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Article

Thirty Risk Factors for Alzheimer's Disease Unified by a Common Neuroimmune-Neuroinflammation Mechanism

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Abstract: One of the major obstacles confronting the formulation of a mechanistic understanding for Alzheimer's disease (AD) is its immense complexity – a complexity that traverses the full structural and phenomenological spectrum, including molecular, macromolecular, cellular, neurological and behavioural processes. This complexity is reflected by the equally complex diversity of risk factors associated with AD. However, more than merely mirroring disease complexity, risk factors also provide fundamental insights into the aetiology and pathogenesis of AD as a neurodegenerative disorder since they are central to disease initiation and subsequent propagation. Based on a systematic literature assessment, this review has identified 30 risk factors for AD and then extended the analysis to further identify neuroinflammation as a unifying mechanism present in all 30 risk factors. Although other mechanisms (*e.g.* vasculopathy) were present in multiple risk factors, dysfunction of the neuroimmune-neuroinflammation axis was uniquely central to all 30 identified risk factors. Though the nature of the neuroinflammatory involvement varied, activation of microglia and the release of pro-inflammatory cytokines was a common pathway shared by all risk factors. This observation provides further evidence for the importance of immunopathic mechanisms in the aetiopathogenesis of AD.

Keywords: Alzheimer's disease; dementia; neurodegeneration; neuroinflammation; neuroimmune; microglia; cytokine

1. Introduction

The brain is the most complex organ in the human body, and Alzheimer's disease (AD) is arguably the most complex disease of the brain. One of the major hurdles encountered when formulating a mechanistic understanding with which to facilitate management strategies for AD is its immense complexity – a complexity that traverses the full structural and phenomenological spectrum, including molecular, macromolecular, cellular, behavioural and neurological processes [1,2]. AD risk factors are excellent examples of this immense complexity; these risk factors include such bewilderingly diverse conditions as medical diseases (diabetes), psychiatric disorders (depression), personal injuries (head trauma), societal factors (social isolation) and environmental issues (air pollution).

To identify a harmonizing mechanistic explanation with which to unify the many and varied risk factors for AD, a comprehensive literature review was initially completed (in PubMed, Web of Science, Scopus and Google Scholar databases including articles published up to November 2023) and identified 30 "risk" factors for AD, employing a broad definition of "risk factor": some are modifiable risk factors connected in a causative manner with AD (*e.g.* smoking, alcohol abuse, obesity); others are concomitant disorders occurring as co-morbidities (*e.g.* glaucoma; people with glaucoma are at risk for also developing AD); others are bidirectional risk factors (*e.g.* chronic pain causes neuroinflammation which is a risk factor for AD, yet the neuroinflammation is a positive

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feedback risk factor for continuing pain). This list of 30 risk factors includes the 12 modifiable risk factors identified in the 2020 *Lancet* commission (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution) as well as 18 others based on our literature review [3].

Next, all literature sources discussing the 30 identified risk factors were searched for common terms providing mechanistic explanations. The term uniting all 30 risk factors was "neuroinflammation", where neuroinflammation is defined as an activation of the brain's innate immune system in response to varied external (infection, trauma, toxin) and internal (ischaemia) challenges, as characterized by a host of cellular (especially microglial) and molecular (especially cytokine: *e.g.* Interleukin(IL)-1β, IL-6 and Tumour Necrosis Factor(TNF)-α) changes within the brain [4,5]. Since many studies provide data strongly implicating neuroinflammation as a major contributor to the aetiopathogenesis of AD, a shared neuroimmune-neuroinflammation mechanism clearly emerges as a unifying thread providing harmonization within the rich tapestry of diverse risk factors associated with AD.

Herein, the 30 risk factors for AD are presented in conjunction with a description of their neuroinflammatory mechanisms (Figure 1).

