



University of Wales
Trinity Saint David
LONDON

The Association Between Life-Course Chronic Psychological Stress and Dementia Risk in Later Life: A Systematic Review

JHANVI CHAUDHARY (2430968)

A Dissertation submitted in partial fulfilment of the requirements for the degree of
Master of Science in Public Health and Social Care in Practice

The Institute of Inner-City Learning
University of Wales Trinity Saint David – London Campus

June 2026

DECLARATION

I, Jhanvi Chaudhary, declare that this dissertation has been composed by myself, that the work contained herein is entirely my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or qualification, in whole or in part, except as specified.

Signed:.....Jhanvi.....

Date :16/06/2026

Acknowledgements

I would like to express my sincere gratitude to my supervisor, for their valuable guidance, support, and constructive feedback throughout the process of completing this dissertation. Their knowledge, encouragement, and academic support have been essential in shaping this research.

I would also like to thank the academic staff at the Institute of Inner-City Learning, University of Wales Trinity Saint David, for providing the knowledge, resources, and learning environment that supported my studies.

My appreciation extends to my friends and colleagues for their encouragement, understanding, and support during the research and writing process.

Finally, I would like to give my deepest thanks to my family for their continuous love, patience, and motivation. Their constant support and belief in me have helped me complete this dissertation journey.

Abstract

Background: Dementia is a major global public health challenge, affecting more than 55 million people worldwide. While age remains the strongest risk factor, increasing attention has focused on modifiable determinants, including chronic psychological stress. Emerging evidence suggests that prolonged stress exposure across the life course may contribute to cognitive decline and dementia through neurobiological and psychosocial pathways.

Aim: This systematic literature review aimed to examine the association between life-course chronic psychological stress and dementia risk in later life and to identify potential mechanisms linking stress exposure to neurodegeneration.

Methods: A systematic literature review was conducted following PRISMA guidelines. Searches were undertaken across PubMed, CINAHL, PsycINFO and Web of Science using predefined search terms related to chronic psychological stress, cognitive decline and dementia. Inclusion and exclusion criteria were applied, and studies were critically appraised using the Critical Appraisal Skills Programme (CASP) framework. Twenty studies met the eligibility criteria and were included in the review. Findings were synthesised using narrative thematic analysis.

Results: Four major themes emerged: (1) chronic psychological stress and dementia risk, (2) biopsychosocial stressors across the life course, (3) biological and psychological mechanisms of stress-related cognitive decline, and (4) implications for public health and social care. Evidence consistently demonstrated associations between chronic stress exposure and increased risk of cognitive impairment, mild cognitive impairment and dementia. Key mechanisms included hypothalamic–pituitary–adrenal axis dysregulation, prolonged cortisol exposure, allostatic load, neuroinflammation and vascular dysfunction. Midlife and cumulative stress exposure appeared particularly important.

Conclusion: Chronic psychological stress is associated with an increased risk of dementia and cognitive decline in later life. Although causality cannot be definitively established, the evidence supports chronic stress as a potentially modifiable risk factor. Public health interventions targeting stress reduction, mental well-being, and social determinants of health may contribute to dementia prevention strategies.

Keywords: Dementia, chronic psychological stress, cognitive decline, allostatic load, HPA axis, systematic literature review.

Table of Contents:

Declaration	2
Acknowledgements.....	3
Abstract.....	4
Chapter 1: Introduction.....	9
1.1 Background of Dementia.....	<u>10</u>
1.2 Epidemiology of Dementia in Later Life	10
1.3 Chronic Psychological Stress Across the Life Course and Ageing	11
1.4 Rationale for the Review	13
1.5 Research Question.....	13
1.6 Research Aim.....	13
1.7 Research Objectives	13
Chapter 2: Literature Review.....	14
2.1 Conceptualising Chronic Psychological Stress	14
2.2 Stress Measurement Tools	19
2.3 Dementia Pathophysiology	19
2.4 Evidence Linking Stress and Cognitive Decline	20
2.5 Theoretical Framework.....	22
Chapter 3: Methodology.....	23
3.1 Introduction	23
3.2 Framing the Research Question	24
3.3 Study Design	24
3.3.1 Strengths of Systematic Literature Review	25
3.3.2 Limitations of Systematic Literature Review	26
3.4 Search Strategy	27
3.5 Database Search Procedure	28
3.5.1 Hand Search	28
3.5.2 Grey Literature.....	28
3.6 Screening and Selection Process.....	28
3.7 Inclusion and Exclusion Criteria	29

3.8 Study Selection and Screening	30
3.9 Summary of Selected Articles	31
3.10 PRISMA Flow Diagram.....	32
3.11 Quality Assessment	33
3.12 Data Characteristics and Extraction	33
3.13 Data Synthesis.....	33
3.14 Ethical Considerations.....	34
3.15 Methodological Justifications.....	35
3.16 Chapter Summary	35
Chapter 4: Findings / Results	37
4.1 Introduction	37
4.2 Overview of Included Evidence	37
4.3 Measurement of Chronic Psychological Stress	45
4.4 Thematic Synthesis of Findings	48
4.4.1 Theme 1: Chronic Stress and Dementia Risk Across the Life Course.....	48
Sub-theme 1.1: Chronic Psychological Stress and Dementia Risk	48
Sub-theme 1.2: Stressful Life Events and Cognitive Outcomes.....	49
Sub-theme 1.3: Psychological Distress and Cognitive Impairment	49
4.4.2 Theme 2: Biopsychosocial Stressors Across the Life Course	50
Sub-theme 2.1: Midlife Stress and Long-Term Cognitive Outcomes	50
Sub-theme 2.2: Cumulative Stress Across the Life Course	50
Sub-theme 2.3: Social Determinants and Stress Distribution	51
4.4.3 Theme 3: Biological and Psychological Mechanisms of Stress-Related Cognitive Decline	51
Subtheme 3.1: HPA Axis Dysregulation and Cortisol-Related Neurodegeneration	52
Subtheme 3.2: Neuroinflammation and Immune System Dysregulation	52
Subtheme 3.3: Vascular Dysfunction and Cerebrovascular Contribution.....	53
Subtheme 3.4: Allostatic Load as a Multi-System Biological Integration Model	53
4.4.4 Theme 4: Public Health and Health and Social Care Implications.....	54
Subtheme 4.1: Population-level Dementia Risk and Attributable Burden.....	55
Subtheme 4.2: Health system burden and Economic impact.....	55

Subtheme 4.3: Socioeconomic Embedding of Stress Exposure	55
Chapter 5: Discussion	62
5.1 Introduction	62
5.2 Interpretation of Main Findings	62
5.3 Relationship Between Chronic Stress and Dementia Risk	64
5.4 Life-Course Perspective and Cumulative Stress Exposure	65
5.5 Biological Mechanisms Linking Stress and Neurodegeneration	65
5.6 Comparison with Previous Research	66
5.7 Implications for Public Health and Social Care Practice	66
5.8 Strengths and Limitations of the Review	67
Chapter 6: Conclusion	68
6.1 Recommendation.....	68
6.2.1 Recommendation for future	69
6.2.2 Recommendation for public health practice	70
6.2.3 Recommendation for policy	71
6.2.4 Recommendation for Clinical Practice	72
6.2.5 Recommendation for Society and Healthy Ageing	73
6.6 Recommendation for Future Research	74
6.7 Limitations of the study	74
References	75
Appendices.....	87
Lists of figures	8
Figure 3.9 PRISMA Diagram	8
List of Tables	8
List of Abbreviations	8
AD: Alzheimer’s Disease.....	8
HPA Axis: Hypothalamic–Pituitary–Adrenal Axis.....	8
MCI: Mild Cognitive Impairment.....	8
PICOS: Population, Intervention/Exposure, Comparison, Outcome, Study Design.....	8
PSS: Perceived Stress Scale	8
SLR: Systematic Literature Review	8
UK: United Kingdom	8

