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Review

Charting Alzheimer's Disease and Dementia: Epidemiological Insights, Risk Factors and Prevention Pathways

Israel Contador [1,2,*], Bárbara Buch-Vicente [1,*], Teodoro del Ser [3], Sara Llamas-Velasco [4,5], Alberto Villarejo-Galende [4,5], Julián Benito-León [4,5,6,7] and Félix Bermejo-Pareja [6,7]

1 Department of Basic Psychology, Psychobiology, and Methodology of Behavioral Sciences, Faculty of Psychology, University of Salamanca, 37005 Salamanca, Spain
2 Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, 17117 Stockholm, Sweden
3 Alzheimer Centre Reina Sofia—CIEN Foundation, Institute of Health Carlos III, 28031 Madrid, Spain; tdelser@fundacioncien.es
4 Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), 28041 Madrid, Spain; sara.llamas@salud.madrid.org (S.L.-V.); alberto.villarejo@salud.madrid.org (A.V.-G.); julian.benito@salud.madrid.org (J.B.-L.)
5 Department of Neurology, University Hospital 12 de Octubre, 28041 Madrid, Spain
6 Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), 28029 Madrid, Spain
7 Department of Medicine, Faculty of Medicine, Complutense University, 28040 Madrid, Spain
* Correspondence: icontador@usal.es (I.C.); barbarabuch@usal.es (B.B.-V.)

Abstract: Alzheimer's disease (AD), the most common cause of dementia, is a complex and multifactorial condition without cure at present. The latest treatments, based on anti-amyloid monoclonal antibodies, have only a modest effect in reducing the progression of cognitive decline in AD, whereas the possibility of preventing AD has become a crucial area of research. In fact, recent studies have observed a decrease in dementia incidence in developed regions such as the US and Europe. However, these trends have not been mirrored in non-Western countries (Japan or China), and the contributing factors of this reduction remain unclear. The Lancet Commission has delineated a constrained classification of 12 risk factors across different life stages. Nevertheless, the scientific literature has pointed to over 200 factors—including sociodemographic, medical, psychological, and sociocultural conditions—related to the development of dementia/AD. This narrative review aims to synthesize the risk/protective factors of dementia/AD. Essentially, we found that risk/protective factors vary between individuals and populations, complicating the creation of a unified prevention strategy. Moreover, dementia/AD explanatory mechanisms involve a diverse array of genetic and environmental factors that interact from the early stages of life. In the future, studies across different population-based cohorts are essential to validate risk/protective factors of dementia. This evidence would help develop public health policies to decrease the incidence of dementia.

Keywords: Alzheimer's disease; prevention; risk factors; public health; epidemiology

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1. Introduction

Dementia is one of the leading causes of dependency and disability worldwide [1]. It is estimated that more than 50 million people suffer from this condition, with Alzheimer's disease (AD) being the primary dementia subtype (60–70%) [2]. Due to the aging of the global population, it is expected that the prevalence of dementia will rise to 131.5 million cases by 2050, especially in low- and middle-income countries [3]. The World Health Organization (WHO) estimates dementia cost around USD $818 billion in 2015, equivalent to 1.1% of global gross domestic product, ranging from 0.2%—low- and middle-income countries—to 1.4%—high-income countries [4,5]. Therefore, dementia is considered a global public health priority.

Currently, it is well-known that AD is a chronic brain disorder with a long silent period of decades (preclinical phase) before its clinical onset [6–8]. This fact, linked to the failure of pharmacological AD therapies, has boosted research on dementia/AD prevention [9]. Thus, recent studies have shown that the age-specific incidence of dementia is unexpectedly decreasing in some countries [3,10–13], but explanatory factors remain undetermined, and further evidence is needed to resolve this enigma [14–17]. During the last few years, there has been growing interest in preventive approaches based on controlling dementia/AD risk factors [18,19]. A scientific report has recently identified 12 modifiable dementia risk factors (i.e., low education, arterial hypertension, hearing loss, smoking, obesity, depression, physical inactivity, diabetes mellitus, low social contact, excessive alcohol consumption, head injury, and air pollution), which collectively account for almost 40% of the worldwide burden of dementia [15]. Accordingly, the WHO has already issued guidelines on risk reduction of cognitive decline and dementia [5]. At the same time, various medical societies have proposed a second generation of memory clinics (Brain Health Services) aimed at developing evidence-based counseling for dementia prevention [20–23]. These efforts have the potential to significantly reduce socioeconomic dementia costs; For instance, the reduction of the incidence of AD by 20% by 2050 is estimated to save Europe up to EUR 33 billion [24].

The main objective of this review is to outline the current state of evidence concerning the modifiable factors associated with dementia/AD. Specifically, we examine epidemiological trends across different cohorts, risk and protective modifiable factors, and general strategies to delay dementia onset.

2. Methods

This research is a critical narrative review compiling several miscellaneous searches in PubMed using the following Medical Subjects Headings (MeSH): "Dementia/AD risk factors", "dementia/AD epidemiology", "dementia/AD meta-analysis", and "dementia/AD review". The leading search was conducted between May and December 2023, and various combinations of Boolean operators were used, along with other search strategies (i.e., backward reference searching), to enhance the quality of the search. English was the primary language for the selection, although high-quality scientific papers in other languages were also reviewed. All authors, who are experts in the field, approved the final information.

3. Is the Incidence of Dementia on the Rise or Declining?

Manton et al. [25] provided initial evidence of declining prevalence (from 5.7% to 2.9%) of dementia in the elderly population of the United States (national register) between 1982 and 1999. This reduction was significant in mixed and vascular dementias, but not in AD. Subsequently, Rocca et al. (2011) [26] conducted a study across various communities in the USA, revealing a decline in the incidence of dementia and cognitive impairment over 10–20 years. Since then, new data on dementia prevalence and incidence have emerged, mainly from population-based cohorts. Table 1 shows the decreasing incidence of dementia among older adults over the past two decades in developed Western countries, a consistent trend in scientific reviews and worldwide reports, including in non-Western countries [13,27,28]. However, other developed non-Western nations such as Japan [29], Korea [30], and China [31] have shown an increased prevalence rates of dementia. In addition, rigorous surveys on dementia trends are lacking in Africa, with the exception of Nigeria, and Latin America [32]. The following epigraphs describe the main RF and PF of dementia.

Table 1. Incidence studies of dementia/AD studies with long-term follow-up intervals.

