [202]. Table 1 below shows the MIND diet's plant-based food recommendations and their corresponding nutrients from this

review. Finally, the WHO guidelines recommend a Mediterranean diet to reduce the risk of cognitive decline or dementia, as is might help and does not harm, but conclude that vitamins B and E, polyunsaturated fatty acid, and multicomplex supplementation should not be recommended [203].

Table 1. MIND diet recommendations and corresponding plant-based nutrients.

MIND Diet Recommendation	Serving Recommendation	Plant-Derived Nutrients	Brief Summary of Benefits of Plant-Based Nutrients, as Described in This Review
Leafy green vegetables	At least 1 serving/day	Vitamin B9, Vitamin K	Vitamin B9: Metabolism of homocysteine Vitamin K: Anti-inflammatory and anti-apoptotic effects in the nervous system. Vitamin K is involved in the metabolism of lipids involved in the proliferation of brain cells and neuron myelination.
		Vitamin C	Vitamin C: Decreases oxidative stress, which is associated with the beta amyloid and tau proteins implicated in AD. Vitamin C also promotes the generation of other antioxidants which results in decreased neuroinflammation.
		Vitamin E	Vitamin E: Decreases oxidative stress, which is associated with beta amyloid and tau proteins. Vitamin E prevents degradation of the cell membrane and may have an inhibitory effect on the enzymes that result in neuroinflammation.
All other vegetables	At least 2 servings/day	Beta carotene	Beta carotene: Decreases oxidative stress, which is associated with beta amyloid and tau proteins. Beta-carotene is associated with increased acetylcholine levels, a neurotransmitter that is important in learning and memory.
		Vitamin B6	Vitamin B6: Metabolism of homocysteine, which is detrimental to brain health. B6 may also play a role in the synthesis of neurotransmitters and is associated with decreased inflammation.
Berries	At least 2 servings/week	Vitamin C	Vitamin C: Decreases oxidative stress, which is associated with the beta amyloid and tau proteins implicated in AD. Vitamin C also promotes the generation of other antioxidants which results in decreased neuroinflammation.
		Fiber	Fiber: Multiple microbiota-dependent and microbiota-independent mechanisms, including fiber's modulatory effects on the gut–brain axis, promotion of beneficial gut bacteria, and decreased neuroinflammation by support of the gut lining.
Whole grains	At least 3 servings/week	Fiber	Fiber: Multiple microbiota-dependent and microbiota-independent mechanisms, including fiber's modulatory effects on the gut–brain axis, promotion of beneficial gut bacteria, and decreased neuroinflammation by support of the gut lining.

Table 1. *Cont.*

MIND Diet Recommendation	Serving Recommendation	Plant-Derived Nutrients	Brief Summary of Benefits of Plant-Based Nutrients, as Described in This Review
		Vitamin B9	Vitamin B9: Metabolism of homocysteine, which is detrimental to brain health.
Beans	3 servings/week	Vitamin B6	Vitamin B6: Metabolism of homocysteine, which is detrimental to brain health. B6 may also play a role in the synthesis of neurotransmitters and is associated with decreased inflammation.
		Fiber	Fiber: Multiple microbiota-dependent and microbiota-independent mechanisms, including fiber's modulatory effects on the gut–brain axis, promotion of beneficial gut bacteria, and decreased neuroinflammation by support of the gut lining.
Nuts	5 servings/week	Fiber	Fiber: Multiple microbiota-dependent and microbiota-independent mechanisms, including fiber's modulatory effects on the gut–brain axis, promotion of beneficial gut bacteria, and decreased neuroinflammation by support of the gut lining.
		Vitamin E	Vitamin E: Decreases oxidative stress, which is associated with beta amyloid and tau proteins. Vitamin E prevents degradation of the cell membrane and may have an inhibitory effect on the enzymes that result in neuroinflammation.
Olive oil	—	Vitamin E	Vitamin E: Decreases oxidative stress, which is associated with beta amyloid and tau proteins. Vitamin E prevents degradation of the cell membrane and may have an inhibitory effect on the enzymes that result in neuroinflammation.
		Vitamin K	Vitamin K: Anti-inflammatory and anti-apoptotic effects in the nervous system. Vitamin K is involved in the metabolism of lipids involved in the proliferation of brain cells and neuron myelination.
Mushrooms (not specifically recommended in MIND diet, but included in table to acknowledge vitamin D's role in cognition)	—	Vitamin D	Vitamin D: Binds to vitamin D receptor (VDR), which plays a role in neurodevelopment and nerve growth factors. Vitamin D may decrease neuroinflammation from increasing glutathione levels and inhibiting iNOS.

4. Conclusions

Research suggests that a plant-based diet is beneficial for cognitive health and may play a role in the prevention or mitigation of symptoms in Alzheimer's disease. Currently, it is not possible to establish a causal relationship between vitamin B, antioxidants, vitamin K, fiber, and vitamin D and the development of dementia. Organizations like the American Medical Association recommend plant-based eating habits, and the National Institute on Aging specifically recommends the MIND diet, which is rich in plant foods, for prevention of AD. Adopting a plant-based diet is a low-risk and beneficial lifestyle change to

address the maintenance of cognitive health and is potentially a method to help prevent cognitive decline.

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Review

Biomarkers for Alzheimer's Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation

Jeffrey Cummings * and Jefferson Kinney

Pam Quirk Brain Health and Biomarker Laboratory, Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas, Las Vegas, NV 89154, USA; jefferson.kinney@unlv.edu

* Correspondence: jcummings@cnsinnovations.com

Abstract: *Background and Objectives*: The US Food and Drug Administration (FDA) defines a biomarker as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Biomarkers may be used in clinical care or as drug development tools (DDTs) in clinical trials. The goal of this review and perspective is to provide insight into the regulatory guidance for the use of biomarkers in clinical trials and clinical care. *Materials and Methods*: We reviewed FDA guidances relevant to biomarker use in clinical trials and their transition to use in clinical care. We identified instructive examples of these biomarkers in Alzheimer's disease (AD) drug development and their application in clinical practice. *Results*: For use in clinical trials, biomarkers must have a defined context of use (COU) as a risk/susceptibility, diagnostic, monitoring, predictive, prognostic, pharmacodynamic, or safety biomarker. A four-stage process defines the pathway to establish the regulatory acceptance of the COU for a biomarker including submission of a letter of intent, description of the qualification plan, submission of a full qualification package, and acceptance through a qualification recommendation. Biomarkers used in clinical care may be companion biomarkers, in vitro diagnostic devices (IVDs), or laboratory developed tests (LDTs). A five-phase biomarker development process has been proposed to structure the biomarker development process. *Conclusions*: Biomarkers are increasingly important in drug development and clinical care. Adherence to regulatory guidance for biomarkers used in clinical trials and patient care is required to advance these important drug development and clinical tools.

Keywords: Alzheimer's disease; biomarkers; plasma; phospho-tau; amyloid; blood; neurofilament light; positron emission tomography; magnetic resonance imaging

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1. Introduction

Alzheimer's disease (AD) becomes increasingly common with aging, and the population of Americans aged 65 and older is projected to grow from 58 million in 2021 to 88 million by 2050 [1]. Five percent of people aged from 65 to 74, 13.1% of people aged from 75 to 84, and 33.2% of people aged 84 and older have AD dementia [1]. There are currently 6.5 million individuals with AD dementia in the United States, including 1.75 million aged from 65 to 74, 2.41 million aged from 75 to 84, and 2.31 million aged 85 and older [1]. In addition to those suffering from AD dementia, five million Americans manifest mild cognitive impairment (MCI) attributed to AD. AD is known to have a long pre-symptomatic phase that occurs before the onset of MCI. During this period, individuals have Alzheimer pathology changes in the brain that may eventually progress to a level of severity that induces cognitive, functional, and behavioral changes [2].

Progress in developing new treatments for AD has been limited. Five drugs were approved between 1993 and 2003, and aducanumab was approved in 2021. Symptomatic agents have modest clinical benefits in improving or delaying the emergence of cognitive, functional, and behavioral symptoms. They do not change the trajectory of the underlying

biology of AD. Aducanumab was the first disease-modifying therapy (DMT) to be approved by the US Food and Drug Administration (FDA). Other monoclonal antibodies are poised to be considered for approval. The goal of treatment with DMTs is to preserve the patients at the highest level of function for the longest time. Initiating treatment during the pre-symptomatic phase of AD is intended to forestall the onset of symptoms; administering DMTs in the MCI phase of AD targets delaying the emergence of AD dementia; using DMTs in the treatment of AD dementia attempts to delay progression, preserve function, and maintain patient quality of life for as long as possible. Biomarkers play a key role in AD drug development, and progress in advancing more therapies that modify the course of AD depends on success of identifying an expanded repertoire of AD-relevant biomarkers and applying emerging biomarkers in clinical trials [3]. These measures of biological activity assist in the diagnosis, risk assessment, efficacy measurement, and safety evaluation of DMTs. Development of new biomarkers is subject to substantial FDA oversight through defined regulatory pathways. In this perspective, we review emerging biomarkers relevant to DMT drug development and AD treatment. We describe the regulatory pathways for advancing biomarkers for their use in clinical trials and their implementation in clinical care. We emphasize blood-based biomarkers because they have the fewest obstacles to use in the clinical care setting.