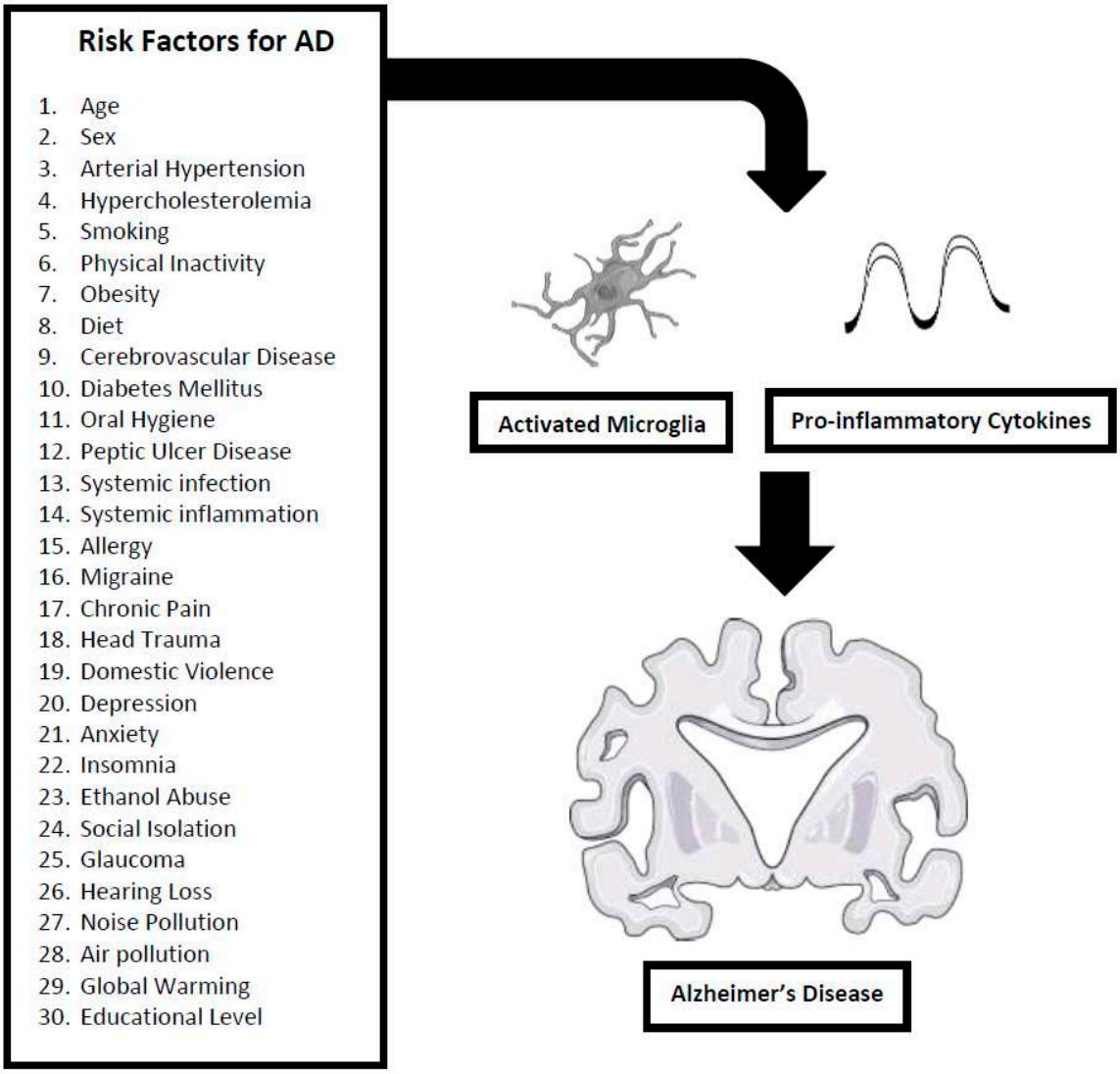

Figure 1. Thirty risk factors for Alzheimer's disease are unified by their common ability to elicit neuroinflammation, manifesting as microglial activation and pro-inflammatory cytokine release, ultimately contributing to the pathogenesis of the disease.

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2. Thirty Risk Factors

2.1. Age

Although AD is not a normal consequence of aging, age is accepted as the most important known risk factor for the disease. The number of people with AD doubles every five years beyond age 65; 40% of people age 90 years and older have AD [6]. For the majority of people with AD, symptoms first appear in their mid-60s or later. When the disease develops before age 65, it is regarded as uncommon.

The links between aging and AD are many and complex; however, neuroinflammation is a key component of this link with aging being associated with neuroinflammation and neuroinflammation being associated with AD. D'Avila *et al.* have shown that aged mice exhibit dystrophic activated microglia in the hippocampus and entorhinal cortex [7]. Aged mice also produce higher levels of pro-inflammatory (IL-1β and IL-6) cytokines in the brain and higher levels of NADPH oxidase 2 (Nox2) expression compared to younger animals [8].

In humans, aging and a chronic inflammatory state frequently co-exist in the periphery and in the brain. Aging impairs functional interactions between brain and the immune system; microglia and astrocytes, functioning in their capacity as innate immune cells, become more pro-inflammatory during aging [9]. This age-associated increase in innate immune reactivity sets the stage for an exaggerated inflammatory cytokine brain response after activation of the innate immune system during the initiation and progression of AD, leading to more severe long-lasting behavioural and cognitive deficits.

2.2. Sex

After age, sex is the other most commonly cited risk factor for AD. Women have a greater risk of developing dementia during their lifetime (even after greater longevity is considered); twice as many women have AD compared to men. A Swedish study by Beam *et al.* followed 16,926 people and found that, beginning at age 80 years, women were more likely to be diagnosed with AD than men of the same age [10]. An analogous Taiwanese study by Liu *et al.* concluded that the likelihood of developing AD over seven years was greater in women than men [11]. Finally a meta-analysis by Niu *et al.* studying the European incidence of AD calculated that annually 13 women out of 1,000 developed AD, compared to only seven men [12].

Immune mediated neuroinflammatory responses are different between men and women. Women are more susceptible to the pathological effects of inflammation than men via neuroimmune alterations including microglial activation, pro-inflammatory cytokine expression, and synaptic plasticity within neural circuitry [13]. In a study involving injecting volunteers with immunogenic lipopolysaccharides (LPS), Engler *et al.* showed that women exhibited a more profound pro-inflammatory response with significantly higher increases in TNFα and IL-6; in contrast, the LPS-induced increase in anti-inflammatory IL-10 was significantly higher in men [14]. Finally, women represent >80% of all cases of autoimmunity, particularly as demonstrated by differences in the incidence for Sjögren syndrome, systemic lupus erythematosus, Hashimoto thyroiditis, Graves disease, scleroderma, and myasthenia gravis [15]; Meier-Stephenson *et al*. have argued that AD is an autoimmune disease. Such sex-based neuroimmune differences provide a possible explanation for the corresponding sex differences in the incidence and prevalence of AD [16].

2.3. Arterial Hypertension

Hypertension is an established and accepted risk factor for AD. Numerous studies have demonstrated a relationship between decline in cognitive function and arterial hypertension across different age groups [17,18]. Systemic arterial hypertension, particularly midlife high blood pressure (BP), has been related to a higher risk of dementia, including AD. In the middle age of life (age 40–64 years) there is a positive association between the elevation of BP and the presence of cognitive

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impairment and AD risk, whilst in elderly population (age ≥ 65 years) this relationship is more controversial.