Author/Year/Country	Follow-Up (Years)	Dementia Subtype	Preval	Incidence	Study Name
Western countries					
Manton/2005/US [25] **	18	Mixed	↓	—	LNLTCS
Langa/2008/US [33] *	9	Dementia	↓	—	HRS
Hall/2009/US [34] *	9	Dementia	#	—	Indianapolis cohort. (African Americans)
Hebert/2010/US [35] *	10	AD	—	#	Chicago neighborhoods
Lobo/2011/Spain [36] *	>10	Dementia	↓	— α	ZARADEMP
Rocca/2011/US [26] **	10–20	Dem/AD	—	↓ #	Several
Schrijvers/2012/Holland [37] *	10	Dem	—	↓ &	Rotterdam
Wiberg/2013/Sweden [38] *	30	Dementia	#	—	Gothenburg cohorts
Abdulrahman/2014/UK [39] **	12	AD	↑	↑	PEDW (Wales)
Grasset/2016/France [40] *	10	Dementia	—	↓ ω	PAQUID-Three City
Matthews/2016/UK [41] *	7–12	Dementia	—	↓	CFAS
Satizabal/2016//US [3] *	30	Dementia	—	↓	Framingham Heart
Kosteniuk/2016/Canada [42] **	8	Dementia	↑	↓	Saskatchewan heath data
Wimo/2016/Sweden [43] *	6	Dementia	↓	—	Sweden, rural area
Ahmadi/2017/UK [44] **	10	Dementia	—	↓	ELSA
Cerasuolo/2017/Canada [45]	12	Dementia	—	↓ ~	Several
Derby/2017/US [34] *	22	Dementia	—	↓	Einstein Aging Study
Noble/2017/US [46] *	7	Dementia	—	↓	WH-I-Aging Study
Peres/2017/France [47] *	20	Dementia	↓	—	PAQUID&AMI
Chen/2018/US [48] **	12	Dementia	↓	—	HR Study
Hendrie/2018/US [49] *	9	Dem/AD	—	↓	WHICAP
Seblova/2018/Sweden [50] **	30	Dementia	—	↓	National Swedish Registry
Rajan/2018/US [51]	18	AD	#	#	CHAP Study
Sullivan/2019/US [52] *	40	Dementia	—	↓	Monongahela Valley
Ding/2020/Sweden [53] *	25	Dementia	—	↓	Stockholm (2 Cohorts)
Wolters/2020/US-Europe [12] *	27	Dem/AD	—	↓	Several
Farina/2022/US [54] **	16	Dem/AD	↓	↓	HRS
Van Bussell/2022/Netherland [55]	12	Dementia	—	#	Dutch Primary Care
Chen-Y-/2023/UK [56]	17	Dementia	—	↓γ, ↑γ	ELS of Aging
Non-Western countries					
Gao/2016/Nigeria [57]	9	Dem/AD	—	#	IIDP
Ohara/2017/Japan [58]	27	Dem/AD	↑	↑	Hisayama
Ding/2020/China [59]	29	Dementia	↑	↑	SESD&SAS (Shanghai)
Shimizu/2022/Japan [60] *	19	Dem/AD	↑	—	Nayakama town
Huang/2024/Taiwan [61]	13	Dementia	—	↑	National Taiwan cohort

All included studies have at least 5 years of follow-up and data are referred to the last waves. ↓ Decrease; ↑ Increase; # Stable; — Not studied; & without statistical significance; * Population cohorts; ** Database, cohorts; α: Only in men; ω: Only in women; ~: only in very old; #: only shown in a group. ↓γ period 2002–2010, ↑γ period 2010–2019. Abbreviations: Preval: Prevalence; Dem = Dementia; UK: United Kingdom; US: United States. Study names: CFAS: Cognitive Function and Ageing; CHAP: Chicago Health and Aging Population; ELSA: English Longitudinal Study of Ageing; HRS: Health and Retirement Study; IIDP: Indianapolis-Ibadan project; LNLTCS: National Long Term Care Surveys; PAQUID: Personnes Agés QUID; PEDW: Patient Episode Database for Wales; SEDS: Shanghai Epidemiological Survey of Dementia and Alzheimer's disease; WHICAP: Washington Heights-Inwood Columbia Aging; ZARADEMP: Dementia Prevalence Study from Saragossa, Spain.

4. Risk Factors

The term "risk factors" (RFs) is a concept widely used in epidemiology that has gained prominence in the field of cardiovascular diseases (see Framingham Heart Study, 1948) [3]. This landmark of cardiovascular research, with an exceptionally long-term follow-up, raised awareness about the identification of RFs and their importance for preventing diseases [62]. Data from this pioneering study and other comparable cohorts marked the beginning of a paradigm shift—the era of prevention, which highlights the importance of lifestyle as the cornerstone of health. Consequently, terms such as "healthy aging" or "successful aging" have been more frequent in scientific publications since the 1980s. Even the World Health Organization (WHO), at the First International Conference on Health

Promotion (Ottawa, 1986), emphasized that individual responsibility and health promotion are essential for healthy aging. Since then, significant progress has been made in the field of disease prevention, including dementia/AD.

4.1. Genetic Risk Factors

The heritability of dementia/AD is still poorly understood [63]. Basically, most of the genetic analyses have been performed in clinically diagnosed AD, while studies in other dementias (mainly vascular) are quite limited [64,65].

In this context, genetic forms of AD, which account for approximately 1% of cases, are due to monogenic mutations that lead to early dementia onset. Most of these mutations (70%) are found in the presenilin 1 gene (chromosome 14). Other known mutations occur in the presenilin 2 gene (chromosome 1) and the APP gene (chromosome 21) [66]. These AD forms exhibit dominant heritability with very high penetrance, but other early AD cases may also have recessive heritability [67]. In contrast, the heritability of sporadic AD cases (i.e., non-familial and usually with a later onset—over 65 years) has a complex polygenic pattern and interacts with diverse environmental RFs [68].

The ApoE gene is a significant susceptibility factor for all forms of AD. It has three major allelic forms—ε2, ε3, and ε4—with the ε4 allele significantly increasing the risk for both familial and sporadic AD [66]. Current research has found that over 95% of individuals (aged 65 years and older) with two copies of the ApoE ε4 gene (i.e., homozygotes) show biological characteristics of AD pathology(abnormal amyloid levels in cerebrospinal fluid) [69]. In addition, these homozygous individuals also develop the disease earlier than those with other variants of the ApoE gene. Nevertheless, the ε2 allele and the Christchurch (APOE3Ch) variant in ε3 may provide resistance to AD [70]. It is worth mentioning that heritability is context-specific, being influenced by ethnicities and ancestries [63,71]. Therefore, caution should be employed when applying genetic findings on AD to diverse populations.