2. Materials and Methods

The goal of this review and perspective is to describe the FDA guidelines for the development of biomarkers as used in clinical trials as drug development tools (DDTs) and as used in clinical care. We identified the major relevant FDA guidances that present the definition of a biomarker, key requirements for biomarker qualification, and the development of companion biomarkers, in vitro diagnostic devices (IVDs), and laboratory developed tests (LDTs) for use in clinical care. Biomarkers for Research Use Only (RUO) are also regulated and subject to FDA oversight. We present examples of the application of these guidelines in the development of biomarkers for AD clinical trials and AD care.

3. Biomarker Definition and Classification

3.1. Biomarker Definition

The FDA defines a biomarker as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention [4,5].

3.2. Biomarker Classification

The FDA outlined the specific use of biomarkers in the Biomarkers, Endpoints and Other Tools (BEST) resource [5,6]. The BEST approach defines the following types of biomarkers: susceptibility or risk biomarkers, diagnostic biomarkers, monitoring biomarkers, pharmacodynamic biomarkers, predictive biomarkers, prognostic biomarkers, and safety biomarkers (Table 1).

3.3. Biomarkers in Alzheimer's Disease

All the BEST categories of biomarkers are represented in the evolving repertoire of biomarkers available for use in characterizing AD biology and pursuing AD drug development. The context of use (COU; discussed below) for a biomarker must be defined prior to application in a trial. Some biomarkers may be used in several ways in a clinical trial. For example, amyloid positron emission tomography (PET) might be used as a diagnostic biomarker to confirm the diagnosis of AD, as a monitoring biomarker serially collected in trials of anti-amyloid monoclonal antibodies, and as a pharmacodynamic biomarker employed as an outcome in support of disease modification in a trial [7]. Similarly, in AD research, fluorodeoxyglucose (FDG) PET can be used to establish normal brain metabolism in an unaffected individual, demonstrate a pattern of reduction in the metabolism of an

individual with AD, and measure a response to treatment that improves metabolism or reduces the rate of metabolic decline [8,9].

Table 1. FDA BEST classification of biomarkers use in drug development [5].

Biomarker	Measurement
Risk/susceptibility	Indicates the potential for developing a disease or medical condition in an individual who does not currently have a clinically apparent disease or medical condition
Diagnosis	Detects or confirms the presence of a disease or condition or identifies an individual with a subtype of the disease
Monitoring	Measured serially to assess the status of a disease or medical condition for evidence of exposure to a medical product or environmental agent or to detect an effect of a medical product or biological agent
Pharmacodynamic/response	Changes in response to exposure to a medical product or an environmental agent
Predictive	The presence or change in the biomarker predicts an individual or group of individuals more likely to experience a favorable or unfavorable effect from the exposure to a medical product or environmental agent
Prognostic	Identifies the likelihood of a clinical event, disease recurrence, or disease progression in patients with a disease or medical condition
Safety	Measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of a toxicity as an adverse event

Figure 1 shows the current landscape of fluid biomarkers available for use in AD drug development (those shown are not an exhaustive list; new biomarkers are evolving rapidly; not all biomarkers shown are in the same state of development and some have more supportive data for their COU than others).

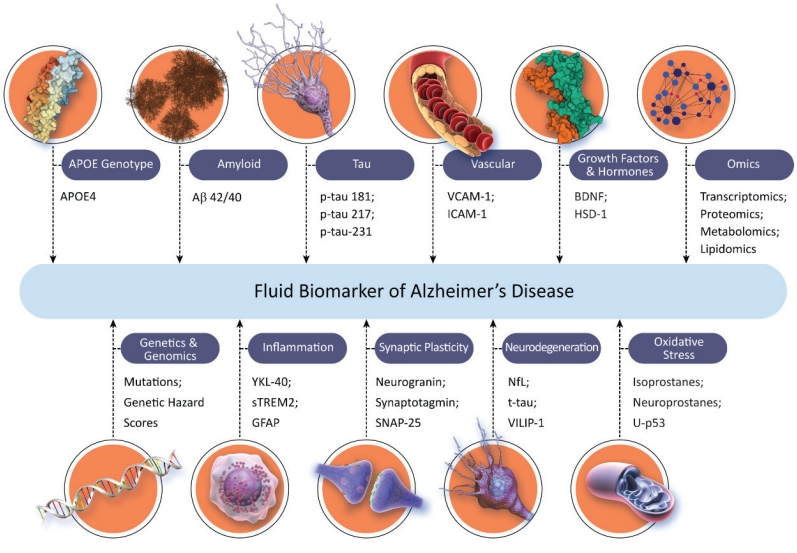

Figure 1. Landscape of fluid biomarkers for Alzheimer's disease (© J Cummings; illustrator M de la Flor, PhD).

The existence of a biomarker does not imply that it will be an acceptable measure of drug effects in a clinical trial. Factors such as abundance in the blood or cerebrospinal fluid (CSF), dynamic range, change over time, intra-individual variability, population variability, and preanalytical factors may influence the potential to use a biomarker in a multisite trial. Similarly, a biomarker for treatment response might not be abnormal at baseline but could represent an important target engagement measure if changed by the intervention. For example, brain amyloid plaque levels measured by standardized uptake value ratios (SUVR) might be normal at baseline in a primary prevention trial and delaying the increase in SUVR could represent a trial outcome indicative of success in ameliorating amyloid accumulation.

Biomarkers are critically important in AD research and drug development because the brain cannot be directly interrogated, and tissue samples will rarely be available as they might be from tumor biopsies for use in oncology drug development. Biomarkers provide inferential evidence of pathological changes in the brain [10]. Fluid biomarkers are subject to metabolism and excretion influences like other metabolic products and drugs, and these affect the dynamics and measurement characteristics of peripheral biomarkers. Chronic kidney disease affects AD-related analyte excretion and is associated with higher levels of plasma biomarkers that could be mistakenly interpreted as indicative of AD [11]. Ethnic minority members often have higher levels of medical comorbidities, and these may affect biomarker levels and their interpretation [12]. Biomarkers collected from CSF are often more closely related to neuropathology than plasma biomarkers, and plasma–CSF discrepancies may reflect the peripheral processing of plasma biomarkers [13]. AD biomarkers have varying sensitivities for reflecting neuropathological findings, an observation that highlights the importance of collecting and reviewing more than one biomarker when using them as a basis for trial interpretation [14]. Biomarkers may be viewed as most clinically actionable when a positive or negative threshold can be defined. Such thresholds, however, have confidence intervals that condition their interpretation and a negative/positive read-out should be accepted with caution. An alternative is to define a high-confidence positive value, a high-confidence negative value, and an intermediate value where further assessment is warranted to interpret the biomarker or come to a clinical conclusion. An example of this strategy is the Amyloid Probability Score (APS) based on the plasma Aß 42/40 ratio, apolipoprotein E (APOE) genotype, and patient age that establishes thresholds for high, intermediate, and low likelihood of a positive amyloid PET scan [15].

3.4. Risk/Susceptibility Biomarkers

A risk biomarker indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or medical abnormalities [4–6].

The most influential risk biomarkers for AD are mutations associated with autosomal-dominant AD (ADAD). Pathologic mutations of the amyloid precursor protein (APP) gene, presenilin 1 (PS1) gene, or presenilin 2 (PS2) gene are fully penetrant and, if present, lead to AD in the mutation carrier [16,17].

Carriers of the APOE ∈4 (APOE4) gene are at increased risk for the development of AD. Noncarriers of this gene have a lifetime risk of developing AD of approximately 15%, individuals who are heterozygous for the APOE4 gene have a lifetime risk for AD of approximately 30–40%, and persons homozygous for the APOE4 gene have a lifetime risk of 70–90% [18]. The risk conferred by the APOE4 gene appears to be attenuated in Black individuals [19]. Polygenic risk scores (containing single nucleotide polymorphisms (SNPs) identified as increasing the risk of AD in genome-wide association studies (GWAS)) explain up to 20% of additional risk beyond that associated with APOE4 [20].

Amyloid imaging can also be a risk marker. Not all individuals with an abnormal amyloid PET scan will progress to AD in their lifetime, and a having a positive amyloid PET can be regarded as a risk state for AD [21].

3.5. Diagnostic Biomarkers

Diagnostic biomarkers can be used to detect or confirm the presence of a disease or condition or to identify an individual with a subtype of a disease [4–6].

The diagnosis of AD requires the presence of biomarker-confirmed amyloid-beta protein (Aβ) in the brain [22]. This can be demonstrated by amyloid PET or CSF studies. PET studies show increased cortical plaque deposition, whereas CSF studies show a decrease in the monomeric form of Aβ. CSF levels of amyloid declines as the protein is progressively sequestered in plaques in the brain [23]. Recent studies of the clinical diagnosis of AD demonstrated that up to 40% of patients diagnosed with early AD (MCI and mild AD dementia) do not have pathologic levels of brain amyloid and do not meet biological criteria for AD [24]. Biomarker confirmation of the diagnosis of AD is critical to ensure that the target of anti-amyloid therapies is present for development programs targeting Aβ and to demonstrate that the diagnosis of AD is correct in programs advancing drugs targeting non-amyloid AD-specific disease processes.

Plasma biomarkers used to confirm the presence of AD are emerging. A reduced Aβ 42/40 ratio is consistent with the diagnosis of AD [25], and plasma tests for this ratio are commercially available (e.g., Precivity AD™ and Quest AD-Detect™). Plasma levels of phospho-tau (p-tau) 181 and p-tau 217 are elevated in patients with amyloid plaques and appear to be measures of plaque-related neuritic changes [26]. These tests might be used for the prescreening of individuals to identify those most likely to have a positive amyloid scan or anormal CSF amyloid studies. Biomarker panels of Aβ 42/40, p-tau, and measures of neurodegeneration such as neurofilament light (NfL) [27] combined with the APOE genotype may eventually be shown to be sufficiently accurate to diagnose AD without requiring CSF or PET confirmation.