Not surprisingly, the link between hypertension and AD is multifactorial with vascular factors playing a major contributing role. However, neuroinflammation is another major mechanism linking hypertension and AD [19]. Animal studies have demonstrated that chronically elevated blood pressure leads to deleterious glial activation and increased brain inflammatory mediators, specifically pro-inflammatory cytokines such as TNFα and IL-1β. Solé-Guardia *et al.* observed that individuals with hypertension had a greater neuroinflammatory response, as illustrated by microglial activation and astrogliosis, and more severe perivascular inflammation compared to normotensives [20]. Carnevale *et al.* has shown that hypertension induced microglial activation and interleukin IL-1β upregulation triggers neuroinflammation before Aβ deposition [21].

2.4. Hypercholesterolemia

Cholesterol dysregulation serves as a risk factor for multiple diseases, including AD. Experimental studies have shown that a high cholesterol diet (HCD) promotes AD development. In rats and mice, HCD also induces significant cognitive impairment and AD-like disease [22,23]; in Japanese white rabbits on HCD, changes in brain metabolism and structure similar to those of human AD were seen [24]. Epidemiological investigations have also suggested a relationship between hypercholesterolemia and AD [25]. Xu *et al.* have suggested that high cholesterol levels were associated with increased AD pathology severity, and that the mechanism for this enhanced pathology is not entirely mediated by cerebrovascular conditions [26]. Thus, mounting evidence indicates that excessive cholesterol accumulates in AD, driving AD-associated pathological changes, and that hypercholesterolemia promotes AD development as a risk factor, especially with elevated cholesterol levels in midlife.

As with hypertension, the link between hypercholesterolemia and AD is multifactorial with vascular factors playing a major contributing role. However, neuroinflammation is another major mechanism linking hypercholesterolemia and AD [27]. For example, Thirumangalakudi *et al.* demonstrated that hyperlipidemic mice showed increased expression of pro-inflammatory microglia and cytokines/mediators including TNFα, IL-1β, IL-6, NOS2 (Nitric oxide synthase 2) and COX2 (Cyclooxygenase-2) [28]. Chen *et al.* also showed in mice that a high cholesterol diet not only enhanced NLRP3 (NLR family pyrin domain containing 3) inflammasome activation and IL-1β expression [29].

2.5. Smoking

Based on a comprehensive review, Durazzo *et al.* concluded that smoking is related to a significantly increased risk for AD [30]. Cigarette smoke/smoking is associated with AD neuropathology in both preclinical models and human studies. Jeong *et al.* have shown that smoking cessation was associated with a lower risk of dementia [31].

The negative consequences of smoking are numerous providing multiple mechanisms by which smoking contributes to pathology. However, immune-based inflammation is a significant contributor to this pathology. Alrouji *et al.* have concluded that smoking inflicts complex immunological effects, which include enhancement of inflammatory responses (activated microglia with increased pro-inflammatory cytokine responses) with a parallel reduction of some immune defences, resulting in an increased susceptibility to a persistent pro-inflammatory environment [32]. In a case-control study, Liu *et al.* found that cigarette smoking was associated with increased at-risk biomarkers for AD, as indicated by higher neuroinflammation biomarkers in the cerebrospinal fluid of participants in the active smoking group [33].

2.6. Physical Inactivity

Based on a comprehensive literature review, Meng *et al.* concluded that physical inactivity is one of the most common preventable risk factors for developing AD and that higher physical activity

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levels are associated with a reduced risk of AD development [34]. Physical exercise is also effective in improving behavioural and neuropsychiatric symptoms of AD, notably cognitive function. Chen *et al*. have likewise concluded that physical exercise is important in the prevention of AD, providing non-pharmacological treatment options [35].

The case correlating physical inactivity with AD via a neuroinflammatory mechanism is strong. Recently, Wang *et al.* demonstrated that exercise ameliorates AD by directly and indirectly regulating brain immune responses and promoting hippocampal neurogenesis [36]. Similarly, Seo *et al*. have shown that neuroinflammation-mediated microglia activation with pro-inflammatory cytokine release is enhanced by physical inactivity and downregulated by exercise [37]. Svensson and co-workers have likewise shown that exercise leads to elevated expression of anti-inflammatory cytokines, and reduced levels of pro-inflammatory cytokines and activated microglia [38].

2.7. Obesity

Obese individuals are at greater risk of developing age-related cognitive decline, mild cognitive impairment and AD [39,40]. An association between body mass index (BMI) and AD has been described with multiple groups studying the relationship between elevated BMI and AD. Obesity is thus a recognized risk factor for AD [41–44].

Miller and Spencer have suggested that neuroinflammation is the link that unites obesity to AD; obesity (and high fat feeding) leads to systemic inflammation and excess circulating free fatty acids and inflammatory mediators; these circulating cytokines and activated immune cells reach the brain and initiate local neuroinflammation, including microglial proliferation and causing synaptic remodelling and neurodegeneration [45]. Similarly, Henn *et al.* also suggest that immune dysregulation, including inflammaging (*e.g.*, increased circulating cytokines) and immunosenescence (declining immune system function), commonly occur in obesity and aging and may impact cognitive impairment, thereby promoting AD [46].

2.8. Dietary Factors

Many studies suggest that diet affects the aging brain's cognitive abilities and susceptibility to AD. In a systematic search of randomized clinical trials, reviews, and meta-analyses investigating the association between diet and AD, Xu Lou *et al*. analysed 38 studies concluding that the western diet pattern is a risk factor for developing AD, whereas the Mediterranean diet, ketogenic diet, and supplementation with omega-3 fatty acids and probiotics are protective factors [47]. The Mediterranean diet, the related MIND diet (which includes elements designed to lower blood pressure), and other healthy eating patterns have been associated with cognitive benefits in studies and a decreased likelihood of AD [48–51].

Kip and Parr-Brownlie have noted that many dietary risks factors are now known to be linked to AD-promoting neuroinflammation, particularly a high saturated and trans fat diet; indeed, dietary modifications in mice can influence levels of pro-inflammatory microglia and cytokines [52]. Conversely, dietary restriction (DR) has been shown to attenuate age-related pro-inflammatory activation of astrocytes and microglia, astrocytes and cytokines while extending lifespan in various organisms [53,54].