Genetic studies have consistently demonstrated that sporadic AD has a significant heritability (i.e., phenotypic variance attributable to genetics). According to the most extensive twin studies, the Swedish HARMONY [72] and the Finnish twin study [64], sporadic AD has a heritability of 58–79% and 60%, respectively. Most twins share genetic and environmental RFs, with a portion of heritability attributed to the interaction between genes and environment -epigenetic changes- [73–76]. However, one of the issues in the genetics of AD is the "missing heritability" (i.e., the difference between the clinical heritability from twin studies versus the genome-wide association studies [GWAS] of single nucleotide polymorphisms) [77–79]. In fact, GWAS studies quantify the heritability of AD between 3% and 53% [71], which represents less than one-third of the clinical heritability. The unexplained heritability in AD, a phenomenon observed in other complex disorders (diabetes mellitus and schizophrenia), may result from the interaction between genes (i.e., epistasis), epigenetic changes, or rare causal variants of small effect [75,80].

In the last decade, our knowledge of AD heritability has been mainly based on the GWAS, which may detect many genetic polymorphisms (SNP) associated with developing AD [81]. This technique has identified up to 73 genetic loci related to AD [82], the majority established in Caucasian ancestries, whereas other loci have been described in other non-western populations such as China [83] or Africa [78]. The weighted sum of the estimated effects of these multiple genetic variants associated with AD can be calculated as an individual polygenic risk score (PRS) [84]. The establishment of a PRS is a very complex genetic work, mainly in dementia/AD, but it may have eventual practical application for prognosis or therapy [17,85]. Extensive databases of dementia patients (mainly AD) and controls are being created in the USA and Europe. The UK Biobank, comprising nearly 200,000 individuals genetically tested [86,87], and the Health and Retirement Study in the USA (>10,000 individuals), are some examples [88]. In this context, some studies have developed specific PRS for dementia and AD [89–91], but they are currently restricted to research [63].

4.2. Early Risk Factors

Barker et al. [92] described the relationship between low birthweight and early mortality by myocardial infarction. This finding posited the possibility that infant undernutrition was associated with developing chronic disorders in later life periods. This evidence is consistent with the controversial hypothesis of developmental origins of health and disease (DOHaD) [93,94]. Borenstein et al. [95] reviewed this issue for dementia and AD, concluding that the risk of AD is likely not determined by a single period but rather a complex interplay between genetic and environmental exposures throughout all the life course. It has been claimed that infant undernutrition [96–98] is an early RF for cognitive decline and dementia, although its impact can be mediated by epigenetic mechanisms [99]. In addition, many studies, including birth registries, cohorts, and systematic reviews, have demonstrated that early life adversities (i.e., toxicities, low education, birth problems, food deficiency, body growth, brain development, and poor learning abilities) are related to mental disorders, cognitive decline, and dementia/AD [100–104]. Other longitudinal studies also emphasize the impact of socioeconomic-related factors—low parental education, poverty, famine, and/or maternal drug consumption [105–110]— on cognitive functioning and dementia/AD risk at later life periods. Experimental animal studies confirm the importance of early life events on cognitive impairment and AD [111,112], which may act through complex and synergistic biological mechanisms [111,113]. Despite these facts, early-life RFs have been ignored in some RFs taxonomies of dementia/AD [15].

4.3. Preventable vs. Non-Preventable Risk Factors

There is a lack of consensus on the extent to which dementia is preventable, and explanatory factors remain unclear [15,112,114]. The initial efforts of Henderson [115] and the EURODEM group (1991) [116] identified over 200 RFs based on case studies. Basically, dementia RFs have been classified into modifiable and non-modifiable categories. On the one hand, non-modifiable factors refer to those inherent to the individual, which cannot be altered through any specific actions, thereby limiting their direct prevention (e.g., genetic factors, gender, age). On the other hand, modifiable factors are those that can be influenced by individual's behaviors, making them open to intervention and preventive strategies. Thus, Framingham's study observed that dementia incidence has decreased within the last 30 years, making education a critical explanatory factor [3]. Other investigations are focused on health behaviors (e.g., healthy diet or cardiovascular risk management) that may reduce the risk of cognitive decline and dementia [117–122]. In addition, recent reviews underscore the influence of good living conditions and healthcare on dementia onset [13]. It is noteworthy that research in the field is typically based on epidemiological studies, making it difficult to avoid reverse causality or the exhaustive control of confounders [123].

Recently, the Lancet Commission, a group of specialized research experts addressing global concerns, conducted a review of modifiable factors that could impact dementia onset. It presented an initial report identifying nine factors [112]: low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact. Three years later, a new report of this Commission added three factors to the list [15]: excessive alcohol consumption, traumatic brain injury (TBI), and air pollution. The report of this group of experts states that these factors collectively account for approximately 40% of worldwide dementia cases [15]. This report is consistent with recent reviews, which underscores the varying impact of these modifiable factors, depending on the individual's life period [15,124], and the importance of prevention actions based on the individual's behavior. To summarize, Figure 1 displays different pathways to developing dementia and prominent modifiable risk factors at different life stages.