WHO: World Health Organisation.....	8
APPENDIX A	87
Full Search Strategy	87
Table A1. Complete Database Search Strategy	87
APPENDIX B	88
PRISMA Flow Summary	88
Table B1. Study Selection Process	88
APPENDIX C	89
Characteristics of Included Studies	89
Table C1. Characteristics of Included Studies	89
APPENDIX D	91
CASP Critical Appraisal	91
Table D1. CASP Assessment of Included Studies	91
APPENDIX E	92
Data Extraction Matrix	92
Table E1. Data Extraction Form	92
APPENDIX F.....	93
Summary of Evidence	93
Table F1. Evidence Strength Matrix	93
APPENDIX G.....	94
Review Strengths and Limitations	94
Table G1. Strengths of the Review	94
Table G2. Limitations of the Review	94
Appendix H: Data Extraction Matrix.....	95
Table 4: Thematic Synthesis Summary	97

List of Abbreviations

AD: Alzheimer's Disease

HPA Axis: Hypothalamic–Pituitary–Adrenal Axis

MCI: Mild Cognitive Impairment

PICOS: Population, Intervention/Exposure, Comparison, Outcome, Study Design

PSS: Perceived Stress Scale

SLR: Systematic Literature Review

UK: United Kingdom

WHO: World Health Organisation

Chapter 1: Introduction

Dementia is a progressive neurological condition characterised by a decline in cognitive functioning, including memory, reasoning, language and the ability to perform everyday activities independently (Scheltens et al., 2021; World Health Organization, 2023). The term dementia does not refer to a single disease but rather represents a group of disorders caused by damage to brain cells that impair cognitive functioning and behaviour (Alzheimer's Association, 2023). Alzheimer's disease is the most common cause of dementia, accounting for approximately 60–70% of cases globally (Livingston et al., 2020; Norton et al., 2014; Deckers et al., 2015). Other common forms include vascular dementia, frontotemporal dementia and dementia with Lewy bodies, which result from different pathological mechanisms affecting brain function (Roman, 2002).

Globally, dementia is recognised as a major public health challenge. Recent estimates indicate that over 55 million people are currently living with dementia, with projections suggesting this figure may rise to approximately 153 million by 2050 due to population ageing (World Health Organisation, 2023; Livingston et al., 2024). Much of this increase is expected to occur in low- and middle-income countries, where ageing populations are expanding rapidly and healthcare resources may be limited (Prince et al., 2016). The growing prevalence of dementia is therefore likely to place increasing pressure on health and social care systems worldwide (Prince et al., 2016; World Health Organization, 2023).

Individuals living with dementia often experience symptoms such as memory loss, confusion, impaired judgement, personality changes and difficulties with communication and problem-solving (Reitz, Brayne and Mayeux, 2011). As the condition progresses, individuals may struggle with daily tasks including managing finances, maintaining personal hygiene and navigating familiar environments (World Health Organisation, 2023). These changes can significantly reduce independence and quality of life for affected individuals (Prince et al., 2016). Furthermore, dementia often places a considerable emotional and physical burden on family members and informal caregivers who provide ongoing support (Livingston et al., 2020).

Despite advances in medical research, there is currently no cure for most forms of dementia, and available treatments mainly focus on managing symptoms rather than preventing disease progression (Alzheimer's Association, 2023). Consequently, increasing attention has been directed towards identifying modifiable risk factors that may reduce the risk of developing dementia or delay its onset (Livingston et al., 2020). Understanding these risk factors is essential for developing effective prevention strategies and improving outcomes in healthy ageing.

1.1 Background/Context

In the United Kingdom, dementia is a significant public health issue and one of the leading causes of death among older adults (Alzheimer's Society, 2023). It is estimated that approximately 900,000 people are currently living with dementia in the UK, and this number is expected to exceed one million by 2030 (Alzheimer's Society, 2023). The rising prevalence of dementia is associated with increasing demand for healthcare services, long-term care facilities and community-based support programmes (Prince et al., 2016).

The economic burden associated with dementia is also substantial. Globally, the total cost of dementia is estimated to exceed one trillion US dollars annually when healthcare costs, social care services and informal caregiving are considered (World Health Organisation, 2023). In addition to financial costs, dementia has significant social implications, including increased caregiver burden, reduced quality of life and increased need for long-term care (Livingston et al., 2020). Dementia places a major economic burden on the UK, with total annual costs estimated at approximately £42 billion, and projections suggest this may rise to £90 billion by 2040 as the population ages and the number of people diagnosed with dementia increases (Alzheimer's Society, 2024). A significant proportion of these costs is related to healthcare services, including hospital admissions, outpatient visits, medication use and specialist dementia care (Prince et al., 2014). Social care costs are also substantial because many individuals with dementia require home care, assisted living or long-term residential care as their condition progresses (Wittenberg et al., 2019). Informal caregiving provided by relatives and friends accounts for nearly half of the total financial burden of dementia in the UK (Alzheimer's Society, 2024).

1.2 Epidemiology of Dementia in Later Life

Dementia prevalence increases exponentially with age, particularly after 65 years. It affects approximately 2–3% of individuals aged 65–69 years, rising to over 30% among those aged 90 years and above (Livingston et al., 2024). Dementia is more common in women than men, partly because women tend to live longer and therefore reach the ages at which dementia is most prevalent (Beam et al., 2018). The most common subtype is Alzheimer's disease, accounting for approximately 60–70% of all dementia cases, followed by vascular dementia, dementia with Lewy bodies and frontotemporal dementia (Livingston et al., 2020). Global estimates suggest that more than 55 million people are currently living with dementia, with nearly 10 million new cases diagnosed each year, making it one of the leading causes of disability and dependency in older adults (World Health Organization, 2023).

Importantly, dementia develops gradually over many years and is influenced by a complex interaction of genetic, biological, environmental and lifestyle factors (Reitz, Brayne and Mayeux, 2011). Research suggests that several modifiable risk factors, including cardiovascular disease, physical inactivity, social isolation, low educational attainment and depression, may contribute to dementia risk across the life course (Livingston et al., 2020). Identifying and addressing these factors is therefore considered a key strategy for reducing the future burden of dementia.

1.3 Chronic Psychological Stress Across the Life Course and Ageing

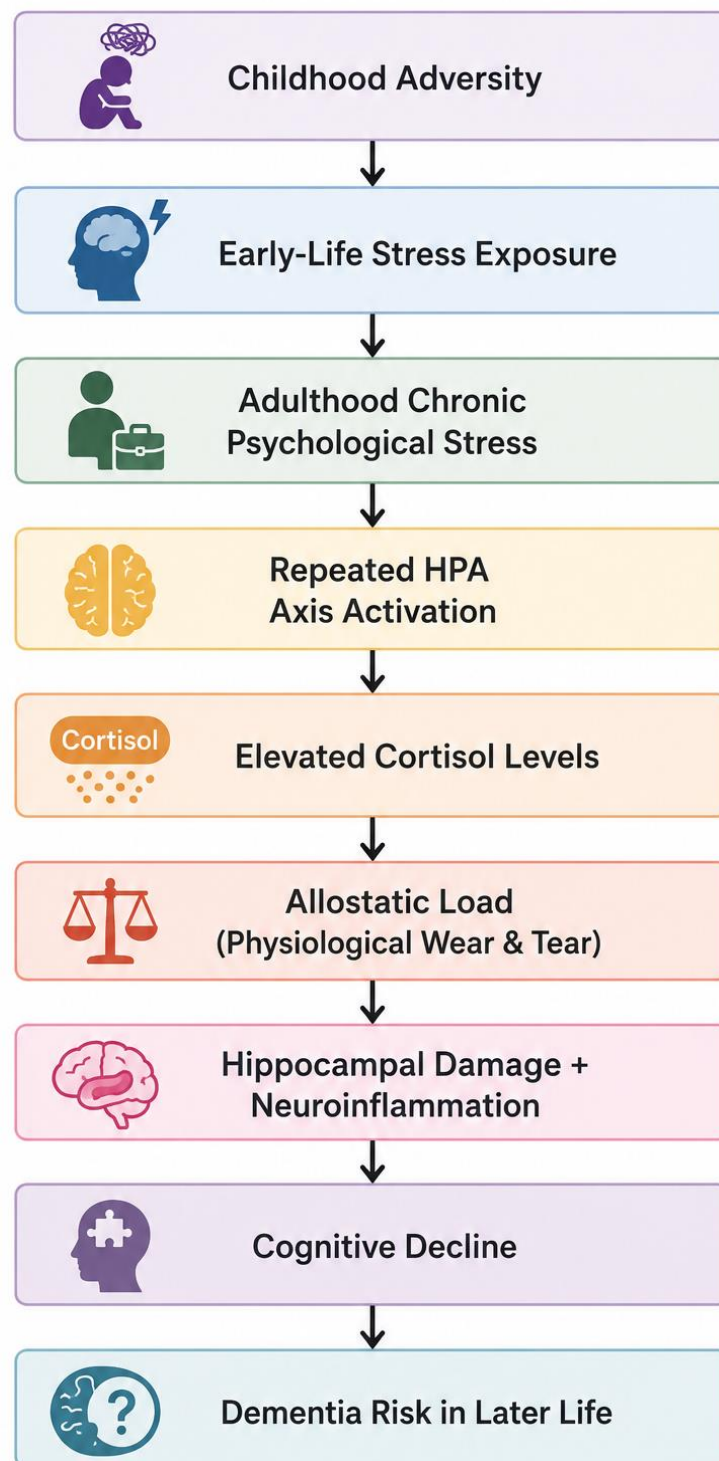
Chronic psychological stress refers to prolonged exposure to psychological demands that exceed coping resources, resulting in sustained physiological activation (Mariotti, 2021). Unlike acute stress, chronic stress involves long-term dysregulation of biological systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis. From a life-course perspective, stress exposure accumulates across childhood, adulthood, and later life, contributing to long-term physiological wear and tear, known as allostatic load (Danese and McEwen, 2022).