The microbiome also plays an essential role in the link between diet and AD. Dietary changes (either deleterious or beneficial) influence the microbiome composition, thereby affecting the gut-brain axis and the subsequent risk for AD progression [55].

2.9. Cerebrovascular Disease

Cerebrovascular disease, manifesting as cerebral atherosclerosis and arteriolosclerosis, is a risk factor associated with AD; thus, cerebral vessel pathology is a pervasive risk factor for both vascular dementia and AD [56]. A number of midlife vascular risk factors are significantly associated with AD – findings consistent with a role of vascular disease in the development of AD [57]. Stroke is a

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common pathology associated with AD among elderly individuals, a co-morbid relationship strongest in the presence of known vascular risk factors [58].

Beyond the obvious vascular contributions (ischaemia, hypoxemia) to dementia, neurotoxic brain inflammation (pro-inflammatory microglia and cytokines) accompanies the ischaemic conditions of cerebrovascular disease, thereby contributing to AD pathogenesis [59–61]. Jurcau and Simion have shown that neuroinflammatory mechanisms significantly contribute to neuronal injury during cerebral ischemia, ultimately increasing the magnitude of cerebral damage and neurological deficit in AD [62].

2.10. Diabetes Mellitus

Many studies indicate that people with diabetes, especially Type 2 Diabetes, are at higher risk to develop AD; indeed, AD has even been referred to as Type 3 diabetes [63–65]. Among people with diabetes, the risk for developing AD has been found to be 65% higher than among non-diabetic controls. In people with AD, the rate of diabetes is very high, measured in one large community study to be 35%. An even higher number of people with AD (46%) have glucose intolerance, which can be a precursor to diabetes. Even without overt diabetes, impaired regulation of glucose levels has been associated with cognitive impairment and AD risk.

Given the complexity of diabetes, the possible mechanistic links between diabetes and AD are multi-fold and include Aβ aggregation, tau hyperphosphorylation, neuroinflammation, oxidative stress and mitochondrial dysfunction. Amongst these, Van Dyken and Lacoste have argued that neuroinflammation is one of the key mechanistic connectors between diabetes and AD [66]. Similarly, based on a systematic review of *in vitro*, preclinical and clinical studies, Vargas-Soria *et al.* concluded that diabetes triggers specific responses that include upregulation of activated microglia and secretion of a wide variety of pro-inflammatory cytokines and chemokines [67]. Pathways commonly activated by diabetes-related conditions include the NLRP3 inflammasome.

2.11. Oral Hygiene (Porphyromonas gingivalis)

Bacteria and their associated inflammatory molecules are able to travel from regions of mouth infections to the brain via the bloodstream [68]. Researchers at the School of Dentistry, University of Central Lancashire, were the first to report the link between gum disease and AD, concluding that periodontitis is a risk factor for AD [69]. The mouth contains 700 bacterial species, including ones that cause periodontal gingivitis; *Porphyromonas gingivalis*, a non-motile, Gram-negative, rod-shaped, anaerobic, pathogenic bacterium from the phylum *Bacteroidota,* is the most common culprit of gum disease. Recent studies indicate that Aβ oligomerization and its associated neuroinflammatory responses may be triggered in response to this infection. *Porphyromonas gingivalis* and the gingipains enzyme which it produces have been identified in AD brains. Thus, periodontitis is a anatomically specific infection and risk factor for AD [70,71].

Neuroinflammatory processes constitute the connection between chronic, inflammatory disease of the oropharyngeal cavity and gums (periodontitis) and AD [72]. This neuroinflammation may occur by two basic processes: a. local (oral) and/or its associated systemic inflammation triggering a neuroinflammatory reaction within the brain via the distribution of pro-inflammatory mediators; or b. direct entry of bacteria into the cranial space eliciting a protective innate immune response manifesting as neuroinflammation. Also, dysbiotic oral bacteria release both bacterial products and inflammatory molecules into the bloodstream, ultimately crossing the brain-blood barrier (BBB); these bacteria can cause alterations to gut microbiota, enhancing inflammation and affecting brain function via the gut-brain axis. The trigeminal nerve has been suggested as another route for connecting oral bacterial products to the brain. Whatever the mechanism, periodontitis leads to microglial activation and pro-inflammatory cytokine release in brain thereby triggering and promoting AD pathogenesis [73,74].

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2.12. Peptic Ulcer Disease (Helicobacter pylori)

There is also an association between peptic ulcer disease and AD – analogous to the connection between oral bacteria and AD, but with the peptic ulcer bacterium (*Helicobacter pylori*) being further down the gastrointestinal tract [75,76]. Studies have shown that peptic ulcer disease increases the risk of AD via the mechanisms of systemic inflammation and altered gut microbiota [77]. In a population-based study, Chang *et al.* showed that eradication of *Helicobacter pylori* is associated with decreased progression of dementia [78]. Thus, periodontitis and peptic ulcer disease are two anatomically specific infections implicated as risk factors for AD.

Noori *et al.* have shown that *Helicobacter pylori* infection contributes to the expression of AD-associated risk factors and neuroinflammation, particularly enhanced concentrations of activated microglia and pro-inflammatory cytokines [79]. In a rat model of peptic ulcer disease, increased levels of circulating pro-inflammatory cytokines such as IL-1β have been documented [80].