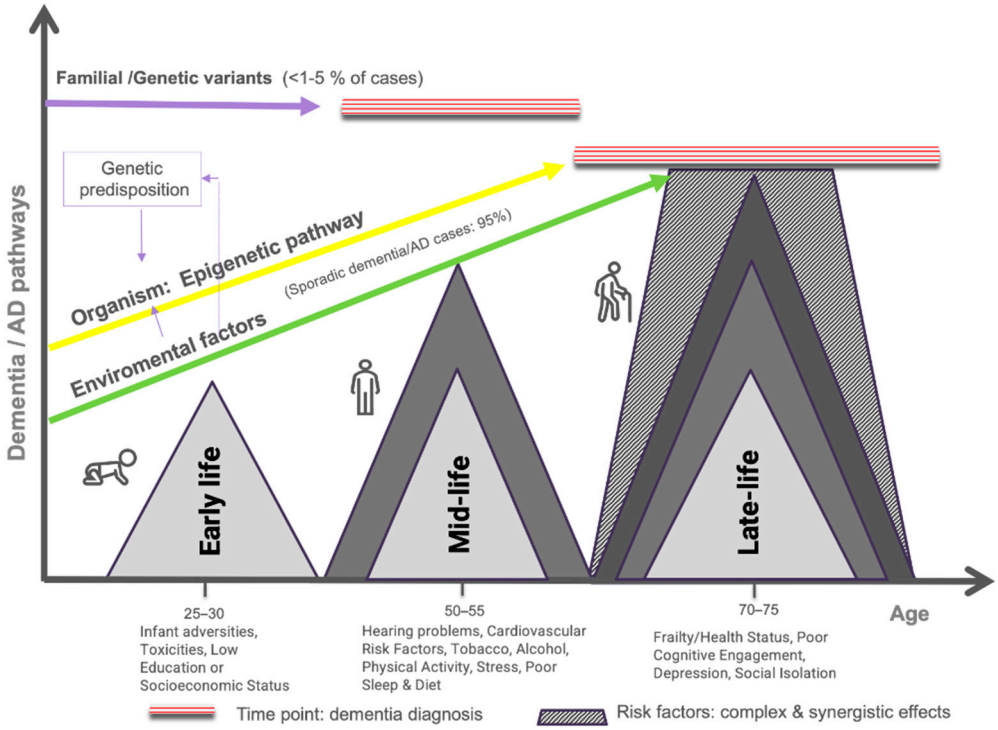

Figure 1. Dementia pathways and main modifiable risk factors across lifespan. The familial dementia category represents a minimal percentage of cases directly explained by autosomal gene mutations. In contrast, modifiable factors may exert their effects on different biological systems of the organism (genes, immunological response, and brain connectivity) at different lifespan periods, raising the likelihood of sporadic dementia/AD. In addition to their weighted specific effects, risk factors may interact in a synergistic and complex way with different lifestyle habits (e.g., diet, sleep), population factors (e.g., air pollution, health system), or unknown conditions converging at late life (represented by the dotted area). Modifiable risk factors may interact with genes (epigenetic pathway is shown in yellow), boosting the probability of AD/dementia compared to those sporadic cases without these traits (green line). It should be noted that dementia onset can vary significantly between individuals at different paths, but it is represented in a simplified visual manner for the readers (see red dotted area).

4.4. Risk Factors: Individual vs. Population Factors

An essential differentiation is the individual versus population-based RFs. The individual factors include genetics, early life conditions, medical issues, lifestyle, and psychosocial aspects. Environmental, socioeconomic, cultural, and public health conditions are population-based RF. Accordingly, the implementation of robust public policies and programs addressing these factors for health promotion could effectively reduce the burden of dementia. Table 2 summarizes the most important reviews and meta-analyses on dementia/AD risk factors.

Table 2. Selection of reviews on dementia/Alzheimer's disease risk factors.

Author/Publication Year	Risk Factors	Dementia Outcome	Preventable %, Study Type
Henderson, (1988) [115]	CRF, SERF, environmental RF	AD	-
EURODEM group [116]	Clinical and environmental RF	AD	
EURODEM group [125]	Lifestyle RF	AD	
Haan and Wallace (2004) [126]	VRF, genetics, and exposure RF	AD/VaD	
Jansson (2005) [127]	Clinical and biological RF	AD	50%
Middleton and Yaffe (2009) [128]	CRF and lifestyle	Dementia	

Table 2. *Cont.*

Author/Publication Year	Risk Factors	Dementia Outcome	Preventable %, Study Type
Ritchie et al. (2010) [129]	CRF	Dementia	Specific % by RFs
Barnes and Jaffe (2011) [130]	7 CRF	EA	up to 50.7% ¥
Song et al. (2011) [131]	Frailty index	Dementia/AD	-
Mangialasche et al. (2012) [23]	Clinical and lifestyle RF	Dementia/AD/VaD	
Anstey et al. (2013) [132]	11 RF and 4 PF	AD	
Di Marco et al. (2014) [133]	Modifiable lifestyle RF	Dementia	Systematic Review of Cohorts
Anstey et al. (2015) [134]	CRF and lifestyle RF	Dementia	-
Baumgart et al. (2015) [135]	CRF and lifestyle RF	Dementia	
Deckers et al. (2015) [136]	CRF (midlife)	Dementia/MCI	Expert Delphi Panel
Xu et al. (2015) [114]	93 clinical, lifestyle, exposure RF	AD	66%
Hazar et al. (2016) [137]	5 CRF	AD	33%
Killin et al. (2016) [138]	Environmental RF	Dementia	
Wu et al. (2016) [139]	11 RF	Dementia	
Bellou et al. (2017) [140]	Environmental RF and CRF	Dem/AD/VaD	
Livingston et al. (2017) [112]	9 CRF	Dementia	
Rakesh et al. (2017) [141]	Multiples CRF and lifestyle RF	Dementia	
Larsson and Markus, (2018) [142]	VRF	Dementia/AD	Systematic Review & MA
Anstey et al. (2019) [143]	RF: AD 34; Dem 69, VaD 8	AD/Dem/VaD	
Armstrong (2019) [144]	51 RF	AD	
Edwards III GA et al. (2019) [145]	CRF and lifestyle RF	AD	
Peters et al. (2019) [146]	Co-ocurring RF	Dementia	Systematic Review & MA
Rochoy et al. (2019) [147]	Multiples RF	AD	
Yu et al. (2020) [148]	104 modifiable RF, 11 interventions	AD	
Liang et al. (2020) [149]	Modifiable RF	Dementia	Bayesian Analysis & MA
Livingston et al. (2020) [15]	12 CRF	Dementia	40%
Kuo et al. (2020) [150]	Modifiable/Non-modifiable RF	Dementia/AD	Review
Rolandi et al. (2020) [151]	Modifiable FR cohort	Dementia	40%
Weiss et al. (2020) [16]	65 RF	Dementia	
Zhang et al. (2023) [17]	210 CRF, lifestyle, SERF	Dementia	47.0–72.6%
Jones et al. (2024) [152]	14 Modifiable RF	AD/VaD	Umbrella-Review & MA
Stephan et al. (2024) [153]	Modifiable RF	Dementia	Systematic Review & MA

Abbreviations: RF: Risk Factor; PF: Protective Factor; CRF: Clinical Risk Factor; VRF: Vascular Risk Factors. VaD: Vascular Dementia; AD: Alzheimer's Disease. SERF; socioeconomic risk factors; MA: meta-analysis. Preventable %: Percentage of Preventable Dementia; ¥ Various risk factors are reduced by 10–25%.