Mutations of the APP, PS1, and PS2 genes cause ADAD (Loy, 2014). They are fully penetrant—in some cases (especially with PS2 mutations) the clinical syndrome may evolve late in life. The occurrence of an MCI or dementia syndrome in a person known to have an ADAD mutation and in whom other causes of cognitive impairment have been excluded (thyroid abnormalities, B12 deficiency, stroke, etc.) can be regarded as having a confirmed diagnosis of AD.

3.6. Monitoring Biomarkers

A biomarker that can be serially measured to assess the status of a disease or medical condition for evidence of exposure to a medical product or environmental agent or can be used to detect an effect of a medical product or biological agent is a monitoring biomarker [4–6]. Monitoring biomarkers are commonly used in clinical care and include serial measurements of blood pressure or cholesterol. Monitoring biomarkers can be important in ensuring the safe use of products through the serial assessment of liver functions, electrocardiograms, or other measures of organ function. Diagnostic markers, pharmacokinetic markers, and safety markers can all be used as monitoring biomarkers in specific circumstances. For example, amyloid PET imaging, p-tau measures, or magnetic resonance imaging (MRI) might be serially conducted to monitor efficacy or safety.

Monitoring biomarkers are increasingly used in AD drug development. For example, in trials of monoclonal antibodies (MABs), serial measurement with amyloid PET has shown increasing plaque reduction with increasing exposure to the MAB [28–30]. Serial measurements of p-tau 181, p-tau 217, and Aβ 42/40 have been used as monitoring biomarkers and demonstrate changes that occur in concert with plaque reduction induced by MABs. MRI is used as a monitoring biomarker and a safety biomarker to detect amyloid-related imaging abnormalities (ARIAs) in patients receiving MABs [31,32].

3.7. Pharmacodynamic/Response Biomarkers

Pharmacodynamic/response biomarkers change with exposure to a medical product or an environmental agent [4–6]. There are several applications of pharmacodynamic biomarkers, including the demonstration of target engagement in the early phases of

drug development, the characterization of biological changes consistent with disease modification in later phases of drug development, use as a surrogate for clinical measures when fully validated, and—in special circumstances—as measures that are considered reasonably likely to predict clinical benefits to support the accelerated approval of an agent.

In AD trials, target engagement biomarkers demonstrate whether a pharmacologic agent has engaged the specific target of therapy. Pharmacodynamic biomarkers are also used as trial outcomes to determine whether an agent has a disease-modifying impact on AD. The lowering of amyloid plaque burden, as shown on amyloid PET, is regarded by the US FDA as a pharmacodynamic biomarker likely to predict a cognitive outcome. Plaque reduction was used in the accelerated approval of aducanumab [33]. Amyloid and tau biomarkers may function as either target engagement biomarkers, showing that the agent has directly or indirectly impacted Aβ- or tau-related processes, or as biomarkers providing evidence in support of disease modification. Their interpretation depends on the COU defined for the biomarker prior to the initiation of the trial.

Target engagement pharmacodynamic biomarkers are particularly important in Phase 2 of AD drug development. In this phase, a proof-of-concept (POC) for the hypothesis being tested is sought. Table 2 presents the Common Alzheimer's Disease Research Ontology (CADRO) classification of drug targets in AD and related dementias (ADRD) created by the National Institute of Health/Alzheimer's Association (NIH/AA) collaboration on the International Alzheimer's and Related Dementia Research Portfolio (IADRP). The table presents biomarkers that link the CADRO class to the biological process on which they report.

Table 2. Target engagement biomarkers (CADRO—Common Alzheimer's Disease Research Ontology); target engagement biomarkers are typically proximal in the cascade of events leading to cell death and dementia in AD. Biomarkers used to demonstrate disease modification using the amyloid, tau, neurodegeneration (A,T(N)) approach are listed in Table 3. Both well-established biomarkers and emerging, partially validated biomarkers are included in the table (the table is not an exhaustive list of all emerging biomarkers).

CADRO Category	Fluid Biomarkers	Imaging, Digital, and Device-Based Biomarkers
Amyloid beta	Inhibition of production of CSF Aβ by beta and gamma secretase inhibitors; increase in Aβ 1–15/16 by gamma secretase inhibitors	Amyloid PET
Tau	CSF and plasma p-tau 181, p-tau 217, and p-tau 231	Tau PET
APOE, lipids, lipoprotein receptors	Lipid peroxidation, isoprostanes, and lipidomics	None identified
Neurotransmitter receptors	None identified	Nicotinic cholinergic receptor PET, muscarinic receptor PET, dopamine transporter SPECT and PET, acetylcholine (VCHAT) and serotonin vesicular transporter PET
Neurogenesis	None identified	MRI measures of hippocampus; fractional and quantitative anisotropy
Inflammation	CSF and plasma GFAP, CSF YKL40, sTREM2, and MCP-1	TSPO PET and evolving ligands

Table 2. *Cont.*

CADRO Category	Fluid Biomarkers	Imaging, Digital, and Device-Based Biomarkers
Oxidative stress	Lipid peroxidation, isoprostanes, neuroprostanes, and u-P53	None identified
Proteostasis/proteinopathies	CSF Aβ and proteomics	None identified
Metabolism and bioenergetics	Metabolomics	FDG PET
Vasculature	Plasma VCAM-1 and ICAM-1; CSF/plasma albumin ratio to assess blood–brain barrier	MRI
Growth factors and hormones	Brain-derived neurotrophic factor (BDNF), HSD-1, and trial-specific hormones	MRI measures of hippocampal volume
Synaptic plasticity/neuroprotection	Neurogranin, synaptotagmin, and SNAP-25	SV2A PET
Cell death	Total tau, neurofilament light, VILIP-1, and GAP-43	Structural MRI (including hippocampal volume), FDG PET, and MR spectroscopy (NAA)
Gut-brain axis	Changes in blood amino acids and inflammatory cells	Changes in the microbe composition of the microbiome
Circadian rhythm	None identified	Polysomnography and actigraphy
Epigenetic regulators	MicroRNA	None identified

Aβ—amyloid beta-protein; APOE—apolipoprotein E; CSF—cerebrospinal fluid; FDG—fluorodeoxyglucose; GAP-43—growth-associated protein 43; GFAP—glial fibrillary acidic protein; ICAM-1—intercellular adhesion molecule-1; MRI—magnetic resonance imaging; HSD-1—hydroxysteroid dehydrogenase—1; MCP1—monocyte chemotactic protein-1;NAA—N-acetylaspartic acid; PET—positron emission tomography; RNA—ribonucleic acid; SNAP25—synaptosomal-associated protein, 25 kDa; SPECT—single-photon emission computed tomography; sTRM2—soluble triggering receptor expressed on myeloid cell 2; SV2A—synaptic vesicle glycoprotein 2A; TSPO—translocator protein; p-tau—phosphorylated tau; VCAM-1—vascular cell adhesion molecule-1; VAChT—vesicular acetylcholine transporters; VILIP-1—visinin-like protein-1.

Table 3. Amyloid, tau, neurodegeneration (AT(N)) biomarkers.

	Amyloid (A)	Tau (T)	Neurodegeneration (N)
Imaging	Amyloid PET	Tau PET	FDG PET; MRI; spectroscopy
CSF	Aβ 42/40	p-tau (181, 217)	Total tau; NfL; VILIP-1
Plasma	Aβ 42/40	p-tau (181, 217)	Total tau; NfL

Aβ—amyloid-beta protein; CSF—cerebrospinal fluid; FDG—fluorodeoxyglucose; MRI—magnetic resonance imaging; NfL—neurofilament light; PET—positron emission tomography; p-tau—phospho-tau.

Examples of target engagement pharmacodynamic biomarkers for amyloid biology include reduction in CSF Aβ by gamma-secretase inhibitors and beta-secretase inhibitors [34,35]. Gamma secretase inhibitors increase the Aβ 1–15/16 fragment, suggesting that this elevation may function as a target-engagement biomarker [36].

Peripheral measures of tau biology in AD include p-tau 181, p-tau 217, and p-tau 231 [37]. Total tau is measurable in plasma, and CSF and may reflect cell death and neurodegeneration [38]. Visinin-like protein-1 (VILIP-1) is an additional cell death reporter detectable in CSF [39]. Amyloid, tau, and cell death (neurodegeneration) biomarkers comprise the amyloid, tau, neurodegeneration (AT(N)) classification of biomarkers used to indicate disease state; they are discussed below (Table 3) [2].

Inflammation is a key element of AD, and plasma glial fibrillary acidic protein (GFAP), YKL 40, soluble triggering receptor expressed on myeloid cell 2 (sTREM2), and monocyte chemotactic protein-1 (MCP-1) measured in the CSF have promise as target engagement biomarkers for anti-inflammatory agents [40–44]. The PET imaging of activated microglia has focused on the development of ligands for the 18 kDa translocator protein (TSPO). This protein is not unique to glia, and more selective ligands are under development [45].

Target engagement biomarkers for synaptic function include CSF neurogranin; synaptotagmin; synaptosomal-associated protein, 25 kDa (SNAP-25); and growth-associated protein 43 (GAP-43) [42,46,47]. These may function as biomarkers in trials of agents affecting synaptic integrity. The PET imaging of synaptic vesicle glycoprotein 2A (SV2A), a presynaptic vesicle membrane present in virtually all synapses, provides a quantitative measure of synaptic density and its changes in the course of AD [48].