A growing body of research suggests that chronic psychological stress may influence brain health and contribute to cognitive impairment and neurodegenerative disease (Franks et al., 2021). Persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis during prolonged stress leads to increased production of cortisol, a stress hormone that has been linked to damage in brain regions involved in memory and learning, particularly the hippocampus (Lupien et al., 2009; Ouanes and Popp, 2019). Elevated cortisol levels over extended periods may also contribute to neuroinflammation, oxidative stress and structural brain changes associated with Alzheimer’s disease (McEwen, 2017).

Researchers increasingly recognise the importance of examining stress from a life-course perspective, as exposure to stress at different stages of life may have cumulative effects on long-term health outcomes (Ben-Shlomo and Kuh, 2002). Early-life adversity, including childhood trauma, socioeconomic disadvantage and family instability, may influence brain development and increase vulnerability to cognitive decline later in life (Luo, Beam and Gatz, 2023). Similarly, stress experienced during adulthood, such as occupational stress, caregiving responsibilities and financial difficulties, may contribute to long-term physiological changes that affect brain health (Franks et al., 2021).

Understanding the relationship between chronic psychological stress and dementia risk is particularly important for public health because psychological stress may be a potentially modifiable risk factor (Livingston et al., 2020). Interventions aimed at improving mental health,

reducing social inequalities and promoting resilience may therefore contribute to reducing dementia risk in ageing populations (Deckers et al., 2015, Willroth et al., 2024).



(Nady et al,2024)

1.4 Rationale for the Review

Dementia represents one of the most significant global public health challenges facing ageing populations (World Health Organisation, 2023). The increasing prevalence of dementia is associated with substantial healthcare costs, social care demands and caregiver burden (Prince et al., 2016). As there is currently no cure for most forms of dementia, identifying modifiable risk factors has become a key priority in public health research (Livingston et al., 2020).

The evidence also highlights the role of chronic stress in cognitive ageing and the development of dementia (Franks et al., 2021), highlighting the neurobiological mechanisms linking stress to neurodegeneration (McEwen, 2017). Evidence further shows that exposure to stress across the life course can influence long-term cognitive health outcomes (Lupien et al., 2009).

However, existing research findings remain inconsistent, partly due to differences in study designs, measures of psychological stress, and study populations (Franks et al., 2021). In addition, many studies examine stress at a single life stage rather than considering cumulative exposure across the life course (Luo, Beam and Gatz, 2023).

Therefore, this systematic literature review is necessary to bring together and synthesise existing evidence regarding the relationship between life-course chronic psychological stress and dementia risk in later life. Such a review may help identify research gaps and inform future public health policies and prevention strategies to reduce dementia risk.

1.5 Research Question

What is the association between chronic psychological stress across the life course and the risk of developing dementia in later life?

1.6 Research Aim

This systematic literature review aims to critically examine the association between life-course exposure to chronic psychological stress and the risk of developing dementia in later life, and to explore the implications of this relationship for public health prevention and social care practice.

1.7 Research Objectives

1. To review and synthesise existing empirical evidence on chronic psychological stress and dementia risk.
2. To identify the main biological, psychological and social stressors experienced across the life course that may contribute to dementia risk.

3. To explore the biological and psychological mechanisms linking chronic stress to cognitive decline and dementia.
4. To identify implications for public health and social care interventions aimed at reducing dementia risk associated with chronic stress.

2. Introduction

Dementia is a growing global public health concern, with significant social, economic, and healthcare implications. It is characterised by progressive cognitive decline affecting memory, reasoning, and daily functioning (Scheltens et al., 2021). While age remains the strongest risk factor, increasing attention has been given to modifiable risk factors, including lifestyle, cardiovascular health, and psychological conditions (Livingston et al., 2020).

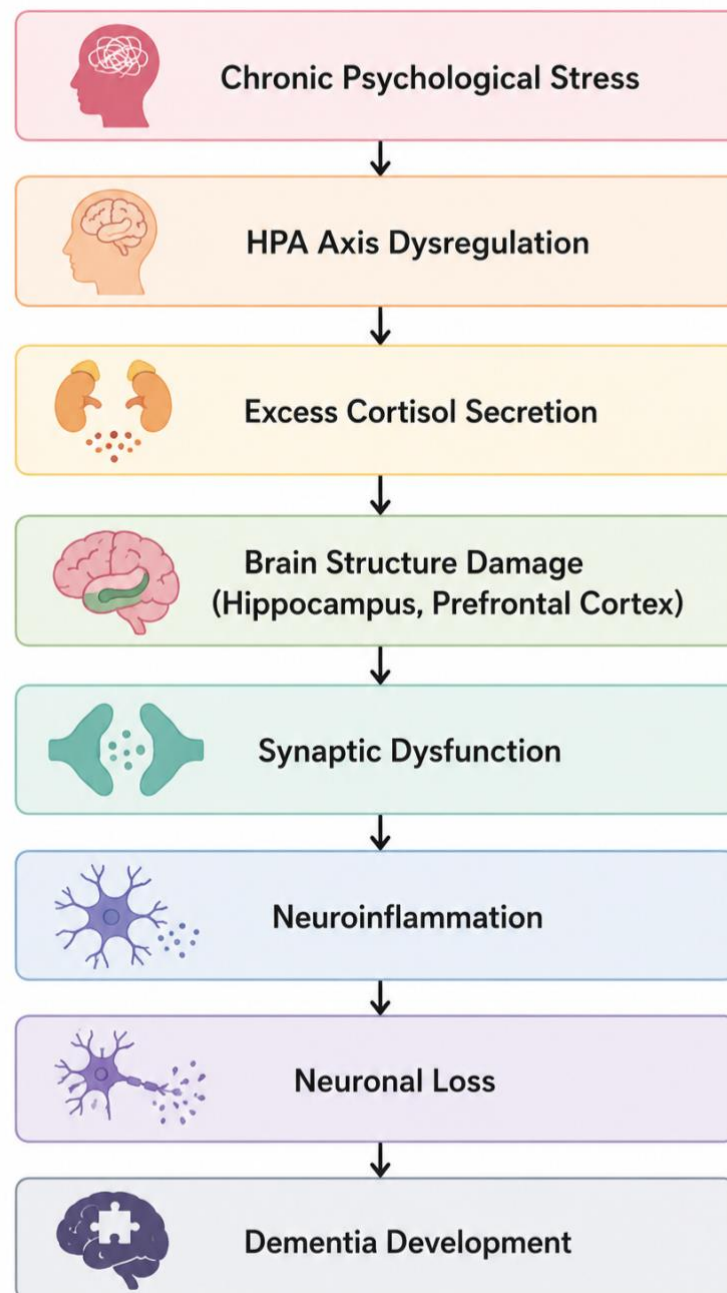
Among these, chronic psychological stress has emerged as a potentially important contributor to cognitive decline and dementia. Unlike acute stress, which is adaptive and short-lived, chronic stress involves prolonged activation of physiological stress systems, leading to sustained biological disruption (Mariotti, 2021). However, despite growing evidence, the relationship between stress and dementia remains complex and not fully understood