2.13. Systemic Infection

The relationship between systemic non-CNS infections and AD is complex but a preponderance of evidence supports the supposition that systemic infection is a risk factor for AD [81]. Giridharan *et al.* showed that sepsis-induced peripheral infection accelerates cognitive decline and AD pathology in the AD mouse model [82]. Based on a systematic review and meta-analysis of human studies, Lei *et al.* showed that surviving sepsis was associated with an increased risk of dementia (OR = 1.62, 95% CI = 1.23–2.15, I^2 = 96.4%, p = 0.001) and that septicaemia is associated with increased risk for dementia and AD [83]. Though many microorganisms have been implicated, Herpes simplex virus 1, *Chlamydia pneumonia* and *Borrelia burgdorferi* have been discussed as infectious agents which are possible specific microbiological risk factors for AD. Conversely, systemic infection exacerbates pre-existing AD, accelerating cognitive decline and disease progression.

Systemic infections provoke a systemic inflammatory response which in turn elicits neuroinflammation. In a prospective pilot study in people with AD, Holmes *et al.* showed that cognitive function can be impaired for at least two months after the resolution of a systemic infection and that cognitive impairment is preceded by raised serum levels of IL-1β [84]. In a post-mortem study, Asby *et al.* provide evidence that systemic infection raises the levels of multiple cytokines (TNFα, IL-1β, IL-6, IL-8 and IL-15) in brain [85].

2.14. Systemic Inflammation

Acute and chronic systemic inflammation is characterized by the systemic production of pro-inflammatory cytokines (*e.g.* TNFα) that play a role in immune to brain communication; systemic inflammation increases pro-inflammatory cytokine secretion in brain, which in turn causes an increase in cognitive decline and disease progression in AD [86]. Walker *et al.* have discussed how systemic pro-inflammatory cytokines can regionally promote a pro-inflammatory environment in the central nervous system (CNS) by crossing the blood-brain barrier, by signalling through endothelial cells, and/or by stimulating the vagus nerve [87]. Through each of these routes, systemic inflammation induces reactive, pro-inflammatory microglia and astrocytic phenotypes which can promote β-amyloid oligomerization, tau hyperphosphorylation, and complement activation. Similarly, Xie *et al.* likewise discuss how peripheral inflammation is a risk factor contributing to AD by means of neuroinflammation [88]. Finally, diseases typically associated with chronic systemic inflammation, such as rheumatoid arthritis, are regarded as risk factors for AD [89,90].

2.15. Allergies

Joh *et al.* studied 6,785,948 adults aged ≥40 years who participated in a national health examination without any history of dementia before baseline; during 8.1 years of follow-up, 260,705 dementia cases (195,739 AD) were identified and three allergic diseases (asthma, atopic dermatitis, allergic rhinitis) were positively associated with dementia risk [91]. Compared with individuals without allergies, those with all three allergic diseases had substantially increased risk of AD

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(multivariable hazard ratios 1.46; 95% CI 1.25-1.70). Bożek *et al.* have also noted a similar correlation between allergies and AD [92]. Conversely, allergies can exacerbate existing health issues for older adults with AD.

Not surprisingly, there is a relationship between allergies and inflammation [93]. Kabata and Artis have described how allergies affect a variety of cytokines, inflammatory mediators and neuropeptides to yield an enhanced neuroinflammatory response [94]. Similarly, Mirotti *et al.* have extensively reviewed the relationship between allergies and brain inflammation particularly microglial activation and pro-inflammatory cytokine release [95].

2.16. Migraine Headache

In a nationwide (South Korea) cohort study, Kim *et al.* showed that the overall incidence of AD was higher in individuals with a history of migraine than in those with no migraine history (8.0 per 1,000 person-years vs. 4.1 per 1,000 person-years) [96]. Similarly, in a population-based cohort study involving 88,390 participants, Hurh *et al.* concluded that migraine is associated with an increased risk of subsequent AD [97]. Multiple other epidemiological studies support the observation that migraine is a risk factor for AD [98,99].

Migraine is a neuroinflammatory disorder [100]. The implications of neurogenic inflammation and neuroinflammation in the pathophysiology of migraine have been clearly demonstrated in preclinical migraine models involving the trigemino-vascular system, including dural vessels and trigeminal endings. Neuroinflammatory pathways, specifically those involving inflammasome proteins, are regarded as clinical biomarkers and promising druggable targets for migraine [101].

2.17. Chronic Pain

In a nationwide propensity-matched cohort using administrative data, Bornier *et al.* noted that among 64,496 French individuals, the incidence of AD was higher in the chronic pain population than in a control group (1.13% vs. 0.95%, p <0.001); chronic pain increases the risk of AD [102]. Supportively, in a systematic review, Innes and Sambamoorthi documented the potential contribution of chronic pain and common chronic pain conditions to subsequent cognitive decline, new onset cognitive impairment, and incident dementia including AD [103]. Also, Cao *et al.* provide evidence that supports a risk factor link between chronic pain and AD [104].

In mechanistic considerations, Vergne-Salle and Bertin discuss how afferent nerve fibres carrying pain information are responsible for peripheral sensitization linked to inflammation molecules; these afferent fibres release neurotransmitters in the dorsal root ganglion and dorsal horn of the spinal cord, activating microglia and producing pro-inflammatory cytokines and chemokines throughout the CNS [105]. Moreover, as with many of these risk factors, the relationship is bidirectional, self-sustaining and mutually triggering, as evidenced by the fact that neuroinflammation enhances chronic pain perception [106].

2.18. Head Trauma

Young adults who experience a moderate or severe head injury have more than double the risk of developing AD and other forms of dementia later in life [107]. In a study based on a population-based prospective historical cohort design, Plassman *et al.* showed that both moderate head injury (hazard ratio [HR] = 2.32; CI = 1.04 to 5.17) and severe head injury (HR = 4.51; CI = 1.77 to 11.47) were associated with increased risk of AD [108]. Thus, there is evidence for an association between a history of previous head injury and the risk of developing AD.

Schimmel *et al.* have shown that neuroinflammation following traumatic brain injury is a chronic response to an acute injury [109]. Simon *et al.* have demonstrated that some individuals with traumatic brain injury develop chronic neuroinflammation, which can last for years after the injury, and is associated with activated microglia and the release of pro-inflammatory cytokines – a conclusion also supported by Xiong *et al.* and Zheng *et al.* [110–112].