4.5. Individual Factors

4.5.1. Education and Cognitive Stimulating Activities

Education is a critical factor influencing the risk of dementia. Lower levels of education are consistently associated with a higher risk of dementia [15,154]. In fact, some authors consider education as the most relevant dementia RF [15,135,140,155]. Moreover, engagement in cognitively stimulating activities throughout life can enhance cognitive reserves and protect from dementia [156,157]. These factors may enable the brain to actively confront damage by promoting compensatory mechanisms through the activation of alternative brain networks or mental strategies that delay the clinical expression of brain damage [158,159]. The effects of education and cognitively stimulating activities on neural tissue may entail complex and diverse mechanisms such as neurogenesis [160–162], angiogenesis [163], synaptic density [164,165], or neural connectivity [166–170].

4.5.2. Medical Conditions

- Cardiovascular Diseases (CVDs)

Longitudinal research, including the well-known Framingham Study, has demonstrated that arterial hypertension increases the risk of dementia/AD [171], with the midlife period being critical for its development [172,173]. A recent meta-analysis highlighted that systolic hypertension is associated with an increased risk of AD by 18% and 25% in

Stages 1 and 2 of hypertension respectively [172]. Antihypertensive drugs may reduce dementia incidence and cognitive decline [57,174]; howeverthese effects are not only due to the mere decrease in blood pressure but also the preservation of brain-vessels interaction and direct action of some hypotensive drugs on neural function [175,176]. In addition, recent reviews and meta-analyses have demonstrated that total cholesterol [177], low ankle-brachial index—peripheral artery disease [178,179], body mass index—underweight and overweight in midlife [114,119,180], high homocysteine levels [105,181], low handgrip strength [182], and metabolic syndrome [183] are significantly associated with dementia, but few studies have examined AD risk combining different cardiovascular factors [184,185]. Finally, population-based studies have underlined the influence of mid-life obesity, which has been linked to vascular dementia in particular [119,186]. Significant weight changes (underweight or obesity) in later life may be associated with dementia risk, but this fact should be taken with caution because the relationship between weight change and dementia is non-linear and depends on the dementia subtype [119,187]. The interactions with comorbidities/associated illness or reverse causality effects are likely explanatory factors of this relationship.

Basically, CVDs hinder the proper brain interaction with blood vessels and the brain's natural processes for clearing neurotoxic waste. In addition, vascular conditions are associated with neuroinflammation and cerebral perfusion alterations [188]. Moreover, VRFs such as hypertension, diabetes, and obesity, especially in midlife, accelerate brain aging (progression of vascular pathology, global, and hippocampal atrophy) and cognitive decline [189]. It is worthwhile to consider that the impact of VRFs is multifaceted and may simultaneously promote microvascular disease, structural brain changes, and AD pathology. Indeed, higher levels of VRFs have also been associated with poorer brain health across grey and white matter brain structures [190]. Lastly, VRFs have also been associated with greater amyloid-β (Aβ) and tau burden [191], but these relationships remain controversial [192].

- Diabetes mellitus

Diabetes mellitus (DM), particularly Type 2 DM [112,193], is also associated with an increased risk of dementia [194,195] and mild cognitive impairment (MCI) in worldwide studies [193,196]. The conversion rate from MCI to dementia is higher in people with diabetes, although the duration and severity of the disease may modulate this relationship [197]. Diabetes increases dementia risk by up to 35% in a vulnerable population with ApoE ε4 allele [198]. Post-mortem evidence suggests that individuals with AD and Type 2 diabetes are more likely to have both AD-type and cerebrovascular pathologies [188], although other researchers assert that diabetes may increase dementia risk through interactions with other associated biological mechanisms (e.g., inflammation, mitochondrial dysfunction) [135]. Finally, few studies have analyzed the influence of prediabetes or insulin-resistance states on dementia risk, making this association inconclusive [114,145].

- Hearing impairment

Hearing loss in midlife (age 45–65 years) has been associated with cognitive decline and dementia [15,199], especially in those individuals with ApoE ε4 [200]. Pathology affecting the ascending auditory pathway and multimodal cortex, the depletion of cognitive reserves due to an impoverished listening environment, and the abnormal auditory processing in the temporal lobe may be responsible for these associations [201]. However, the specific mechanisms underlying the association between hearing loss and cognitive decline remain undetermined [202–204].

- Neurological diseases

Neurological conditions may increase dementia risk, although specific pathways to different dementia subtypes are not established.

Current evidence suggests that individuals with a history of TBI are more vulnerable to suffering dementia [15,205–208], especially Parkinson's disease and Lewy body subtypes.

However, data on AD are inconsistent [206,209]. Dysfunction of the blood–brain barrier, mitochondrial function, β-amyloid pathology, chronic neuroinflammation, tau deposition, vascular damage, and white-matter degeneration have been suggested to explain the link between TBI and neurodegeneration [200].

Stroke is linked to vascular and AD dementia subtypes [210]. AD patients may have stroke events [211]. It is known that at least 20% of patients with stroke develop dementia at 3 months [212]. A history of previous stroke is not unusual for post-stroke dementia [145], whereas around 15% of stroke patients have pre-stroke dementia [213]. Hence, there is a mutual risk relationship between dementia and stroke, which primarily share modifiable risk and protective factors [118]. It is noteworthy that vascular conditions are associated with neuroinflammation and alterations in cerebral perfusion, resulting in increased gray matter atrophy [201]. However, the association between VRFs with greater amyloid-β (Aβ) and tau burden remains controversial [159,192].

Other neurological symptoms, such as migraines or pain, are being investigated as potential RFs for cognitive impairment [214].

- Epilepsy

Various researchers have underlined the possible relations between epilepsy and AD [147,202]. Two recent meta-analyses have determined that late-onset epilepsy is a dementia RF [215]. In fact, seizures are related to all causes of dementia, including AD [216]. A recent review underlines that epilepsy and AD share pathophysiological mechanisms (e.g., hyperexcitability and excitatory–inhibitory dysregulation), leading to dysfunctions in the GABAergic and glutamatergic systems [217].