Vascular factors contribute to AD, and cell adhesion molecules detectable in plasma may reflect this vascular pathology. Soluble plasma vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are elevated in the plasma of patients with AD dementia [49]. The CSF/plasma albumin ratio can be used to assess the integrity of the blood–brain barrier (i.e., the neurovascular unit). This ratio has been found to be normal in most studies of AD but may be abnormal in other disorders from which AD must be differentiated [50].

Growth factors and hormones comprise a CADRO category. A meta-analysis of available studies showed that the level of brain-derived neurotrophic factor is decreased in the later stages of AD but not in early AD [51]. Structural MRI measures of hippocampal size and white matter measures of fractional and quantitative anisotropy have been proposed as measures of growth-factor effects in trials [52]. CSF 11-ß-hydroxysteroid dehydrogenase type 1 (HSD-1) has been used a target engagement biomarker to detect the effects of HSD-1 inhibitors [53].

Neurotransmitters and transmitter receptors represent a CADRO category. Nicotinic and muscarinic cholinergic receptors can be labeled with PET ligands [54,55]. The vesicular acetylcholine transporter (VAChT) can be labeled and visualized with PET [56]. PET ligands are available to assess the integrity of serotonin transporters in AD [57]. The dopamine transporter (DaT) can be labeled for use with PET or single-photon emission computed tomography (SPECT) imaging and can assist in distinguishing AD from dementia with Lewy bodies and Parkinson's disease dementia; the latter two are characterized by dopamine transporter depletion [58].

Evolving biomarkers that have promise as target engagement reporters but are not yet fully established include plasma and CSF biomarkers of oxidative stress such as lipid peroxidation, isoprostanes, and neuroprostanes [59]. Plasma and CSF measures of u-P53 are considered measures of oxidation-induced protein changes in neuronal cells [60,61]. Lipid measures that may have a role as AD biomarkers or target engagement biomarkers include cholesterol (including 24S-hydroxycholesterol), oxysterols, fatty acids, and phospholipids [62]. Lipidomic assays may contribute vital information on a slate of lipid-related molecules but have thus far been relatively under-explored [63]. FDG has been used a measure of target engagement in studies of AD treatment with glucagon-like protein 1 (GLP-1) agonists [64]. Some specific microRNAs involved in the epigenetic regulation of protein synthesis have been shown to be decreased in blood from patients with AD, suggesting that specific microRNAs might function as target engagement biomarkers of epigenetic regulators [65].

Mechanistically nonspecific evidence of target engagement can be garnered from electroencephalography (EEG), evoked potentials, and functional MRI (fMRI) [66–69]. The restoration or slowing of deterioration of these measures suggest that circuit function has been beneficially affected compared to placebo, demonstrate that the drug has entered the brain, provide preliminary evidence in support of the POC of drug activity, and may show drug–placebo differences in smaller samples than those required to demonstrate clinical effects.

Many AD-related disease mechanisms and the associated impacts of the test agents have no pharmacodynamic target engagement biomarker. The development of these drugs is particularly challenging because long large trials may be necessary to determine the biological impact of the therapy and the absence of a more immediate target engagement biomarker means that no information is available to determine if such trials are warranted or to guide calculation of the necessary trial sample size. Increase in the number of accurate, reliable, valid, and scalable target engagement biomarkers is an unmet need for AD drug development.

Multiomic studies are an emerging area of biomarker development in AD. Genomic, proteomic, transcriptomic, metabolomic, and lipidomic profiles have been shown to be abnormal in AD [70–73]. These tools have promise because the measures reflect many levels of processing in the central nervous system and can be used to identify disturbed pathways and networks that may comprise targets for treatment. The identification of multiple affected networks may help guide combination therapy trials. Advanced bioinformatic skills are required to interrogate the large datasets, and consensus is evolving on best practices for these analyses.

The amyloid, tau, neurodegeneration (AT(N)) research framework [2] defines the most widely used suite of pharmacodynamic biomarkers supportive of disease modification (Table 3). Each of the members of the AT(N) framework can be measured with brain imaging, CSF biomarkers, and plasma or blood-based biomarkers. Amyloid levels can be measured by amyloid PET [74], CSF measures of Aβ 42/40, or plasma measures of Aβ 42/40 [15,25]. Tau protein in neurofibrillary tangles is measured with tau PET [75], and p-tau monomers are measured in CSF and plasma [76]. Evidence of neurodegeneration is provided by MRI atrophy or reductions in metabolism on FDG PET [77]. N-acetylaspartate (NAA) detectable with MR spectroscopy is largely sourced from neurons, and its decrease functions as a measure of nerve cell loss [78]. CSF and plasma measures consistent with neurodegeneration include total tau, NfL, and VILIP-1 [79–81]. The AT(N) framework is elastic and can expand to include additional biomarkers as more evidence of their accuracy and potential role in trials and care accrues [82].

The goal of disease modification is to prevent or slow neuronal loss that is the key to ameliorating cognitive and functional decline in AD and other neurodegenerative disorders [83]. Markers of neurodegeneration such as total tau, NfL, and VILIP-1 offer supportive information regarding whether neurodegeneration has been impacted and disease modification has occurred. Biomarkers related to neurodegeneration such as tau, amyloid, and inflammation can contribute to the weight of evidence in favor of disease modification.

Another application of pharmacodynamic biomarkers is their use in the accelerated approval of therapeutic compounds. This regulatory mechanism is used when clinical information from trials for treatment of a life-threatening illness is not complete and the changes in a biomarker demonstrated in the trial are considered reasonably likely to predict clinical benefits [84]. A post-approval trial to confirm clinical benefits can be required to support accelerated approval. A reduction in plaque amyloids demonstrated by amyloid PET—a pharmacodynamic response—was considered reasonably likely to predict clinical benefits from treatment with the anti-amyloid MAB aducanumab and was the basis for approval by the FDA [33].

3.8. Predictive Biomarkers

Predictive biomarkers are defined by the finding that the presence or change in a biomarker identifies an individual or group of individuals more likely to experience a favorable or unfavorable effect from exposure to a medical product or environmental agent [4–6]. Predictive biomarkers may be used in enrichment strategies in the design and conduct of clinical trials. Enrichment using predictive biomarkers is intended to make the therapeutic effect clearer by recruiting those individuals most likely to respond to treatment into the clinical trial. Predictive biomarkers must be distinguished from prognostic biomarkers. Prognostic biomarkers are associated with differential disease

outcomes; predictive biomarkers discriminate those who will respond or not respond to therapy.

The APOE4 genotype is a predictive biomarker of ARIA in patients receiving treatment with an anti-amyloid MAB. In the clinical trials of aducanumab, for example, participants without an APOE4 gene had a 20% occurrence rate of ARIAs, heterozygotes for the gene had a 36% occurrence rate of ARIAs, and homozygotes had a 66% occurrence rate of ARIA [85].

Surrogate biomarkers are biomarkers whose performance has been fully confirmed and can serve as trial outcomes in place of clinical measures since their predictive value for clinical benefits is known. Surrogate status depends on demonstrating the relationship between the biomarker changes and clinical outcome across multiple trials and several mechanisms affecting the pathway and the biomarker [6]. There are no fully validated surrogate biomarkers for AD.

3.9. Prognostic Biomarkers

A prognostic biomarker is used to identify the likelihood of a clinical event, disease recurrence, or disease progression in patients with a disease or medical condition of interest [4–6]. Prognostic biomarkers are differentiated from susceptibility/risk biomarkers that identify the likelihood of the transition from a healthy state to disease. Prognostic biomarkers are distinguished from predictive biomarkers that identify factors associated with the effect of intervention or exposure. In clinical trials, prognostic biomarkers are routinely used as entry criteria to identify patients who are most likely to progress during the trial. Prognostic biomarkers influence the power to draw conclusions from a clinical trial by affecting the rate of progression or the number of events occurring in the placebo group.

Several biomarkers that provide prognostic information for AD have been identified. P-tau-181 and p-tau 217 elevations have been associated with progression from normal cognition to MCI and from MCI to AD dementia [76,86]. Neurofilament light and VILIP-1 are biomarkers of neurodegeneration and have been shown to have prognostic value for progression in patients with MCI or dementia due to AD [81,87]. GFAP, a marker of astrogliosis, predicts decline in those with subjective cognitive impairment [88]. Tau PET offers prognostic information and forecasts MCI and AD dementia progression [89,90]. Positive amyloid PET increases the likelihood of the development of MCI or dementia due to AD but is present in the brain for 15–20 years prior to the onset of cognitive symptoms. Many patients with brain amyloid to not show cognitive decline prior to death, and amyloid PET by itself does not provide strong prognostic information [21].

3.10. Safety Biomarkers

A safety biomarker is measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of a toxicity as an adverse event [4–6]. Commonly used safety biomarkers include measures of drug-induced changes in hepatic, renal, or cardiovascular function.

The MRI monitoring of ARIA is an important application of a safety biomarker in AD drug development and clinical care. Patients receiving anti-amyloid MABs may develop ARIA with edema (ARIA-E) or ARIA with hemorrhage (ARIA-H). This is particularly likely during the initial phases of treatment. MRIs are scheduled at routine intervals in the first months of therapy, and additional imaging is performed if symptoms suggestive of ARIA occur [31,32].

4. Biomarker Qualification

Biomarker qualification refers to the FDA process that establishes the evidentiary framework for use of a biomarker in a drug development program [4]. Experience with biomarkers in clinical trials frequently provides critically important data that inform the use of biomarkers in clinical care, and confidence in the biomarker is built through application in trials.