2.1 Conceptualising Chronic Psychological Stress

Long-term exposure to stresses that are beyond the capacity of an individual to cope and result in persistent physiological and psychological reactions is referred to as chronic psychological stress (Mariotti, 2021). In contrast to acute stress, chronic stress involves long-term activation of stress pathways as opposed to transient adaptive reactions (Russell and Lightman, 2021). The theory of allostasis, which explains the body's capacity to preserve equilibrium through physiological change in response to stress, is strongly related to the idea of persistent psychological stress (Danese and McEwen, 2022). Allostatic load, which represents cumulative wear and tear on the body and brain, can result from prolonged activation of the stress response (Guidi et al., 2021). It is becoming increasingly acknowledged that allostatic stress plays a significant role in long-term health consequences such as metabolic disorders, neurological illnesses, and cardiovascular disease (McEwen and Akil, 2020).

According to life-course perspectives, stress exposures accumulate during different phases of life, such as challenges in childhood, occupational stress during middle age, and social stressors in later life (Ben-Shlomo et al., 2022). Through processes including neuroendocrine dysregulation and chronic inflammation, these cumulative exposures can affect biological systems (Slavich, 2020). Research indicates that the hypothalamic-pituitary-adrenal (HPA) axis, which regulates cortisol secretion and stress reactivity, is frequently dysregulated in those who are under ongoing stress (Russell and Lightman, 2021). Changes in the structure and function of brain areas related to memory and cognition have been linked to dysregulation of the HPA axis (Justice, 2022).

Research has increasingly demonstrated that chronic psychological stress affects brain structures such as the hippocampus, amygdala, and prefrontal cortex (McEwen and Morrison, 2021). These regions play critical roles in learning, emotional regulation, and executive function (Justice, 2022). Prolonged cortisol exposure may contribute to hippocampal atrophy and neuronal damage, which are also commonly observed in neurodegenerative diseases such as dementia (Sotiropoulos et al., 2022). Consequently, chronic stress is now considered a potential modifiable risk factor for cognitive decline and dementia (Livingston et al., 2020).



(Chaudhari, A. and Gupta, D.K.,2025)

Table 2.1: Summary of Key Concepts Linking Chronic Stress and Dementia Risk

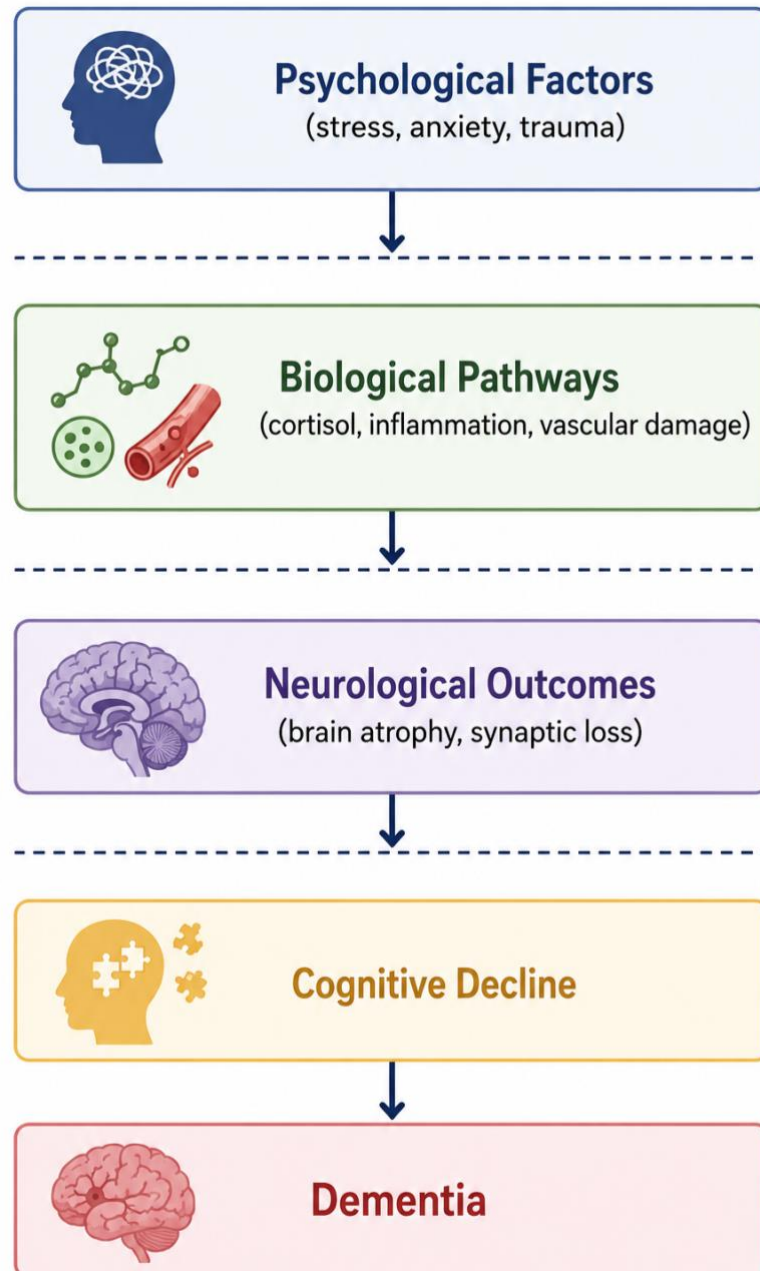
Concept	Meaning in This Dissertation	Relevance to Dementia Risk
Chronic psychological stress	Long-term psychological pressure that exceeds coping capacity, resulting in persistent emotional and physiological responses.	May contribute to cognitive vulnerability through prolonged stress-system activation.
Life-course perspective	The view that exposures across childhood, adulthood, midlife, and later life can accumulate and shape later health outcomes.	Supports the argument that dementia risk may be influenced by stress long before diagnosis.
HPA-axis dysregulation	Prolonged activation of the hypothalamic-pituitary-adrenal axis is often linked with cortisol imbalance.	May affect memory-related brain regions, especially the hippocampus.
Cortisol exposure	Repeated or prolonged exposure to the main stress hormone released during stress responses.	May be linked with hippocampal atrophy and worsening cognitive outcomes.
Allostatic load	Cumulative wear and tear on the body is caused by repeated activation of stress-response systems.	Provides a biological explanation for how chronic stress may affect cognition over time.
Neuroinflammation	Inflammatory activity in the brain involves immune and glial responses.	May interact with Alzheimer's disease-related processes and cognitive decline.
Vascular and metabolic pathways	Stress-related effects on blood pressure, sleep, diabetes risk, obesity and cardiovascular health.	May indirectly increase dementia risk through wider modifiable health factors.

2.2 Stress Measurement Tools

Identifying the long-term health effects of persistent psychological stress requires accurate measurement (Stalder et al., 2022). Both biological biomarkers and psychological self-report tools can be used to quantify stress; each captures a distinct facet of the stress response (Guidi et al., 2021). People's subjective perceptions of stress in daily life are frequently assessed using self-report instruments like the Perceived Stress Scale (PSS) (Cohen et al., 2021). The PSS evaluates respondents' perceptions of their life during a specific time period in terms of how unpredictable, unmanageable, and overloaded they are (Cohen et al., 2021). Because perceived stress frequently predicts mental and physical health consequences more strongly than objective stress exposure, these subjective assessments are crucial (Slavich, 2020).