- Depression and Anxiety

Depression is a widely accepted RF for dementia/AD [15,112,114,202,218–220]. However, it is challenging to ascertain whether old-age depression acts as an RF or represents an initial psychological symptom of an underlying neurodegenerative process [15,140,147]. It is known that depression may impact brain circuits at midlife, inducting distinct forms of neural dysfunctions [221], although not all depression subtypes will have the same effect [134,141]. The severity and long-term maintenance of symptoms are essential to induce neurobiological changes (e.g., increased Aβ levels) linked to an increased dementia risk [222]. In addition, anxiety may be associated with dementia markers such as amyloid or tau [223,224], increasing the probability of vascular dementia and AD [225]. Finally, recent evidence indicates that stressful life events (e.g., loss of a parent, psychological stress in midlife, post-traumatic stress disorder) correlate with a higher risk of dementia [226].

- Sleep disorders

A recent meta-analysis conducted by Bubu et al. [227], including nearly 70,000 participants, estimates that individuals with sleep problems—including poor quality and short and long sleep duration—show a higher risk of developing cognitive impairment and/or AD. Other high-quality research confirms that daily hours—short and long sleep duration—of sleep may be related to cognitive decline [228,229]. Accordingly, limited sleep duration significantly predicted higher t-tau and p-tau in older adults, mainly observed in *APOE* ε4 carriers [230]. In general, sleep disturbances have been linked to different subtypes of dementia, such as vascular and AD [231,232]. Hypoxia associated with sleep disturbances is a major contributor to neurodegenerative changes [233].

- Frailty/Poor health

Poor health status and frailty are associated with increased comorbidities in older adults, including neurocognitive deficits [234–236] and AD [114]. Recent models indicate that cognitive frailty is driven by dysregulation across multiple cellular processes, such as genetic alterations, metabolism of nutrients and lipids, and higher levels of pro-inflammatory proteins [237]. Furthermore, frailty interacts with AD pathology, showing that individuals with a low level of AD pathology may be at a higher risk for dementia if the level of frailty is high [238].

4.6. Lifestyle/Environment Preventable Risk Factors

4.6.1. Alcohol Consumption

A recent study that followed 40,435 subjects for 27 years revealed that frequent alcohol consumption was significantly associated with dementia [239]. This observation is corroborated by other studies, indicating that alcohol abuse disorder is linked to cognitive impairment and dementia [240]. Actually, substantial alcohol consumption, which is associated with other dementia RFs—education, tobacco smoking, and depression — has neurotoxic effects and may lead to structural and functional brain damage [241]. Furthermore, a recent meta-analysis discerned that dementia risk varies depending on the doses and types of ethanol consumed [242]. Thus, modest alcohol consumption ($\leq$12.5 g/day) was associated with a reduced risk of dementia, with wine being a more suitable alcohol type. Apparently, dementia risk is increased when consumption exceeds 21 units (168 g) of alcohol weekly versus lighter drinking [15]. Different observational studies have found that light-to-moderate alcohol consumption is associated with a decreased risk of cognitive impairment and dementia [114,132,243–245]. Still, there are contradictory findings, and a direct causality of this association has not been traced [241]. Remarkably, the WHO advocates for the reduction of alcohol consumption [5], as it is considered a direct contributor to more than 200 diseases, including dementia. Likewise, the NICE guidelines [246] also recommend minimizing alcohol consumption, especially in midlife, to mitigate the risk of age-related diseases and frailty.

4.6.2. Smoking

Smoking has been widely linked to numerous diseases, including dementia and AD [15,247,248]. Hence, exposure to cigarette smoking is associated with higher amyloid-β (Aβ42) levels, excessive oxidative stress, neuroinflammation, and neurodegeneration, which may increase the probability of dementia [249]. Controversially, in some cohort studies, this risk appeared to be more pronounced in individuals who were non-carriers of the ApoE ε4 genotype [248]. The authors suggest that smoking effects may be masked in ApoE ε4 individuals due to the predominant genetic risk effect.

4.6.3. Dietary Patterns

It is known that unfavorable nutrition increases the risk of dementia. For instance, a poor diet based on saturated fats may lead to cardiovascular abnormalities, increasing the risk of AD by up to 39% [250]. There is also growing data indicating that gut dysbiosis can trigger metabolic diseases and the progression of low-grade systemic inflammation, and that it is involved in many of the major modifiable dementia RFs [251]. In contrast, diverse population studies have determined that adherence to particular healthy dietary patterns, such as the Mediterranean diet, can reduce the incidence of dementia [117,252]. The prevention of oxidative stress, inflammation, protein accumulation (amyloid and tau), and brain atrophy seem to be the main physiological mechanisms that lead to this association [117,253]. Regarding specific food intake, a recent meta-analysis found a significant linear relationship between fish consumption and the reduced risk of dementia [254]. In this sense, omega-3 (monounsaturated fatty acids) and polyunsaturated fatty acids (especially n3-PUFA) have been associated with a protective effect against dementia/AD [216,255,256]. Moreover, some antioxidants such as Vitamin E have also been linked to a protective effect against AD [257]. Finally, a recent meta-analysis has provided clear evidence that low levels of Vitamin D (25-hydroxyvitamin D) are associated with increased cognitive decline and AD [258–262]. This vitamin, present in some foods and synthesized in the skin by sun exposure, plays a significant role in vascular and immune systems.

4.6.4. Physical Activity (PA)

It is well-known that regular exercise reduces the risk of dementia [15,112,263–265], whereas poor physical activity (PA) may be responsible for 13% of AD worldwide cases [130]. While the benefits of PA in brain health have been well-documented, the influence of

sedentarism remains to be understood [266]. Basically, regular exercise provides numerous benefits to physical and mental health, including the prevention of metabolic and cardiovascular diseases, obesity, inflammatory processes, hormonal disequilibrium, and depression, which may exert a significant influence on individuals' health. In addition, PA is also associated with larger brain volumes, specifically in brain regions vulnerable to dementia and improvements in brain connectivity [267,268]. PA increases the production of neurotrophic molecules (e.g., BDNF) and reduces the expression of other molecules associated with neuropathology (amyloid and/or tau). These changes support processes associated with better brain health (neurogenesis, angiogenesis) compared to other factors that have a negative influence (e.g., inflammation or oxidative stress) [268].