For a biomarker development effort to be successful, the biomarker must be clearly identified and characterize, and its method of measurement must be fully described. The evidence necessary for this process includes: (1) describing the drug development need, (2) defining the COU, (3) considering potential benefits if the biomarker is qualified for use, and (4) considering potential risks associated with the use of the proposed biomarker in a drug development program [4]. Risks arise from the consequences of false positives or false negatives regarding the identification of disorders important to a patient's health.

A biomarker needs assessment describes why a biomarker is needed for drug development and how a biomarker might promote drug development in an area where there is an unmet medical need. The added value of the novel biomarker for the drug development process is described. The COU is a concise description of the biomarker's specified use in drug development. The COU includes the identification of the type of biomarker (Table 1) and the proposed use of the biomarker in the drug development program. The COU process includes submitting a Letter of Intent (LOI) describing the intention to advance a biomarker COU, submitting a Qualification Plan (QP) that defines the intended development proposal to generate the necessary information to support the qualification of the biomarker, submitting a Full Qualification Package (FQP) that contains all the accumulated data to support the qualification of the biomarker, and obtaining a Qualification Recommendation (QR) that contains the FDA's determination regarding whether the biomarker is qualified for the proposed COU [91]. Figure 2 presents the COU process required by the FDA. The potential benefits of a biomarker for use in a drug development plan depend on the biomarker's proposed COU and the needs assessment. The potential risk of a biomarker depends on the consequences of incorrect decision making or harm to patients if the correlation between the biomarker and the outcome of interest are at variance.

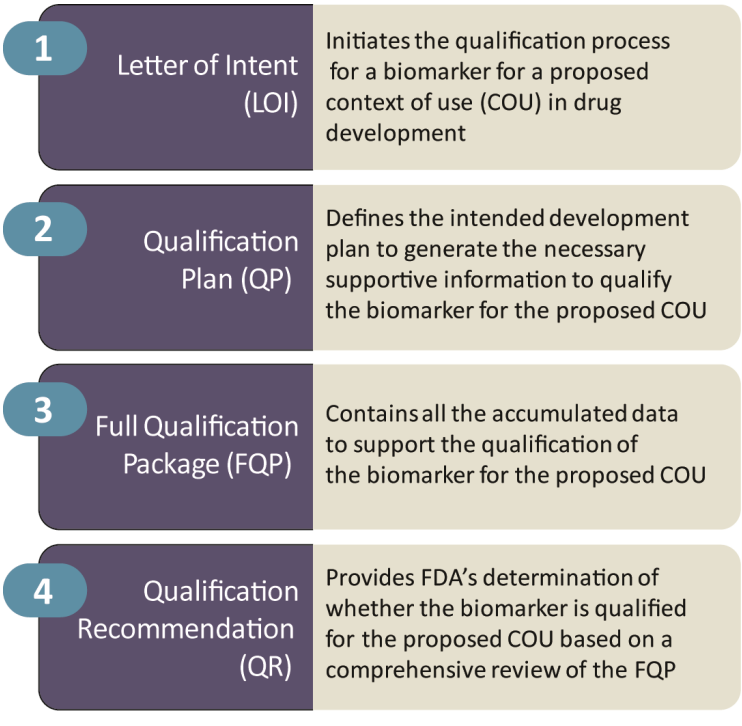

Figure 2. Context of use (COU) process required by the FDA for use of a biomarker as a drug development tool (DDT) in a clinical trial (© J Cummings; M de la Flor, PhD, illustrator).

The analytical validation of the biomarker must be presented as part of the proposed COU description [92]. The test's reliability, validity, accuracy, sensitivity, specificity, precision, and reproducibility—as well as preanalytical factors such as collection, storage, and stability—must be determined before the COU can be approved. This information is included in the Full Qualification Package submitted for regulatory review.

5. Biomarkers for Use in Clinical Care

There are four clinical use pathways and one research pathway by which fluid biomarkers can be made available to clinicians for use in clinical care: as a companion diagnostic, as an in vitro diagnostic device (IVD), through the 510(k) pathway, as a Laboratory Developed Test (LDT), or as a test for Research Use Only (RUO). Table 4 lists and describes the five ways that biomarkers can be used in the clinical setting.

Table 4. Pathways of biomarkers to progress to clinical use.

Pathway	Characteristic
Companion diagnostic	Required for appropriate use of a specific agent
In vitro diagnostic device (IVD)	Review by the FDA varies according to level of risk associated with the biomarker
510(k) pathway	Shown to be substantially equivalent to an approved IVD with performance characteristics at least as good as the approved IVD
Laboratory Developed Test (LDT)	Performed in a single laboratory; relatively limited FDA review
Research Use Only (RUO)	Cannot be used in diagnosis; may be used to gather additional information on the biomarker

5.1. Companion Diagnostic

A companion diagnostic device is an IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product [84]. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product. An IVD companion diagnostic device is considered essential for the safe and effective use of a corresponding therapeutic product to: identify patients who are most likely to benefit from the therapeutic product, identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product, monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, and discontinuation) to achieve improved safety or effectiveness, or identify patients in the population for whom the therapeutic product has been adequately studied and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population. This final category applies to patients with AD who are candidates for treatment with anti-amyloid MABs. Aducanumab has been studied only in patients with early AD, with amyloidosis confirmed by amyloid PET. The Appropriate Use Recommendations specify that the establishment of amyloid abnormalities through amyloid PET or CSF amyloid measures is required for the use of aducanumab since it is only in this population that the efficacy and safety of this agent have been studied [31,32]. Other MABs may be administered to restricted populations (early AD with positive amyloid studies) and may have similar requirements for safe and effective use.

5.2. In Vitro Diagnostic Devices (IVDs)

In vitro diagnostic devices (IVDs) include tools used to diagnose conditions and guide treatment decisions but are not required for the approved use of a specific product [93]. Unlike LDTs (discussed below), their measurement is not limited to a single laboratory. The

test originators typically develop measurement kits that can be purchased and used in many laboratories. The terminology of "complementary diagnostic" may be used to describe a test that identifies a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients but are not prerequisites for receiving the drug. Complementary diagnostics are IVDs and are subject to the same regulatory requirements as other IVDs [94,95].

The FDA regulation of IVDs is risk-based: Class I tests pose relatively little risk to patients and the public health if they are inaccurate (such as a cholesterol test), Class II tests pose moderate risk if they are inaccurate, and Class III tests pose the greatest potential risk if they are inaccurate (an incorrect therapy could be chosen or a correct therapy could not be administered with severe health consequences) [93,96]. The three categories correspond to increasing levels of regulatory scrutiny.

Premarket approval (PMA) is required for some Class II tests and most Class III tests. PMA requires a demonstration of safety and effectiveness, including both analytical validity and clinical validity before the test is marketed. Analytical validity refers to how a test performs in detecting or measuring the presence of the analyte of interest. Analytically valid tests are precise, accurate, and reliable [92,93]. Clinical validity refers to how accurately a test predicts the presence of or risk for the condition of interest. The demonstration of clinical validity requires data from human testing and might include data generated in clinical trials. The FDA defines valid data in support of an IVD as evidence from well-controlled investigations, partially controlled studies, studies and trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its COU [97]. Laboratories performing tests on human specimens such as blood tests are subject to regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). This regulation governs the accreditation, inspection, and certification of clinical laboratories.

The Lumipulse-G measure of CSF Aβ 42/40 is an AD-related IVD approved for use in the US [98].

5.3. 510(k) Pathway

The 510(k) pathway is a variant of the IVD approval pathway. It is used if a test is substantially equivalent to a product already on the market. The sponsor provides evidence that the device has safety and efficacy characteristics at least equivalent to the existing approved IVD. Approval can be granted through a premarket notification process (510(k) pathway) [99].

5.4. Laboratory Developed Test (LDT)

Laboratory developed tests (LDTs) are biomarkers that are measured in a single laboratory and are available only from the identified resource [100]. Laboratories providing LDTs are CLIA-certified. LDTs are typically less rigorously scrutinized by the FDA than IVDs. Plasma Aβ 42/40 measures (Precivity AD™ and Quest AD-Detect™) are LDTs (available through C2N and Quest, respectively). If kits are created so an analyte can be assessed in other laboratories, an LDT could be re-classified as an IVD when sufficient data are available to satisfy FDA requirements.

5.5. Research Use Only (RUO) Test

Research Use Only (RUO) tests can be made available to clinicians and researchers to allow additional information regarding a biomarker's performance or feasibility of use to be gathered. An RUO biomarker must be labeled as "not to be used for diagnosis" [101]. RUO biomarkers may be advanced to LDTs or IVDs with data development.

6. Five-Phase Roadmap for Biomarker Development

A European work group proposed a five-phase approach to IVD and diagnostic imaging data generation that begins with non-clinical exploratory studies (Phase 1), progresses to clinical assay development and validation (Phase 2), then advances to retrospective and longitudinal studies (Phase 3), moves to prospective studies and real world evidence (Phase 4), and concludes with implementation and studies of impact on clinical outcomes and cost-effectiveness, as well as the assessment of reimbursement (Phase 5) [102–104]. This pathway is based on the analysis of requirements for a biomarker to achieve routine clinical use and is not a regulatory requirement; it encompasses processes before and after regulatory review. Figure 3 shows the five phases of biomarker development. Phase 1 is the biomarker discovery phase based on the identification of biological processes that may have fluid or imaging markers. Phase 2 includes analytic validation and the preliminary analysis of accuracy in case control studies. Phases 2 and 3 provide evidence of clinical validity, and Phases 4 and 5 address clinical utility. Establishing a COU for a biomarker in trials typically occurs in Phase 4 after clinical validity has been demonstrated in Phases 2 and 3. Phases 4 and 5 provide the basis for widespread clinical use and reimbursement. Most AD biomarkers are in Phase 2 and 3, and some have established a COU for use in clinical trials. Few AD-related biomarkers have advanced to Phases 4 or 5 [103,105–110].