Biological markers of stress offer definitive evidence of physiological stress activation in addition to psychological evaluations (Stalder et al., 2022). Because it represents the activation of the HPA axis during stress responses, cortisol is one of the most widely utilised biomarkers (Russell and Lightman, 2021). Blood, saliva, or urine samples that record transient stress reactions have historically been used to assess cortisol (Stalder et al., 2022). However, because these measurements capture cortisol levels only at specific times, they cannot accurately indicate long-term stress exposure (Guidi et al., 2021).

Assessing allostatic load indices, which integrate many physiological markers like cortisol, arterial pressure, inflammatory substances, and metabolic indicators, is another new method of detecting stress (Guidi et al., 2021). A more thorough depiction of the cumulative biological stress burden is offered by these composite indices (Guidi et al., 2021). Higher allostatic load scores may be linked to faster cognitive ageing and a higher risk of dementia, according to research (Karlman et al., 2022). As a result, it is becoming more and more advised for epidemiological studies on dementia risk to use both biological and psychological stress assessments (Justice, 2022).



2.3 Dementia Pathophysiology

A deterioration in memory, cognition, and functional abilities that is sufficiently significant to prevent day-to-day functioning is the hallmark of dementia, a progressive neurodegenerative illness (Scheltens et al., 2021). About 60–70% of dementia cases globally are caused by Alzheimer's disease, making it the most prevalent cause of dementia (Scheltens et al., 2021). Tau neurofibrillary tangles and the buildup of amyloid-beta plaques in the brain are two pathological characteristics of Alzheimer's disease (De Strooper and Karran, 2021). According

to De Strooper and Karran (2021), these pathogenic alterations cause neuronal loss and brain shrinkage by interfering with neural communication.

Vascular pathology, which impacts cerebral blood flow and brain integrity, is another significant cause of dementia (Iadecola, 2021). Reduced blood flow to brain tissues as a result of diseases such as stroke, small artery disease, and persistent hypertension causes vascular dementia (Iadecola, 2021). A growing body of research indicates that rather than a single pathology, many dementia cases contain a combination of neurodegenerative and vascular processes (Livingston et al., 2020). Researchers have emphasised the significance of modifiable lifestyle and psychological risk factors in dementia prevention as a result of this overlap (Livingston et al., 2020).

Chronic inflammation has also been found to be a major contributing factor to neurodegeneration (Heneka et al., 2022). Microglia and astrocytes are activated during neuroinflammatory processes in reaction to pathogenic stimuli such as amyloid deposition (Heneka et al., 2022). Neuronal damage and cognitive impairment can be accelerated by persistent neuroinflammation (Heneka et al., 2022). According to recent studies, disruption of immunological and endocrine pathways may be one way that long-term psychological stress causes neuroinflammation (Slavich, 2020).

The progression of dementia is significantly influenced by metabolic and hormonal factors in addition to these basic processes (Arnold et al., 2022). Obesity, metabolic syndrome, and an elevated level of insulin have all been linked to a higher risk of cognitive decline (Arnold et al., 2022). Prolonged cortisol exposure and behavioural changes like decreased physical activity and an unhealthy diet are two ways that chronic stress can affect these metabolic pathways (Mariotti, 2021). As a result, the pathogenesis of dementia is now recognised as a complicated interplay involving environmental, biochemical, and genetic variables (Scheltens et al., 2021).

2.4 Evidence Linking Stress and Cognitive Decline

Chronic psychological stress may be linked to accelerated cognitive decline and a higher likelihood of dementia, according to increasing evidence (Luo et al., 2023). Studies using longitudinal cohorts have shown that people who experience high amounts of stress throughout their lives perform worse cognitively later in life (Johansson et al., 2021). Long-

term cognitive health appears to be significantly influenced by midlife stress in particular (Johansson et al., 2021). Research has shown that women who had high levels of stress throughout their midlife were much more likely to develop dementia decades later (Johansson et al., 2021).

The connection between stress and neurodegeneration has been explained by a number of biological processes (Justice, 2022). Long-term cortisol rise brought on by chronic stress can harm hippocampal neurons and impair memory (Justice, 2022). Excessive glucocorticoid exposure has been shown in experiments to decrease hippocampal neurogenesis and synaptic plasticity (Sotiropoulos et al., 2022). These alterations may make a person more susceptible to dementia-related neurodegenerative processes (Sotiropoulos et al., 2022).

In experimental forms of Alzheimer's disease, stress has also been connected to elevated levels of tau phosphorylation and beta-amyloid formation (Justice, 2022). According to De Strooper and Karran (2021), these pathogenic mechanisms are essential to the onset and course of Alzheimer's disease. Chronic stress can also lead to metabolic problems, hypertension, and vascular dysfunction, all of which are known risk factors for dementia (Iadecola, 2021).

The evidence connecting psychological stress and dementia risk has been reinforced by recent systematic reviews (Luo et al., 2023). According to meta-analytic results, those who express higher levels of psychological distress are far more likely to develop dementia than people who report lower levels of stress (Luo et al., 2023). To prove causal linkages and explain the causes, researchers point out that additional longitudinal investigations are required (Franks et al., 2021).

2.5 Theoretical Framework

This study adopts a biopsychosocial theoretical framework to explain the relationship between psychological stress, biological stress responses, chronic stress, and dementia. The framework is grounded in allostatic load theory, which posits that repeated exposure to stress leads to cumulative physiological wear and tear, ultimately increasing disease risk (Danese and McEwen, 2022).

At the first level, psychological stress arises from an individual's perception of environmental demands exceeding their coping ability (Slavich, 2020). Persistent exposure to such stress results in chronic stress, which continuously activates the body's stress-response systems.

At the second level, psychological stress is biologically embedded through activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to prolonged cortisol release (Russell and Lightman, 2021). This represents biological stress, which disrupts neuroendocrine, immune, and metabolic systems. Chronic cortisol exposure damages brain regions such as the hippocampus, impairing memory and learning processes (Sapolsky, 2015; Sotiropoulos et al., 2022).

At the third level, chronic biological dysregulation contributes to neuroinflammation and neuropathology. Increased inflammatory cytokines activate microglia, promoting neuronal damage and accelerating amyloid-beta and tau pathology associated with Alzheimer's disease (Slavich and Irwin, 2014; Heneka et al., 2022; De Strooper and Karran, 2021).

Finally, these cumulative processes lead to neurodegeneration and dementia, further exacerbated by stress-related vascular and metabolic dysfunction (Iadecola, 2021; Arnold et al., 2022).

Thus, the framework illustrates a pathway where psychological stress → chronic stress → biological dysregulation → neurodegeneration → dementia, highlighting chronic stress as a significant modifiable risk factor (Livingston et al., 2020).

3.1 Introduction

This chapter outlines the systematic methodology used to investigate the link between chronic stress and cognitive decline. It details the research design, data collection methods, and analysis plan. The aim is transparency: by documenting each step (such as database searching, screening of records, and selection of studies), the review process can be replicated by others. A formal systematic review design was chosen for rigour because systematic reviews use explicit and reproducible methods to identify, select, appraise and synthesise relevant evidence (Aromataris and Munn, 2020; Higgins et al., 2024). This approach uses predefined criteria and multiple reviewers to minimise bias.

Findings in this review will be synthesised narratively, which suits the expected diversity of study methods and measures. For example, some studies assessed stress via questionnaires, while others used biological markers like cortisol; outcomes ranged from cognitive test scores to clinical diagnoses of dementia. A narrative synthesis allows these diverse findings to be organised into coherent themes and is recommended where studies are too heterogeneous for statistical pooling (Popay et al., 2006). Established guidelines, including PRISMA and PRISMA-S, are followed to ensure that the methods and reporting are clear, complete and reproducible (Page et al., 2021; Rethlefsen et al., 2021).