4.6.5. Social Isolation

Recent studies indicate that social isolation increases the risk of dementia by 28% [269]. Individuals who live alone have less cognitive stimulation, making them more susceptible to early cognitive decline [269,270]. Moreover, unmarried men have a higher risk of dementia, although this relationship was not confirmed in women [271]. Likewise, widows are particularly susceptible to developing AD [272], with a higher risk of dementia in those without offspring [273]. According to some researchers, the feeling of loneliness rather than the social network size determines the increased dementia risk [274]. Social isolation has been associated with AD biomarkers such as amyloid and tau deposition [275]. Otherwise, it may increase the occurrence of collateral risk dementia/AD factors such as depression, anxiety, VRFs, reduced cognitive activity, or the failure to benefit from social resources (e.g., information and health-care access).

4.7. Population Factors

4.7.1. Air Pollution

There is consistent evidence that air pollutants increase the risk of dementia and cause cognitive decline [15,276–280]. Basically, air pollution exposure, especially to fine particulate matter, may increase the risk of hypertension, lipid accumulation, atherosclerosis, oxidative stress, insulin resistance, endothelial dysfunction, propensity toward blood coagulation, inflammation, and stroke, all of which are related to an increased risk of dementia [281].

4.7.2. Other Population Risk Factors

Exposure to pesticides or heavy metals may increase dementia risk by up to 50% [138,144]. Additional exposures, including other metals, solvents, or electromagnetic fields, might contribute to increased dementia risk, although scientific evidence remains inconclusive [138]. It is also worth noting that unfavorable socioeconomic statuses (e.g., unemployment, lower income) have been significantly associated with an increased risk of developing AD [17]. In brief, exposure to unfavorable environmental conditions can impact health status and increase the risk of dementia/AD, but future investigations should elucidate how these factors are related to different dementia subtypes.

5. Implications of Modifiable Risk Factors for Intervention Programs

Our knowledge about modifiable factors should ultimately lead to implementing prevention strategies and targeted intervention programs aimed at reducing dementia/AD risk. Basically, it is essential to consider that dementia is a complex, multifactorial heterogeneous syndrome, and preventive interventions should be focused on targeting several risk factors [282]. Accordingly, Ritchie et al. (2010) [129] published the first attempt to model the effects of a theoretical population-wide prevention strategy (ESPRIT study), comparing the relative effect of removing risk exposures over 7 years. In the absence of effective treatments, the authors underlined the importance of multicomponent health population-based plans aimed at reducing cognitive impairment and dementia RFs (i.e., control of diabetes, depression, high blood pressure, and CVD, fruit, vegetable and fish consumption, enhance-

ment of crystallized intelligence, promotion of physical exercise),. According with this idea, the FINGER study [19,283], a pioneering long-term randomized controlled trial, examined a multimodal program of preventive interventions in 1260 subjects at risk of dementia from the general population. Six hundred thirty-one participants were randomly assigned to a program that included diet, exercise, cognitive training, and vascular risk management. After 2 years, the study showed that the intervention significantly benefited the global cognitive performance (main outcome) regardless of participants' baseline characteristics. Other similar studies, such as the French MAPT trial [284] and the Dutch PreDIVA trial [285], designed with the same objectives, could not achieve similar cognitive results.

Recent reviews and meta-analyses have grouped RFs considering specific preventive strategies (i.e., targeting the body, compensatory interventions for brain aging, and health promotion) [284]. Particularly, Hussenoeder et al. (2018) [282] proposed a public brain health agenda following 10 key actions: (1) increasing physical activity, (2) fostering social integration, (3) improving education and fostering lifelong learning, (4) providing mentally stimulating workplaces, (5) fostering a cognitively active lifestyle, (6) proposing a Mediterranean-like diet, (7) reducing alcohol consumption, (8) stop smoking, (9) managing chronic conditions, and (10) reducing anticholinergic medication. A major challenge in establishing the effectiveness of these interventions is the limited number of long-term clinical trials, selection bias, and difficulty controlling for confounding variables. Despite this, it is essential to develop collaborative efforts to enhance new multicomponent intervention models to prevent cognitive decline and dementia at population and individual levels.

6. Discussion

Since dementia is a complex and multifactorial condition, genetic and lifestyle factors, environmental exposures, and diverse medical conditions may increase the associated risk due to synergistic and complex interactive effects. Basically, it is known that autosomal cases (i.e., presenilin-1 and 2, APP) linked to AD, the most common cause of dementia, represent a very small percentage of AD cases ($\leq$1%) versus those with a sporadic late-onset disease [286]. In fact, new investigations are covering more than 300 genes related to AD [287]. Furthermore, environmental factors may play an important role in sporadic cases, explaining between 40 and 60% of the variability [15,114]. Within this framework, the epigenetic hypothesis claims that dementia is not a suddenly occurring state, but rather a gradual change in the cellular activity that finally impacts on the baseline healthy status [288]. Thus, accumulated environmental hits may produce latent epigenetic changes (e.g., DNA methylation), altering biochemical pathways/mechanisms until a pathological threshold is reached and clinical dementia becomes apparent. It is noteworthy that dementia/AD syndrome results from numerous brain pathologies [289], involving complex neurobiological mechanisms [290].

Different scientific reports have shown that the incidence of dementia/AD among older adults over the past two decades has declined in developed Western countries. However, further evidence is needed to prove this in non-Western and developing countries. Apparently, improvements in education, lifestyle, and public health may underlie these observations, but the explanation of this enigma is controversial. The Lancet Commission had proposed 12 main modifiable risk factors associated with dementia at different weights (range: 1–8%, with education and hearing loss being the highest versus alcohol, obesity, and diabetes as the lowest) and life periods [15]. However, other reports extend them to over 200, and the Manifesto of Berlin indicates that 35% of dementia cases could be avoided just by preventing stroke and VRFs [17,118]. In fact, the precise weight of each RFs on dementia risk is difficult to establish across different worldwide populations, and there are many questions about how the RFs and PFs exert their effect. For instance, it remains unclear which type of PA (intensity, frequency and duration) offer the greatest protective effect. Different studies have also pointed out the benefits of the Mediterranean diet on brain and cognitive functioning, but there is no universal diet pattern, and how these patterns affect the brain remains undetermined. Lastly, it is necessary to understand better the interplay

between socio-behavioral habits and individual dementia RFs. Indeed, Knopman et al. (2010) [291] have pointed out that the genesis of VRFs has its roots in childhood social class, education, and culture.