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2.19. Domestic Violence

Intimate partner violence (IPV; also termed spousal abuse or domestic violence) forms a sub-group of head trauma scenarios uniquely correlated with AD [113]. However, IPV is more than a focussed sub-type of head trauma. Unlike the head trauma typically seen during accidents or in professional athletes, IPV also comprehensively encompasses psychological, sexual, and financial abuse and not infrequently is accompanied by alcohol or substance abuse; the nature of the physical violence in IPV is also different, frequently involving manual or ligature partial strangulation.

A 1990 case report by Roberts *et al.* describing a 76-year-old woman with dementia connects IPV and AD [114]. A woman was found unconscious with head contusions; her relatives disclosed that her husband had been abusive for years. A post-mortem brain examination revealed morphological and immunological characteristics showing that the woman's IPV-associated brain trauma contributed significantly to the development and progression of her dementia. The consequences of traumatic brain injuries (TBI) are significant, with evidence suggesting a single TBI may double one's likelihood of developing dementia. Traumatic brain injuries are highly prevalent amongst victims of IPV, arguably leaving hundreds of millions of women worldwide at increased risk for developing dementia.

The connection between IPV and AD is clear, and involves multiple mechanisms including neuroinflammation. Newton *et al.* have shown that IPV histories are associated with biologic mediators of inflammation, particularly elevated levels of IL-6 [115]. Similarly, Madison *et al.* have shown that IPV is associated with augmented pro-inflammatory cytokine response including IL-6 and TNFα [116].

2.20. Depression

Various studies support that depression is a risk factor for AD. Growing evidence implies that timing of the depression may be important to defining the nature of its association with AD. In particular, earlier-life depression or depressive symptoms have been consistently shown to be associated with a 2-fold or greater increase in risk of dementia; in contrast, studies of late-life depression have been less definitive but the majority support an association [117]. A variety of studies support these conclusions that depression is a risk factor for AD [118–123].

Multiple studies suggest that neuroinflammation is the key process linking depression to dementia [124]. In depression, chronic activation of innate immunity accelerates central inflammation leading to higher levels of inflammatory cytokines, most consistently IL-1β, IL-6, and TNFα, which in turn correlates with greater depressive symptomatology [125]. Neuroinflammation is involved in the pathophysiology of depression by increasing pro-inflammatory cytokines, activating the hypothalamus–pituitary–adrenal axis, increasing glucocorticoid resistance, and affecting serotonin synthesis and metabolism, neuronal apoptosis and neurogenesis, and neuroplasticity [126].

2.21. Anxiety

Based on a comprehensive literature review, Becker *et al.* concluded that anxiety is a risk factor for AD (n = 26193, hazard ratio 1.53, 95% CI 1.16-2.01, P < 0.01) [127]. Similarly, based on a meta-analysis of prospective cohort studies listed on PubMed or Web of Science from January 2018 to January 2020, Santabárbara *et al.* evaluated nine prospective cohorts representing 29,608 participants and identified an overall relative risk of dementia of 1.24 (95% CI: 1.06–1.46) and a population fraction of dementia attributable to anxiety of 3.9%; they concluded that anxiety is significantly associated with an increased risk of AD [128].

The relationship between anxiety, neuroinflammation and AD is complex and bi-directional: anxiety causes neuroinflammation and neuroinflammation causes anxiety. Studies by Won and Kim suggest that anxiety leads to hypothalamic–pituitary–adrenal axis and autonomic nervous system disruption, which in turn induces neuroinflammatory conditions manifesting as enhanced pro-inflammatory cytokine levels from activated microglia particularly in prefrontal and limbic brain structures – this enhances AD progression [129]. Conversely, based on animal and clinical studies,

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Zheng *et al.* and Guo *et al.* have concluded that neuroinflammation induces anxiety by modulating neuronal plasticity in multiple brain regions, but particularly the basolateral amygdala [130,131]. Thus, anxiety triggers neuroinflammation central to the pathogenesis of AD.

2.22. Insomnia

Insomnia and sleep disorders constitute a well-documented risk factor for AD [132]. The majority of neurodegenerative diseases are known to cause sleep disruption, but insomnia is itself a risk factor for neurodegenerative diseases, including AD. Sleep has important roles in learning and memory consolidation and sleep deprivation affects not only the symptoms but also the pathogenesis of AD. Sleep contributes to the removal of Aβ from neural tissue: Kang *et al.* showed in transgenic mice that chronic insomnia leads to Aβ accumulation and thus AD progression [133]. Many studies have now shown that sleep deprivation is a risk factor for AD [134–139].

Neuroinflammation is central to the linkage between insomnia and AD. Zhu *et al.* showed that sleep disturbance increased IL-6 pro-inflammatory cytokine levels and induced microglia activation in mouse hippocampus, impairing hippocampus-dependent learning and memory [140]. Zielinski and Gibbons have described the altered role of the IL-1β and TNFα inflammatory cytokines and the NLRP3 inflammasome during dysregulated sleep [141]. Sleep impairment leads to neuroinflammation through increasing levels of pro-inflammatory cytokines and inflammatory agents and enzymes such as TNFα, IL-6, and IL-1, and COX levels. Chronic insomnia has also been associated with compromised BBB integrity resulting in an increased entry of peripheral immune cells and cytokines into the CNS, thus further contributing to the neuroinflammation implicated in AD pathogenesis [142].

2.23. Ethanol Abuse

Alcohol abuse has been identified as a risk factor for cognitive decline, AD and dementia and [143]. Alcoholism is associated with extensive and varied cognitive problems, including alcoholic dementia and AD. Because alcohol's effects on cognition, brain disorders, and brain chemistry share some features with AD's effects on these three areas, it is postulated that alcohol abuse increases the risk of developing AD [144–148].