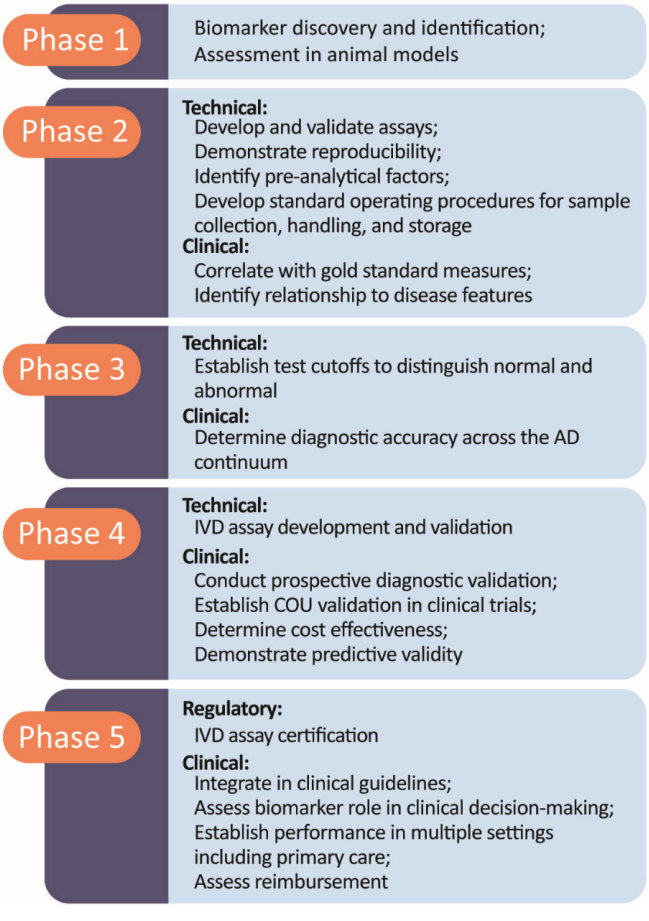

Figure 3. Five-phase process of biomarker development (© J Cummings, M de La Flor, PhD, Illustrator).

7. Biomarker Collaborations and Cohorts

An important challenge to biomarker development is accessing a sufficient number of well-characterized patients in whom the biomarker can be assessed and qualified. The Alzheimer's Disease Neuroimaging (ADNI), Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing (AIBL), Amsterdam Dementia Cohort, and the BioFinder study host cohorts of well-studied patients that allow for the assessment of biomarkers [111–114]. Following the study of biomarkers in research centers, biomarkers require assessment in community-based practices to determine their robustness and utility in real world settings.

8. Conclusions

AD is a complex disease with many abnormal biological processes including amyloid accumulation, neurofibrillary tangle formation, neurodegeneration, inflammatory responses, and many other cell and network disturbances. These processes contribute to disease progression, and many of them may be targets for AD interventions. The clinical identification of these processes and the development of drugs to ameliorate them depends on biomarkers. Biomarkers for some processes have been developed, but many cell and network changes have no corresponding biological measure. The development of biomarkers for use in clinical trials and of IVDs and LDTs for use in clinical care is a critical part of the next step in the AD research agenda. Biomarker development requires rigorous data generation and regulatory review. Adherence to regulatory guidance for both biomarker development and introduction into the clinical setting is key to informative clinical trials and to successfully integrating biomarker use into clinical care settings.

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Review

The Knowledge and Attitudes of Primary Care and the Barriers to Early Detection and Diagnosis of Alzheimer's Disease

Donna de Levante Raphael

National Memory Screening Department, The Alzheimer's Foundation of America, New York, NY 10001, USA; draphael@alzfdn.org; Tel.: +1-(917)-688-8518

Abstract: Primary care physicians play a vital role in the clinical care of their patients, early identification of dementia, and disease advocacy. It is essential to assess the knowledge and attitudes of physicians in the diagnosis of Alzheimer's disease and other dementias. In primary care, the diagnosis of Alzheimer's disease is often missed or delayed. With the increased prevalence of Alzheimer's disease and the growing impact of dementia on health care resources, early detection by primary care physicians (PCP) is essential. Thus, their knowledge and attitudes about early detection and diagnosis are crucial. To examine the knowledge and attitudes of primary care physicians regarding early detection and diagnosis of Alzheimer's disease and how barriers may contribute to missed and delayed detection and diagnosis. An interpretive scope review was used to synthesize and analyze a body of literature published over the past decade. The study population are physicians in the United States. The current health systems experience challenges in providing early, safe, accurate, and comprehensive Alzheimer's diagnosis and care by a primary care physician trained or knowledgeable in diagnosing the various forms of dementia. This article identifies several interrelated obstacles to early detection and diagnosis in primary dementia care, including gaps in knowledge, attitudes, skills, and resources for person with dementia (PWD)/caregivers and their primary care providers and systematic and structural barriers that negatively impact dementia care. Research shows that Alzheimer's disease has gone underdiagnosed and undertreated. Delays in detection, diagnosis, and resource utilization may have social and clinical implications for individuals affected by Alzheimer's disease and their families, including challenges in obtaining an accurate diagnosis. Until the issues of missed and delayed Alzheimer's screening become more compelling, efforts to promote early detection and diagnosis should focus on the education of physicians and removing the barriers to diagnosis.

Keywords: Alzheimer's disease; primary care physicians; dementia; knowledge and attitude; early diagnosis and management; barriers to diagnosis

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1. Introduction

This study aims to examine how the knowledge and attitudes of primary care physicians (PCP) contribute to the barriers to early detection and diagnosis of Alzheimer's disease (AD) using an interpretive scoping review to synthesize and analyze an extensive body of literature on this topic. Alzheimer's disease is a significant and growing public health issue in the United States for which early detection and diagnosis are essential. An estimated 6.5 million Americans live with AD right now. The projected number of people is estimated to reach 12.7 million by 2050 [1]. America's health care will be challenged in both training and size. Currently, Alzheimer's diagnosis in the primary care setting has been dependent mainly on clinical suspicion based on the patient's or caregiver's concerns rather than the use of assessment tools and is often prone to missed or delayed diagnoses. Early accurate detection and diagnosis are consistent with high-quality care and offer several direct benefits to individuals with AD. For example, treating reversible causes of dementia, implementing interventions to slow the progression of the disease, and commencing

advanced planning while the patient is still competent. Other examples may be receiving access to education, participating in clinical trial options, engaging family and caregivers with support resources, and potentially delaying institutionalization [2]. Alzheimer's disease has a wide range of adverse consequences, including functional limitations affecting the routine performance of daily living and self-care activities, complications due to other co-existing medical conditions, increased healthcare services utilization, and increased caregiver burden. Major contributory factors to missed and delayed detection and diagnosis often include issues with knowledge deficits and attitudes of healthcare professionals and patient-care provider communication [3]. Over the past 20 years, there has been a global commitment to seeking a more active approach to PCPs for older adults with dementia, with PCPs again at the center of attention. Experts have repeatedly acknowledged the crucial role of PCP in delivering an early diagnosis, responsive treatment, overall care management, and provision of support services to older adults with dementia and their families. The overall goal of this article was to identify the barriers to providing optimal primary Alzheimer's care and reduce missed and delayed detection and diagnosis. Until the issue of missed and delayed Alzheimer's screening is addressed, efforts to enhance the use of screening tools by primary care physicians and remove the barriers to their use are essential to promoting early detection and diagnosis.

Due to the increased prevalence of AD and other dementias, the United States healthcare systems are shifting the care of these patients to primary care [3]. Many patients and caregivers view their primary care physician (PCP) as their key point person for managing their care. Thus, PCPs are a significant stakeholder in our care system for people with Alzheimer's and other dementias. The critical role of the PCP includes early screening, identification, and diagnosis of dementia; outcome/course of the disease; and support services available in the community. However, the signs and symptoms of AD and other dementias often are insidious and difficult to diagnose in the early stages of the onset of dementia.

2. Materials and Methods

The methodology used for this review was an interpretative scoping review based on the framework developed by Arksey and O'Malley and the more recent work of Davis and colleagues. This framework was used to guide the review process. This methodology systematically examines, synthesizes, and analyzes an extensive body of relevant literature. The extensive nature of this type of review offered a mechanism to thoroughly and systematically map various forms of the existing evidence, including a range of primary research and non-research sources. An interpretive approach established an in-depth scope and interpretive analysis of the findings that inform future research, practice, and policy.

An electronic search of nine databases was conducted to secure relevant information on geriatric and gerontology topics: MEDLINE, EbscoHost, ProQuest, Google Scholar, PsycARTICLES, PsycINFO, CINAHL, PubMed, and the National Institute on Aging. The search strategy used to incorporate the selected 22 articles was the Boolean method. This method allowed the combination of modifiers and operators with keywords, such as Cognitive impairment, dementia, Alzheimer's disease, dementia, training, screening, barriers, assessment, detection, diagnosis, or educational interventions. To extract the relevant literature for this review, the following key search terms and combinations of search terms to search for the related literature resulted in: primary care physician, primary care, primary health care, physician, family doctor, family physician, general practitioner, AND dementia, Alzheimer's Disease, or cognitive disorders, or cognition AND Alzheimer's disease diagnosis, early diagnosis, early detection unmet needs, support, knowledge, dementia training, and barriers to diagnosis. Both the PICO question and the framework were used to guide the search and find relevant keywords for the literature review.