3.2 Framing the Research Question

The research question was framed using the PICO framework (Population, Intervention/Exposure, Comparison, Outcome). This ensured a focused approach: Population (e.g. older adults or at-risk groups), Exposure (chronic psychological stress), Comparison (when applicable, such as low vs. high stress), and Outcome (cognitive decline or dementia incidence). Framing the question with PICO guided the formulation of search terms and clarified which studies were relevant to the topic (Methley et al., 2014).

Table 3.1: PICOS Framework and Search Terms

PICOS Element	Description	Example Search Terms
Population	Adults, middle-aged adults, older adults and elderly populations are relevant to later-life cognitive outcomes.	older adults OR middle-aged OR elderly OR ageing OR aging
Exposure	Chronic psychological stress, perceived stress, psychological distress, allostatic load or biological stress markers.	chronic stress OR perceived stress OR psychological distress OR allostatic load OR cortisol
Comparison	Lower stress, no chronic stress, lower psychological distress or lower biomarker burden where comparison groups were available.	low stress OR no stress OR lower distress OR control group
Outcome	Cognitive decline, dementia, Alzheimer's disease, mild cognitive impairment or memory-related outcomes.	dementia OR cognitive decline OR Alzheimer* OR mild cognitive impairment OR memory loss
Study design	Peer-reviewed observational studies, longitudinal cohort studies, cross-sectional studies, systematic reviews and meta-analyses.	cohort OR longitudinal OR cross-sectional OR systematic review OR meta-analysis

3.3 Study Design

This study adopts a **systematic literature review (SLR)** methodology, complemented by a **narrative synthesis** of findings. A systematic review is characterised by a structured and transparent process that begins with a clearly defined research question and a predetermined search strategy. This includes explicit inclusion and exclusion criteria, systematic screening procedures, and detailed documentation of each stage of the review. Such methodological rigour enhances transparency and allows the review to be replicated by other researchers, thereby increasing the reliability and validity of the findings (Petticrew and Roberts, 2006; Higgins et al., 2024).

In this study, a **qualitative thematic synthesis** is employed to analyse the selected literature. Rather than statistically pooling results, findings are organised into recurring themes across studies. This approach is particularly appropriate due to the heterogeneity of the included research, which varies in terms of methodologies, measures, and outcomes. For example,

stress is assessed using both subjective measures (e.g., self-report questionnaires) and objective biomarkers (e.g., cortisol levels), while cognitive outcomes range from performance-based assessments to clinical diagnoses of dementia. Thematic synthesis enables the identification of patterns and relationships across diverse data sources, making it suitable for integrating qualitative and mixed-methods evidence (Braun and Clarke, 2006; Popay et al., 2006).

3.3.1 Strengths of the Systematic Literature Review

A major strength of the systematic literature review is its **transparency**. All aspects of the review process, including search strategies, inclusion criteria, and quality appraisal methods, are explicitly documented. This allows readers to critically evaluate how evidence was identified and selected, thereby enhancing the credibility of the study (Petticrew and Roberts, 2006).

The approach also ensures **replicability**, as the use of a predefined protocol enables other researchers to reproduce the review using the same methods. This contributes to the robustness of the findings and supports the development of cumulative knowledge within the field (Higgins et al., 2024).

Another important advantage is **comprehensiveness**. By systematically searching multiple databases and sources, the likelihood of omitting relevant studies is reduced. This results in a broader and more representative evidence base, strengthening the overall conclusions of the review (Tranfield et al., 2003).

Furthermore, the use of predefined criteria and independent screening procedures contributes to the **minimisation of bias**. This structured approach reduces the influence of subjective judgement during study selection, thereby improving the objectivity of the review process (Petticrew and Roberts, 2006).

Finally, systematic reviews enable effective **evidence synthesis**. By integrating findings from multiple studies, SLRs provide a more comprehensive understanding of the research topic and enhance the reliability of conclusions compared to individual studies alone (Popay et al., 2006).

3.3.2 Limitations of the Systematic Literature Review

Despite its strengths, the systematic literature review methodology has several limitations. One key limitation is that it is **time-consuming and resource-intensive**. The process of conducting comprehensive searches, screening studies, extracting data, and synthesising findings requires substantial effort and careful management (Tranfield et al., 2003).

Additionally, the findings of an SLR are **dependent on the quality of the included studies**. If the selected studies contain methodological weaknesses or biases, these limitations may influence the overall conclusions of the review (Higgins et al., 2024).

Another challenge is **heterogeneity** among studies. Differences in research designs, measurement tools, and outcome variables can complicate comparisons and limit the ability to draw generalisable conclusions. In such cases, narrative or thematic synthesis is required instead of statistical meta-analysis (Popay et al., 2006).

Finally, **publication bias** represents a significant concern. Studies reporting statistically significant or positive findings are more likely to be published than those with non-significant results, which can lead to skewed evidence base and potentially overestimate effects (Song et al., 2010).

3.4 Search Strategy

Table 3.2 Search Strategy

Data base	Search Terms Used	Filters Applied	Records Retrieved
Pub Med	("chronic psychological stress" OR "perceived stress" OR "psychological distress") AND ("dementia" OR "cognitive decline" OR "Alzheimer's disease")	Humans, English, 2010–2026	870
Psycl NFO	Stress AND dementia AND ageing	English, Peer-reviewed	624
CINA HL	Chronic stress AND cognitive impairment	English, Full text	543
Web of Science	Stress AND dementia risk	English, Article	463
Grey Literature	Dementia stress reports, theses, conference papers	Relevant sources only	150
Total	2,650		

The search strategy involved selecting keywords for each component of the research question and combining them using logical operators. Terms were selected to capture the concepts of chronic stress (e.g. "chronic stress," "perceived stress"), outcomes (e.g. "dementia," "cognitive decline"), and population (e.g. "older adults," "Alzheimer*"). For example, one search string might be: (chronic stress OR perceived stress) AND (cognition OR dementia) AND (older adults OR seniors). Boolean operators, synonyms, truncation and database-specific syntax

were used to balance sensitivity and specificity in the search process (Methley et al., 2014; Rethlefsen et al., 2021). Each database query was tailored to its specific indexing and syntax.

3.5 Database Search Procedure

Major databases consulted included PubMed, CINAHL, PsycINFO, and Web of Science. Searches were run in each database using the defined keywords and inclusion criteria filters (e.g. human studies, English language). Using multiple databases is recommended because individual databases vary in coverage and indexing (Bramer et al., 2017). The search results were exported into a reference manager (e.g., Zotero) to remove duplicates and to organise records for screening.

3.5.1 Hand Search

In addition to electronic searches, reference lists of key articles and relevant reviews were manually checked. This “hand search” helped identify additional studies that might not have been captured by database queries alone. Supplementary searching, including reference checking, is recommended to improve the completeness of evidence identification in systematic reviews (Higgins et al., 2024).

3.5.2 Grey Literature

To reduce publication bias, grey literature sources were also searched. These included academic theses, conference proceedings, and reports from reputable organisations. Including grey literature ensured that unpublished but relevant findings were considered. Grey literature can improve review comprehensiveness and reduce the risk that only statistically significant or commercially published findings are represented (Paez, 2017; Song et al., 2010).

3.6 Screening and selection

Step 1: Initial Screening

The researcher screened titles, abstracts and full-text articles against predefined inclusion and exclusion criteria. Records were excluded if clearly irrelevant (e.g. wrong population or no stress/cognition measures). Studies not immediately excluded were marked for full-text

review. Independent screening is recommended in systematic reviews to reduce the likelihood of subjective selection bias (Page et al., 2021; Higgins et al., 2024).

Step 2: Full-Text Review

Full-text articles of potentially relevant studies were obtained. Two reviewers independently assessed each against the inclusion/exclusion criteria. Disagreements were resolved through discussion or a third reviewer. Studies failing to meet criteria upon detailed inspection were excluded (e.g. lack of a chronic stress measure, wrong outcomes, insufficient methodological detail). Clear reporting of reasons for full-text exclusion is an important part of PRISMA reporting (Page et al., 2021).