Neuroinflammation is a major histochemical component of alcohol-induced neural damage [149]. Alcohol abuse is characterized by induction of peripheral inflammation and neuroinflammation, a hallmark of which is the activation of innate immunity TLR4 (Toll-Like Receptor 4) with associated microglial and inflammatory cytokine involvement. Based on mouse studies, Lowe *et al.* established that chronic alcohol consumption promotes the recruitment of peripheral macrophages into the CNS and microglia alterations through the CCR2/5 (C-C chemokine receptor types 2 and 5) axis [150].

2.24. Social Isolation

Loneliness and social isolation are widespread and significant public health risks affecting many people and placing them at risk for AD and other related dementias. In a study of 502,506 UK Biobank participants and 30,097 participants from the Canadian Longitudinal Study of Aging, Shafighi *et al.* analysed risk factors for developing AD and related dementias in the context of loneliness and lack of social support, identifying strong links between social isolation and multiple indicators of AD [151]. Similarly, in a study to establish Cox proportional hazard models with social isolation and loneliness as separate exposures, Shen *et al.* concluded that social isolation is a risk factor for AD that is independent of loneliness and many other covariates and that social isolation is an early indicator of and a risk factor for an increased risk of dementia [152].

Neuroinflammation is a definite immunological concomitant of the psychosocial problems inflicted by social isolation. In a study on eight-week-old male C57BL/6 mice, Al Omran *et al.* showed that social isolation resulted in microglial activation and the release of pro-inflammatory cytokines [153]. Analogously, in a study with BALB/c mice, Ayilara and Owoyele demonstrated evidence of

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neuroinflammation manifesting as increased activated microglial count and elevated IL-1β and TNFα cytokine levels in a social isolation rearing model [154]. Also, Vu *et al.* have shown that social isolation produces brain region-specific activation of microglia state in C57Bl/6 mice [155].

2.25. Glaucoma

Glaucoma refers to a group of diseases characterized by optic neuropathies that are commonly associated with degeneration of the retinal ganglion cells. Evidence of a link between AD and glaucoma has emerged from studies showing that patients with AD have a significantly increased rate of glaucoma occurrence [156]. Cesareo *et al.* studied 51 AD subjects and 67 sex-matched controls: subjects underwent measurements of intraocular pressure, visual field testing, and retinal nerve fibre layer thickness assessment by slit-lamp biomicroscopy – patients with AD had a higher frequency of glaucoma-like alterations [157]. Crump *et al.* studied 324,730 persons diagnosed with glaucoma from 1995-2017 in Sweden and 3,247,300 age- and sex-matched population-based controls without prior dementia: in 16 million person-years of follow-up, 32,339 (10%) persons with glaucoma and 226,896 (7%) controls were diagnosed with dementia [158]. Persons with glaucoma had increased risks for AD (adjusted HR, 1.39; 95% CI, 1.35-1.43); among glaucoma subtypes, both primary open-angle and normal-tension glaucoma were associated with increased risk for AD. Thus, people with glaucoma have an increased risk of developing AD [159,160].

Preclinical and clinical evidence supports the notion that glaucoma is a widespread neurodegenerative condition whose shared pathogenic mechanism with AD is neuroinflammation. Williams *et al.* have shown that the neuropathology of glaucoma extends beyond the visual pathways and involves pro-inflammatory neuroinflammation at both a cellular (microglia, astrocyte) and molecular (cytokine) level in other CNS locations [161]. Studies by Rolle *et al*., Rutigliani *et al*. and Soto & Howell have reached similar conclusions [162–164].

2.26. Hearing Loss

Hearing loss in ages 45-65 is a significant risk factor for dementia, possibly accounting for 8 percent of all dementia cases; the 2020 *Lancet* report determined that hearing loss across a wide variety of types and aetiologies approximately doubles the risk of dementia with even subclinical hearing loss enhancing AD risk [3]. Extensive studies by Lin *et al.* have concluded that hearing loss is associated with increased cognitive decline and incident AD and other dementias in older adults [165]. Based on an analysis of a UK biobank cohort, Jiang *et al.* concluded that in people with hearing loss, restorative hearing aid use is associated with a reduced risk of dementia of a similar level to that of people without hearing loss, thereby highlighting the urgent need to take measures to address hearing loss as a remediable risk factor for AD [166].

Seicol *et al.* have shown that age-related hearing loss is accompanied by chronic inflammation in neural structures with elevated expression of pro-inflammatory cytokines and microglial activation [167]. Similarly, Frye *et al.* have demonstrated that pro-inflammatory cytokines including TNFα and IL-1β, and chemokines including CCL2, are induced by hearing loss [168].

2.27. Noise Pollution

Despite their obvious interconnection, hearing loss and exposure to noise pollution are regarded as separate risk factors. Hearing loss caused by factors other than noise exposure is a risk factor for AD; chronic noise exposure of insufficient magnitude to cause obvious hearing loss is likewise a risk factor for AD. Epidemiological studies are increasingly identifying the association between external noise exposure (via noise pollution) and dementia [169]. Weuve *et al.* for example, showed that an increment of 10 A-weighted decibels (dBA) in noise corresponded to 36% and 29% higher odds of prevalent mild cognitive impairment (MCI; odds ratio [OR] = 1.36; 95% confidence interval [CI], 1.15 to 1.62) and AD (OR = 1.29, 95% CI, 1.08 to 1.55) [170]. Cantuaria *et al.* estimated that as many as 1,216 out of the 8,475 cases of dementia registered in Denmark in 2017 could be attributed to noise

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exposures, indicating a great potential for dementia prevention through reduction in ambient noise such as that arising from roadway traffic [171].