3. Results

Over the past two decades, there has been an extensive list of papers on the clinical practice, best practice recommendations, and evidence of actual practice guidelines for diagnosing and managing the care of people with AD or another dementia. Despite the many forms of care systems, they are consistent with the recommendations that patients experience changes in their cognition and should first seek care with their primary care physician (PCP). The chart Figure 1 is the Flow Chart of Manuscript Identification and Selection of the extensive list of papers reviewed and those that contributed in part to the practice guidelines for diagnosis and care management of patients with dementia. It is agreed that this PCP should first begin care with the identification of the early signs and symptoms of AD or another dementia. The second step is followed by a multidisciplinary evaluation, a collaborative care plan with the input of other support team members, and ongoing follow-up monitoring and management.

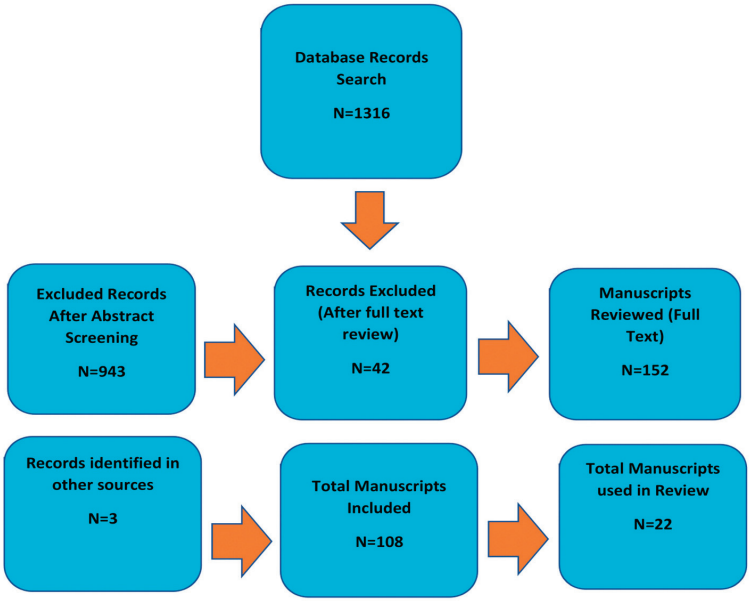

Figure 1. Flow Chart of Manuscript Identification and Selection.

A substantial number of PCP throughout several studies acknowledged that though there are challenges in primary care, diagnosis can be conducted by PCP in the form of clinical evaluations, brief cognitive testing, lab tests, and structural imaging, if necessary. However, this agreement on the clinical practice of dementia research has consistently shown a lack of consensus between agreed-upon best practice recommendations and actual acts related to dementia diagnosis and management [3–5].

According to several studies, general concerns of PCPs or general practitioners (GP) show that the early stages of AD and other dementias remain under-detected, under-diagnosed, under-disclosed, under-treated, and mismanaged [6–8]. Several study surveys revealed that the PCPs agreed with the enablers of early AD or dementia recognition, such as planning for the future and arranging care and support. At the same time, some respondents perceived barriers to early diagnosis, such as time limits to carrying out diagnosis. Evidence shows that AD and other dementias are mainly diagnosed at the middle to late stages of the disease and not sufficiently disclosed or followed up with a timely, comprehensive approach [4,8]. Dementia diagnosis delays often occur even though suspicion of the disorder is brought about by family members or the presence of negative cognitive screen results [7,9].

In a few recent large-scale international surveys, it was confirmed that physicians and the general public had significant difficulties in recognizing and acknowledging early dementia symptoms. There were also significant delays in seeking help and providing a diagnosis. According to these studies, from the initial presentation of dementia symptoms to the diagnosis of dementia, it often took months to years. Delays occurred from the initial recognition of symptoms by family to physician consultations [5,7,9]. Throughout the studies, family caregivers generally waited approximately two to three years before reporting the presentation of symptoms to the PCP [8]. Though there were high rates of referrals of suspected presentations of dementia from PCP and other specialists, referrals did not necessarily lead to a proper diagnostic investigation. Though dementia was detected and documented in patient medical files, PCP failed to disclose the diagnosis and did not follow up with their patients [9,10]. According to the studies many PCP reluctantly shared the diagnosis of dementia.

Failure to disclose a diagnosis as significant as dementia may be unethical. There are many benefits to an early dementia diagnosis disclosure. A review paper summarizing studies reported an estimated 50 percent of physicians standardized withholding dementia diagnosis from their patients [8]. In comparison, 71 percent of the survey respondents without cognitive impairment indicated a solid desire to be informed of a dementia diagnosis [9,11,12]. The surveys also revealed that patients felt that it was critical to be informed of their diagnosis so they could access information, plan, and participate in treatment options [11–13].

3.1. Main Challenges Encountered

Though there are structured processes for other health conditions, there are none for cognitive diseases [8]. There are no specific standardized tests or guidelines established for cognitive assessments. The cognitive assessments and diagnosis approach has been reactive when patients raise issues or self-report their cognitive experiences or challenges. This approach can make cognitive screenings challenging in a clinical setting. Some of these challenges may include:

- The PCP does not have special dementia training for cognitive screenings;
- Screenings cause a delay in the clinic's workflow;
- Time limitations, fear of giving a diagnosis;
- Lack of cultural competency in the patient's understanding of the cognitive changes;
- Not knowing how to start the conversation;
- Alzheimer's disease stigma;
- Fear of harm to the older patient by conducting a cognitive assessment that may lead to depression or anxiety;
- Discrimination.

With these challenges and barriers, many PCPs remain hesitant to initiate the concerns of cognitive testing with their older patients [14]. Providers often wait for the older adult or family member to initiate the conversation about their problems.

Physicians are in an ideal position to observe potential signs of cognitive decline and ask pertinent questions. As the provider to the individual, they may have long-established relationships with the individual and their family. When the patient is concerned about any changes regarding their memory functions, they would most likely take the concern to their providers [14]. However, older adults will rarely initiate the conversation about their cognitive challenges for various reasons. Some reasons may include:

- Fear;
- Cultural perceptions of the disease;
- Stigma;
- Past experiences;
- Not believing there is a benefit to knowing about the disease;
- Why bother? Dementia is incurable.

3.2. Barriers to Diagnosis—PCP Attitudes and Perceptions

Throughout this review, the literature disclosed many interrelated obstacles and challenges, such as the complex nature of AD and other dementia disorders and significant gaps in knowledge, skills, resources, and attitudes of PCP, patients, and caregivers. Additional significant barriers were reported as the systematic and structural barriers which negatively affect dementia care. There is significant evidence that PCP experience difficulty recognizing early AD or other dementia symptoms and overlook the importance [5,8,15]. For example, many PCP conveyed low confidence in producing a dementia diagnosis, especially in the early stages of the disease. They often felt their training was insufficient to prepare them to accurately and confidently screen or give diagnoses [15–17] and preferred their patients to participate in a specialist consultation [16]. The studies also showed that many PCP viewed dementia diagnosis and management to be more complex than other chronic conditions.

Many PCPs and other medical providers are unaware of Medicare's mandatory annual cognitive assessment for older adults aged 65 and older. There is also difficulty managing communication and management skills. Many PCP also admitted that they felt uninformed about the next steps after diagnosis and the available support services for patients and caregivers [12,15,18].

A significant body of research has shown that PCP dementia diagnosis and management practices may be influenced by their beliefs and attitudes. The literature also highlighted that those PCPs who had negative attitudes and perceptions might threaten their commitment to early diagnosis and disease management. A few of these perceptions concern the lack of real therapeutic benefits of early diagnosis and disclosure leading to depression and anxiety in a person with dementia (PWD) and their caregivers. Other perceptions are concerned with the harmful effects of the various forms of stigma experienced immediately upon diagnosis. Throughout the disease, low priority is given to dementia symptoms instead of physical health issues and the belief that care for the diagnosed person would increase the strains of the already strained health care system [8,13,17]. The question of insufficient time was a significant issue as it constrains the ability of the PCP to provide optimal care to the patients and caregivers. Insufficient time was also the primary and most significant barrier to optimal dementia care, according to PCPs [17]. Another issue was the inadequate payment models and reimbursement structures that did not accurately reflect the time needed to care for the needs of the elderly patient, especially those with AD or other dementia [17].

3.3. Attitudes

Though there was wide understanding, agreement, and confirmation of the benefits of early detection and diagnosis of AD and other dementia, PCP attitudes toward AD and other dementia, including administering cognitive assessments, disclosing diagnosis and guiding and referring patients to specialists, and caregivers to community based organizations, revealed that they felt strongly that their level of confidence in their ability to perform the aforementioned care was significantly associated with their lack of dementia specific training and knowledge that would allow them to improve their overall care and support to dementia patients.

PCPs' attitudes reflected that it was important to assess older adults for cognitive impairment from the age of 65 years. It also reflected their understanding that early detection and diagnosis of cognitive decline had benefits to the individual to include social, financial, medical, and planning. In several studies, PCPs felt that patients were too ill to proceed with cognitive testing.