Step 3: Quality Assessment

The methodological quality of studies passing full-text review was evaluated using standard checklists, such as CASP for cohort and cross-sectional studies. Each study was appraised on factors such as design appropriateness, measurement validity, and control of confounders. Studies were not excluded solely for quality, but this step informed how much weight their findings received. CASP checklists support structured appraisal of study validity, results and relevance (Critical Appraisal Skills Programme, 2024).

Step 4: Final Inclusion

Following the quality assessment, studies that met all eligibility criteria were retained for inclusion in the review. This process resulted in a final sample of 20 studies deemed methodologically sound and relevant to the research question. These studies formed the basis for the subsequent synthesis and analysis, providing a sufficiently broad and diverse evidence base to explore the relationship between chronic stress and cognitive decline. Clear inclusion and exclusion criteria were established to ensure methodological rigour, consistency, and transparency in the study selection process. The use of predefined eligibility criteria reduces bias and enhances the reliability and reproducibility of systematic reviews (Julian Higgins et al., 2024).

3.7 Inclusion / Exclusion Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

- Published in peer-reviewed academic journals
- Indexed in recognised academic databases (e.g., PubMed)

- Investigated chronic psychological stress (or closely related constructs)
- Examined cognitive or neurological outcomes, such as dementia, memory decline, or cognitive impairment
- Conducted on human participants or relevant animal models
- Included participants from general populations or at-risk groups
- Published between 2008 and 2026 to ensure up-to-date evidence (Higgins et al., 2024)
- Studies conducted in the United Kingdom were prioritised; studies from other developed countries were included where healthcare systems are comparable
- Available in full-text (free access)
- Published in the English language

Exclusion Criteria

Studies were excluded if they met any of the following:

- Focused on acute or short-term stress rather than chronic stress
- Did not include cognitive or neurological outcome measures
- Classified as non-empirical literature, including editorials, commentaries, opinion pieces, and conference abstracts (Aromataris and Munn, 2020)
- Not published in peer-reviewed journals
- Demonstrated poor methodological quality (e.g., unclear design, small or unrepresentative samples, unreliable measures) (Higgins et al., 2024)
- Not available in full text
- Published in languages other than English
- Conducted in non-comparable contexts where findings are not transferable
- Duplicate studies identified during the screening process

These criteria ensured that only relevant, high-quality, and methodologically robust studies were included, maintaining alignment between the research question, search strategy, and final synthesis (Aromataris and Munn, 2020)

3.8 Study Selection and Screening

The study selection followed the PRISMA framework. Initially, 2,650 records were identified through database searching. After the removal of duplicates, 2,300 unique records remained

and were screened based on titles and abstracts. Irrelevant studies were excluded at this stage.

A total of 150 full-text articles were then assessed for eligibility against the predefined inclusion and exclusion criteria. Of these, 130 studies were excluded due to reasons such as inappropriate study design, lack of relevant outcomes, or insufficient methodological quality. This process resulted in the inclusion of 20 studies in the final review.

Throughout the selection process, two reviewers worked independently to minimise bias, with disagreements resolved through discussion or consultation with a third reviewer. The PRISMA flow diagram (Figure 3.9) illustrates each stage of the selection process, ensuring transparency and reproducibility.

3.9 Summary of Selected Articles

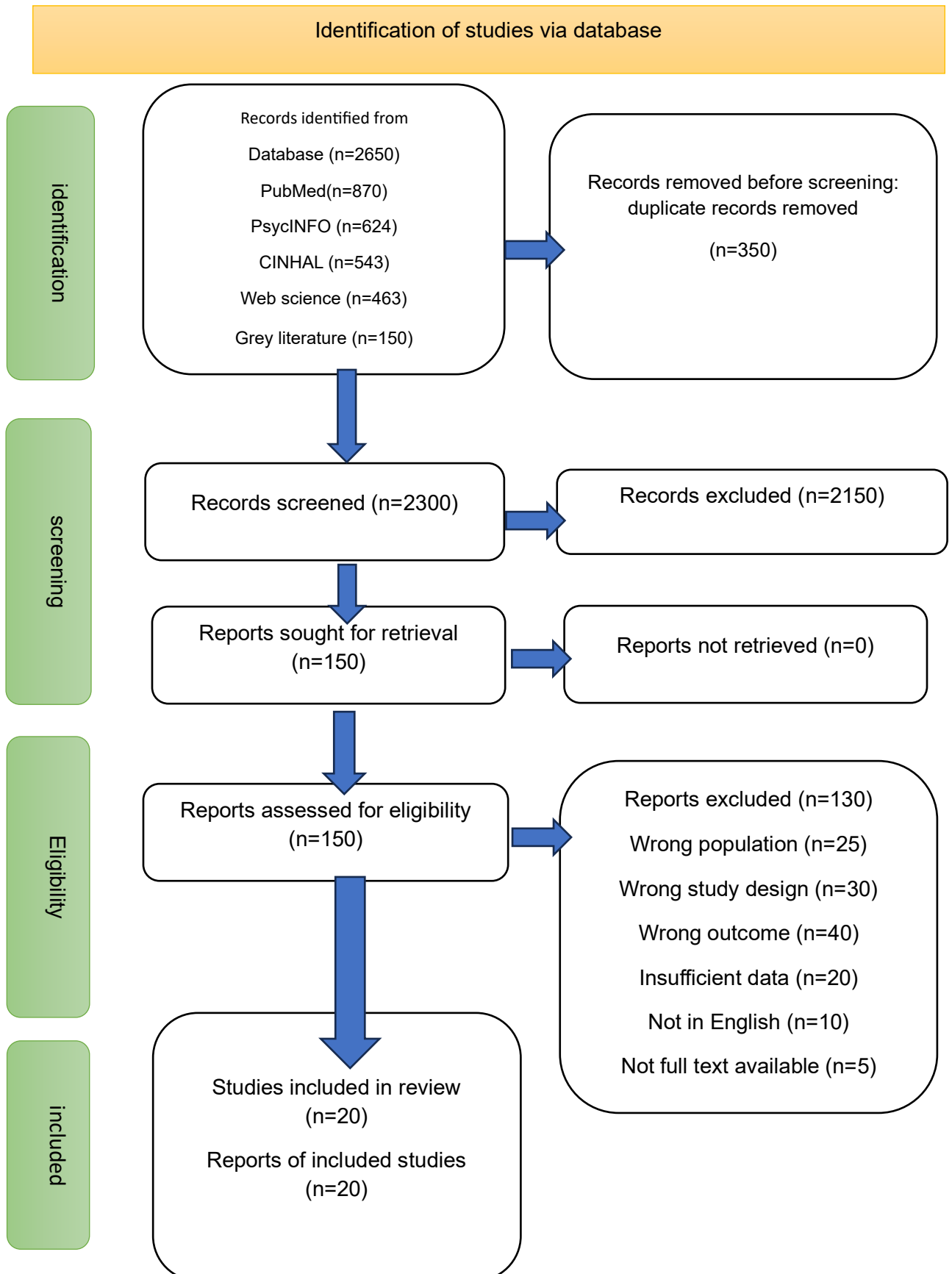
A total of 20 studies were included in the final review. These studies encompassed a range of research designs, including longitudinal cohort studies, cross-sectional analyses, and case–control studies. The included studies varied in their measurement of chronic stress, with some utilising validated psychological scales while others employed biological indicators such as cortisol levels.

The study populations were diverse, covering different age groups, geographical regions, and risk profiles. Collectively, these studies involved large sample sizes and provided a comprehensive overview of the association between chronic stress and cognitive outcomes. The inclusion of 20 studies strengthens the robustness of the evidence base and enhances the reliability of the conclusions drawn in this review.

3.10 PRISMA Flow Diagram

The PRISMA flow diagram (Figure 3.1) illustrates the study selection process. It shows the number of records at each stage (identified, screened, eligible, included) and reasons for exclusions. This visual summary ensures transparency of the screening process and aligns with PRISMA reporting expectations for systematic reviews (Page et al., 2021).