As with hearing loss, neuroinflammation is a central mechanistic player in the pathogenesis of noise-induced AD. Wang *et al.* showed that noise exposure is associated with elevated expression of pro-inflammatory cytokines and microglial activation in the primary auditory cortex; genetic knockout of TNFα or pharmacologically blocking TNFα expression prevented neuroinflammation [172]. Similarly, Cui *et al.* have shown that chronic noise exposure acts cumulatively to exacerbate AD pathology and neuroinflammation in rat hippocampus [173].

2.28. Air pollution

Based on a systematic literature review, Peters *et al.* concluded that greater exposure to PM2.5, NO2/NOx, and CO were all associated with increased risk of dementia, where PM2.5 is airborne particulate matter ≤2.5 μ in size [174]. Subsequently, Peters and Li have reaffirmed this observation, claiming that constituents of PM2.5, namely black carbon, organic matter, sulphates (SO_4^{2-}), and ammonium (NH_4^+) from traffic and fossil fuel combustion are significantly associated with the development of AD [175]. Also, a national cohort study (2000–2018) of long-term air pollution exposure and incident dementia in older adults in the United States showed that exposures to $PM_{2.5}$ and NO_2 are associated with an increased incidence of AD [176,177].

Campbell *et al.* have shown that particulate matter in polluted air increases biomarkers of inflammation in mouse brain, including activated microglia, and levels of pro-inflammatory cytokines such as IL-1β and TNFα [178]. Tin-Tin-Win-Shwe *et al*. have likewise shown changes in pro-inflammatory cytokine mRNA expressions in mice following nanoparticle air pollution exposure [179]. These data and others have led Block and Calderón-Garcidueñas to conclude that the emerging evidence implicates air pollution as a chronic source of neuroinflammation instigating AD with activation of microglia as key to this process [180].

2.29. Global Warming

In 2021, the World Health Organization (WHO) announced that climate change is the biggest global health threat to humanity. A 1.5°C ambient temperature increase may not influence what clothing people wear but it does induce acclimatization effects on neural pathways and mechanisms that underlie normal brain functioning; these pathways, including oxidative stress and neuroinflammation, are implicated in neurodegeneration [181]. Thus, it is possible that global warming secondary to climate change will emerge as a risk factor for AD. In addition, climate warming puts people with AD at risk for symptom worsening and disease progression [182–184]. Gong *et al.* predict a 4.5% increase in risk of dementia hospital admission per 1°C increase above 17°C and a 300% increase in hospital admissions for AD by 2040 because of climate change [185].

Given the relationship between ambient temperatures and inflammation, it is probable that neuroinflammation is part of the pathological spectrum response to global warming [186,187]. In mice subjected to heat exposure, Lee *et al.* found: 1) an increased number of glial fibrillary acid protein (GFAP)- and macrophage-1 antigen (Mac-1)-positive cells, 2) up-regulated nuclear factor (NF)-κB, a master regulator of inflammation, and 3) marked increases in COX-2, inducible nitric oxide synthase (iNOS), and cytokine IL-1β and TNFα in the mouse hippocampus [188].

2.30. Educational Level

Lower education is associated with a greater risk for AD and related dementias [189]. The 2020 *Lancet* Commission that examined dementia risk factors found 7% of worldwide dementia cases could be prevented by increasing early-life education [3]. The study found higher childhood education levels and higher lifelong educational attainment could reduce AD and dementia risk. A focussed sub-type of educational attainment is the ability to speak multiple languages; multiple studies indicate that bilingualism or multilingualism offer a degree of protective delay against the development of AD [190–192].

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The correlation of educational level with neuroinflammation is not as immediately apparent as for other risk factors, such as head trauma. Nonetheless, there are data clearly supporting a relationship between education and brain inflammatory markers. Steinvil *et al.* found a statistically significant inverse association between number of school years and high-sensitivity C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR) concluding that level of education was inversely associated with inflammatory biomarkers even within highly educated populations [193]. Similarly, Maurel *et al.* found a relationship between educational attainment and five inflammatory biomarkers (CRP, fibrinogen, IL-1β, IL-6 and TNFα) whereby a low educational attainment was associated with higher inflammation even after adjusting for health behaviours and body mass index [194]. A 2015 study by Okonkwo and co-workers showed that older adults who completed at least 16 years of education had less evidence of AD biomarkers in their cerebrospinal fluid (CSF) than people with fewer years of education [195].

Another theory suggests that education is associated with a higher socioeconomic status and quality of life that helps keep people healthy and lowers AD risk. Education can impact the type of job a person has, the environment they live in, the quality of food they can eat and the health care they receive – all of which are directly related to levels of neuroinflammation. Higher levels of education were associated with lower prevalence of diabetes and smoking in both genders and lower prevalence of hypertension and dyslipidemia in women. A combination of these factors over time add up to increased neuroinflammation and a higher AD risk.

3. Conclusions

The development of effective diagnostics and therapeutics for AD is one of humankind's pressing neuropharmacologic priorities. A hurdle in the successful attainment of these priorities is the immense cellular and molecular complexity of AD. This complexity is reflected by the equally complex diversity of risk factors associated with AD. However, more than merely mirroring disease complexity, risk factors also provide fundamental insights into the aetiology and pathogenesis of AD as a neurodegenerative disorder since they are central to disease initiation and subsequent propagation. Based on a systematic literature review, this analysis has identified 30 risk factors for AD and then extended the analysis to further identify neuroinflammation as a unifying mechanism present in all 30 risk factors. Although other mechanisms (*e.g.* vasculopathy) were present in multiple risk factors, dysfunction of the neuroimmune-neuroinflammation axis was key to all 30 identified risk factors. Though the nature of the neuroinflammatory involvement varied, activation of microglia and the release of pro-inflammatory cytokines was a common pathway shared by all risk factors. This observation provides further evidence for the importance of immunopathic mechanisms to aetiopathogenesis of AD.

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