Other attitudes reflected that there was a higher barrier in the United States compared to other countries utilizing the PET testing regularly. In the United States the barrier was that testing was significantly lower than other countries due to the cost and challenges around the reimbursement of the PET imaging process. Attitudes toward the routine use of objective tests during the Medicare Annual Wellness Visit (AWV) are more common in

the United States. The required AWV implemented in 2010 required direct observation of cognitive function, concerns, and symptoms that should initially prompt cognitive testing.

3.4. Barriers to Diagnosis—PCP Knowledge

Meeting the educational needs of PCPs has become crucial to diagnosing and management of older adult patients. Various knowledge-based interventions have been developed and utilized with varied success. Provider-related barriers included lack of training and confidence in knowledge. According to seven studies, approximately 10–63% of respondents lacked knowledge and training [19]. Lack of confidence or comfort due to knowledge and skill deficits was reported by 23–66% of respondents in four studies [12]. Many PCPs often find themselves having to discuss dementia diagnosis despite their limited knowledge of symptoms, causes, treatment options, and other diseases or reversible dementias that present with cognitive symptoms [12]. A recent study with 343 PCPs working in hospice settings showed that PCPs tended to give inaccurate information about their prognosis, and the errors were highly optimistic instead of very pessimistic [12]. This behavior extended the patient/physician relationship and delayed the diagnosis. Gaps in knowledge and skills and an understanding of dementia can stigmatize people affected by dementia. They can also result in barriers to health care access, diagnosis, and quality of care. Though some medical education programs offer education on dementia, very few offer in-depth focus on cognitive health and aging [18].

Education content of AD or other dementias and geriatric education has not been standardized and varies significantly across the board. Education in family medicine programs ranges from optional to one lecture or a tour of clinical rotation in geriatrics [18]. This content is not significant enough to be knowledgeable enough to deliver appropriate care [15,17,18]. The studies also called attention to the situation that very few family medicine students receive or pursue opportunities in caring for the older adult population [15,17,18]. Furthermore, the older adult population with dementia in the United States is diverse, and family medicine students will need to provide quality care. To deliver quality care, medical students require clinical training and education, including dementia education that recognizes the unique needs of the various socio-cultural groups that their patients identify with and those in different geographical settings [15,17,18].

Given the United States' aging population, there is a critical gap in the requirements for improved education and training on dementia in family medicine training programs to improve early dementia detection, diagnosis, treatment, management, and quality of care [20]. The health care field requires more education on risk reduction strategies; proactive management vital to addressing nihilistic attitudes, with the belief that to provide a patient with a dementia diagnosis that has no cure is providing them with a diagnosis that was not actionable in a clinical manner [20]; stigmatic beliefs; helplessness and strain of the healthcare system; and the widespread under-diagnosis of dementia. Furthermore, it is crucial to be educated and abreast of non-pharmacologic interventions that can support brain health promotion [13]. Though there is no known cure for AD or other dementia, education on risk factors that are modifiable is vital because it can delay the onset or slow the progression of the disease [13].

Consequently, when dementia education is prioritized to reduce stigma and improve brain health promotion, early diagnosis, and quality of care for people with AD or another dementia, patients are satisfied, and patient outcomes improve. In working to elevate physician education on AD and other dementia, an essential source of information is the Alzheimer's Foundation of America (AFA). They offer educational programs and materials for both the communities and professionals who work with those with dementia, persons with dementia, and their caregivers and provide resources on memory screening and diagnosis. They also run the national memory screening program, which allows individuals concerned with memory loss and other cognitive changes to be screened. Though not a diagnosis of any illness, this screening offers the individual the opportunity to obtain a baseline of their thinking skills and then return to follow up at a later date. When there is

an apparent concern, the AFA recommends the screened individual to follow up with their PCP. The Alzheimer's Foundation of America also provides the opportunity for healthcare providers to refer people with cognitive impairment, diagnosed or undiagnosed, to receive accurate information and support on AD and other dementias.

Throughout the various studies there was no indication that health insurance played a role as a barrier to PCPs conducting cognitive assessments. The Medicare Wellness Visit (AWV) plan covers older adults ages 65 years and older. The cognitive assessment is part of a routine visit and includes a brief cognitive test. Medicare covers a separate visit to conduct a more detailed cognitive assessment and development of a thorough care plan.

4. Discussion

4.1. Early Dementia Diagnosis

Most efforts in the United States to improve primary dementia care have been either isolated or limited in scope, usually addressing any minor subset of barriers with a modest intensity and limited coordination [19]. Many experts believe that achieving meaningful and sustained improvements in dementia diagnosis and disease management and care should ideally be developed and mandated by active and specific national dementia strategies [19]. The evidence reviewed suggests that timely diagnosis and quality care of people with AD or other dementia is more an exception than a rule in many parts of the United States. Research has steadily shown that dementia diagnosis commonly occurs in the middle to later stages of the disease [21]. Diagnosis often occurs at the time of crisis [21].

4.2. Barriers to Diagnosis—Professional and Public Education

Dementia education is key to positively affecting professional providers' and the public's help-seeking behaviors. Evidence suggests low dementia awareness of the early signs and symptoms of AD or another dementia. There is evidence that delayed PCP responses may be due to a limited understanding of disease experience, attitudes associated with nihilism, stigma, ageism, and deficits in diagnosis disclosure, communication, and disease management skills.

Currently, most educational efforts to enhance PCP practice focus on improving their formal knowledge of dementia, such as pathophysiology and pharmacology. Primary care physicians believe that educational interventions should have a broader scope that addresses the gaps in attitudes, behaviors, knowledge, and skills. The term "knowledge" should include disease recognition, conceptual framework, and therapeutic interventions and their perspectives in learning and support requirements to provide AD and other dementia care. Relevant topics to explore more thoroughly and that would be relevant to PCP and other medical professionals are:

(a) Professional and public expectations of PCP roles and responsibilities;
(b) Consistent, standardized, and effective educational tools and training strategies;
(c) Integrated models of dementia care (e.g., feasibility and long-term care cost-effectiveness;
(d) Dementia care collaborations between PCPs and specialists;
(e) Barriers and incentives to PCP participation in multidisciplinary dementia care and delivery systems.

Finally, the generation of new knowledge revised cognitive assessment tools that consider the diverse older adult population differences in information, education, experiences, culture, language, beliefs, and attitudes. There is also a critical need to effectively transfer knowledge gained and convert the evidence into tangible and substantial practice and interventions.

Without forward and consistent movement on recommendations, AD and other dementias may be the main problem, causing more under-detection, under-diagnosis, and misdiagnosis that escalates caregiver burden, additional illnesses, and economic issues. Therefore, medical education regarding AD and other dementias should evolve from a mainly disease-focused emphasis to a broader view that dementia is a complex, chronic, and progressive disorder that can be responsive to early, comprehensive, and personalized

treatment and management plans. These plans should focus on the support of PCPs in their practice and plans and would require a shift in acquiring new and diverse skills in medical training and practice, including in wider society [22]. Consistent medical training should be a part of awareness-raising and educational interventions to reexamine dementia more accurately and increase the public's understanding of it [22].

5. Implications to Advance Physician Practice

These studies represented the challenges primary care physicians must overcome to improve early detection and diagnosis of cognitive impairment related to AD and other dementias. Moreover, they reveal the need to train physicians, medical students, and other medical staff to screen the cognitive functions of patients, especially those 65 years and older. Furthermore, the implementation of either national or statewide educational programs that help educate the medical staff will contribute to increasing their clinical skills and equip them to accurately screen patients' cognitive functioning. Hence, identifying cognitive changes leading to AD or other dementias. According to Islam et al. (2020), the training of medical staff in primary care needs to be ongoing from medical school through practice to ensure long-term sustainability.

6. Limitations

One of the primary limitations of this review was that the studies were only targeted to primary care physicians and were not inclusive of other healthcare professionals. Furthermore, another limitation is that many of the studies focused on primary care physicians who belonged to medical centers. Furthermore, another constraint worth mentioning is the integrity of the participants. Moreover, being able to identify studies that represent the diverse population of physicians in the United States is difficult.

7. Recommendations

Cognitive impairment requires the attention of the healthcare community because it is a medical condition. Cognitive impairment assessment has been included in the Medicare Annual Wellness Visit (AWV) since it was implemented in the Affordable Care Act in 2010. However, in primary care, cognitive impairment, AD, and other dementias have been under-diagnosed. According to the Alzheimer's Association Report (2019), approximately 50 percent of patients have their cognitive functioning routinely assessed by primary care physicians. This literature review was used to understand and improve PCPs cognitive screening accuracy, knowledge, and confidence.

8. Conclusions

This review was conducted to determine whether educational intervention in a primary care setting would improve cognitive screening accuracy and rates. The review concluded that educational intervention was needed to train PCPs on the proper use of cognitive assessment tools and to initiate the conversations about memory loss and cognitive functioning in patients aged 65 years and over. This is essential to reducing the dementia detection and diagnosis gap. It is necessary for organizations to have a culture that promotes learning. Strong leadership receptive to change may push the system towards mandatory training for dementia, but PCPs need to follow the set guidelines. More work is needed to overcome the barriers associated with the implementation of interventions in order to increase feasibility and effectiveness. Further research can contribute to a better understanding of the disease and the experience of U.S. PCPs. Consistent forward-moving strategies and actions are needed to change attitudes and decrease knowledge deficits as the numbers of older adults with AD and other dementias increase.

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MDPI AG
Grosspeteranlage 5
4052 Basel
Switzerland
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