At this point, it is worth considering whether dementia can be avoided. A recent robust meta-analyses (4677 subjects from 17 population-based cohorts) report that one-third of community-dwelling older adults with intermediate–high levels of AD neuropathology are not clinically demented [292]. Furthermore, some individuals reach the age of 100 having preserved their cognitive abilities, showing that exceptional longevity may be associated with neuroprotection mechanisms: resistance (i.e., avoiding pathologies) and resilience (i.e., coping with pathologies) [293,294]. These general terms (see Figure 2) are complementary and comprise specific underlying processes that are operationalized in detail elsewhere [295–297]. Basically, resilience entails three mechanisms: Brain Reserve (BR), Cognitive Reserve (CR), and Brain Maintenance (BM). BR is conceived as neurobiological capital (i.e., neurons, synapses). Therefore, some authors indicate that individuals with a more significant number of neurons and synapses may withstand a more significant neuropathological load before manifesting dementia symptoms [298]; CR refers to the active capacity of the brain to deal with brain damage, essentially activating compensation mechanisms (i.e., alternative brain networks and/or cognitive strategies) [299]. Finally, BM is defined as reduced development of age-related brain changes and pathology to preserve cognitive abilities. Higher resistance to the progression of neuropathology may be a form of BM. In brief, resilience describes individual differences in terms of brain structure and functioning, including compensation processes, based on genetics or lifestyle factors (e.g., cognitive stimulating activities). In general, the brain is plastic and can accumulate capacities and/or resources over time to cope with adverse situations. Otherwise, resistance mainly refers to the absence or lower rates than expected of pathology. This terminology is useful for communication across investigators, but more consensus is required in terms of terminology and operationalization [300].

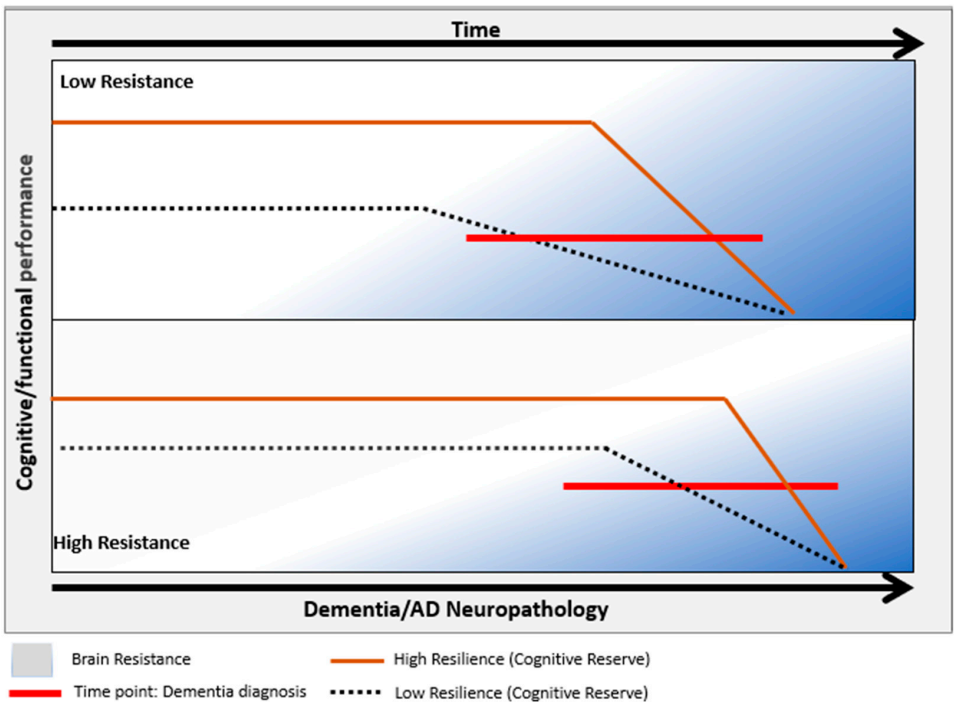

Figure 2. Coping against dementia: resilience and resistance mechanisms. The term resistance implies slower or delaying the onset of AD-associated neuropathology represented by blue color. However, resilience refers to the brain's capacity to maintain cognitive and functional performance against pathology, with cognitive reserve being the most known form. Thus, people with higher CR (brown line) may show better performance than those with lower CR when facing similar levels of pathology.

The primary limitations of this review should be considered. First, this review was not systematic, and the selection of information was based on the authors' expertise, facilitating a potential selection bias. However, it is remarkable that we covered a comprehensive number of high-quality publications (i.e., longitudinal population-based cohorts, systematic reviews, and meta-analysis) related to dementia/AD worldwide. Second, most studies evaluate the specific risk of dementia, rather than AD, in specific countries/populations. Moreover, there are significant differences in terms of methodology between studies (e.g., intervals, statistical analyses), which were not specifically addressed in this review. These aspects invite caution about the generalization of results.

7. Conclusions

Currently, scientific evidence suggests that dementia/AD is preventable, but there is a lack of consensus on the potential extent of prevention and no sure way to prevent all types of dementia exists. Accordingly, well-designed longitudinal population-based cohorts, across different populations, are needed to chart the specific weights of dementia/AD risk factors and their complex interactions, underpinning their specific mechanisms of action. Thus, it is mandatory to investigate further how environmental exposures impact our organic systems, in particular the genes and brain, across different life periods. The future of prevention comprises the development of tailored interventions and, especially, public health strategies. The design of specific preventive strategies by dementia subtypes is a present challenge in the field. Finally, dementia requires a broad and coordinated social response, designing policies to promote preventive strategies at a population-based level and high-risk groups. The development of comprehensive programs, through a coordinated and multisectoral approach in each country, is a promising perspective for preventing dementia in the future.

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Abbreviations

Aβ	Amyloid Beta
AD	Alzheimer's Disease
ApoE	Apolipoprotein E
CHAP	Chicago Health and Aging Project
CFAS	Cognitive Function and Ageing Study
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DOHaD	Developmental Origins of Health and Disease
GWAS	Genome-Wide Association Studies
IIDP	Indianapolis-Ibadan Dementia Project
MCI	Mild Cognitive Impairment
NICE	National Institute for Health and Care Excellence
PA	Physical Activity
PRS	Polygenic Risk Score
RF	Risk Factors
SAS	Survey of Aging Shanghai
SESD	Shanghai Epidemiological Survey of Dementia
SNPs	Single Nucleotide Polymorphisms
TBI	Traumatic Brain Injury
VaD	Vascular Dementia
VRFs	Vascular Risk Factors
WHO	World Health Organization

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