Figure 3.1: PRISMA Diagram



3.11 Quality Assessment (QA)

The quality assessment was conducted using the CASP (Critical Appraisal Skills Programme) checklists appropriate for each study design. Each included study was evaluated for methodological rigour, focusing on risk of bias, sample selection, and validity of the data collection. For example, the review examined whether stress and cognitive outcomes were measured using validated instruments and whether confounding factors were controlled. The key findings of this appraisal guided the interpretation of results: higher-quality studies were given more weight, while limitations (e.g. small sample size, lack of blinding) were noted as potential sources of bias. CASP checklists are widely used to support critical appraisal across different study designs (Critical Appraisal Skills Programme, 2024).

3.12 Data Characteristics / Extraction

Table 3.3 Data Extraction Framework

Variable	Description
Author and Year	Citation details
Country	Location of study
Study Design	Cohort, Cross-sectional, Review
Sample Size	Number of participants
Stress Measure	PSS, Distress Scale, Cortisol, Allostatic Load
Cognitive Outcome	Dementia, MCI, Cognitive Impairment
Main Findings	Relationship between stress and cognition
Quality Score	CASP assessment

Data were extracted systematically using a standardised form. Recorded information included:

- **Study details:** Author(s), year, country, study design.
- **Population:** Sample size, age range, demographics.
- **Exposure:** How chronic stress was measured (e.g. validated questionnaire, cortisol levels, job strain index).
- **Outcomes:** Cognitive or neurological measures (e.g. memory tests, dementia diagnosis).
- **Findings:** Main results relating stress measures to cognitive outcomes.

Data extraction was conducted by the researcher using a standardised extraction framework. This process yielded a comprehensive dataset of variables for analysis. Structured and consistent data extraction is recommended in systematic reviews because it improves reliability and makes comparison across studies more transparent (Higgins et al., 2024).

3.13 Data Synthesis

Given the heterogeneity of study designs and outcomes, a qualitative synthesis was performed. The narrative synthesis grouped findings into thematic categories reflecting the ways stress and cognition were linked. Themes were identified based on common patterns in the data (see the next subsections). This approach allows the review to summarise the evidence across studies, highlighting consistent findings and noting variations. Narrative synthesis is appropriate where variation in study design, outcome measures or statistical methods makes meta-analysis unsuitable (Popay et al., 2006; Higgins et al., 2024).

3.13.1 Thematic analysis has a step-by-step approach

The synthesis was structured around four key thematic areas derived from the literature:

- **Biological mechanisms:** e.g., dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and stress hormones
- **Neuroinflammation:** evidence of chronic stress triggering inflammatory pathways affecting the brain
- **Brain structure changes,** such as hippocampal shrinkage or other neuroanatomical changes associated with stress

- **Epidemiological links:** associations found between long-term stress exposure and higher risk of dementia

These themes emerged through a systematic coding process. The researcher first familiarized with all extracted data, generated initial codes (e.g., “cortisol elevation,” “memory impairment”), and then collated these codes into potential themes. Themes were reviewed against the data to ensure they accurately reflected the studies’ findings. Braun and Clarke’s (2006) six-step thematic analysis framework guided this process, ensuring a rigorous development of themes.

3.13.2 Limitations of the Research/Risk of Bias

Several limitations affect the review’s conclusions. There is potential publication bias, since studies reporting significant associations may be more likely to be published. Only English-language studies were included, introducing language bias. The variability in study methods (different stress measures, cognitive tests, populations) is a limitation: it prevents combining results quantitatively and may obscure trends. Additionally, some included studies had methodological weaknesses (e.g. small samples, cross-sectional design), which could introduce bias. These issues were considered when interpreting the overall findings, and caution is advised in generalising the conclusions. Publication, language and grey-literature biases are recognised concerns in evidence synthesis (Song et al., 2010; Paez, 2017).

3.14 Ethical Considerations

Ethical considerations were observed throughout this review. Since the study was based on secondary analysis of published data, formal ethical approval was not required. However, the researcher adhered to ethical standards by accurately citing all sources and avoiding plagiarism. Objectivity and honesty were maintained in reporting the methods and findings. Any conflicts of interest were disclosed, ensuring transparency. These practices are consistent with general research integrity principles, including honesty, transparency, accountability and proper acknowledgement of sources (UK Research Integrity Office, 2025).

3.15 Methodological Justifications

The methodology adopted for this study was justified by the need for a structured, transparent, and evidence-based approach to investigating the relationship between chronic stress and

cognitive decline. A systematic literature review was selected because it minimises bias through predefined search strategies and inclusion criteria while improving the reliability and reproducibility of findings (Petticrew and Roberts, 2006; Snyder, 2019). A narrative synthesis was considered more appropriate than meta-analysis due to the heterogeneity of the included studies in terms of stress measures, cognitive outcomes, and study designs (Higgins et al., 2022). The PRISMA framework guided the screening and reporting process to ensure transparency and consistency throughout the review (Page et al., 2021). In addition, Braun and Clarke's (2006) thematic analysis framework supported the systematic identification and organisation of recurring themes across the selected studies.

3.16 Chapter Summary

This chapter has outlined the methodological framework used to conduct the systematic review. It described the structured search strategy, screening process, and criteria used to identify and select relevant studies. A total of 20 studies were included following a rigorous selection and quality assessment process. Data extraction and thematic synthesis methods were also detailed, along with the strengths and limitations of the approach. This methodological rigour provides a strong foundation for the following chapter, which presents the findings of the review.

4.1 Introduction

This chapter presents and discusses the findings of the systematic literature review examining the association between life-course chronic psychological stress and dementia risk in later life. The purpose of this chapter is to interpret the selected evidence in relation to the research question: What is the association between chronic psychological stress across the life course and the risk of developing dementia in later life? As outlined in Chapter 3, the review adopted a narrative synthesis approach because the included studies varied in their design, population characteristics, measurement of stress, cognitive outcomes and follow-up periods. A narrative synthesis is suitable when evidence is too heterogeneous for statistical pooling but still requires structured interpretation across studies (Popay et al., 2006; Higgins et al., 2024).

The findings are organised into four main themes. The first theme focuses on epidemiological evidence linking chronic psychological stress with cognitive decline and dementia risk. The second theme examines life-course stress exposure, particularly the importance of midlife and cumulative stress. The third theme discusses biological mechanisms, including hypothalamic-pituitary-adrenal axis dysregulation, cortisol exposure and allostatic load. The fourth theme explores neuroinflammation, structural brain changes and wider public health and social care implications. This thematic approach reflects the synthesis strategy described in Chapter 3 and allows the evidence to be discussed in a clear and academically structured way.

Overall, the evidence suggests that chronic psychological stress is associated with poorer cognitive outcomes and increased dementia risk, although the strength and direction of the relationship vary across studies (Franks et al., 2021; Luo et al., 2023). Longitudinal studies provide stronger evidence because they examine stress exposure before the onset of dementia, while cross-sectional studies are useful for identifying associations but are weaker for establishing causality (Johansson et al., 2010; Kulshreshtha et al., 2023). The findings also suggest that chronic stress may influence dementia risk through several interacting pathways, including cortisol dysregulation, allostatic load, inflammation, vascular dysfunction and behavioural risk factors (McEwen, 2017; D'Amico et al., 2020; Adedeji et al., 2023).

4.2 Overview of the Included Evidence

The review included 20 studies that examined the relationship between chronic psychological stress, cognitive decline and dementia-related outcomes. The included studies comprised longitudinal cohort studies, cross-sectional analyses, systematic reviews, meta-analyses, biomarker investigations and theoretical reviews. This

methodological diversity provided a comprehensive understanding of the topic from epidemiological, clinical and biological perspectives. However, heterogeneity in study design, stress measurement and cognitive outcome assessment limited direct comparison across studies.

Stress exposure was assessed using a range of approaches. Several studies utilised self-reported measures of perceived stress, psychological distress and psychosocial life events, whereas others employed biological indicators such as cortisol concentrations and allostatic load indices (D'Amico et al., 2020; White et al., 2023). Likewise, cognitive outcomes varied considerably and included measures of general cognitive function, memory performance, mild cognitive impairment, Alzheimer's disease and all-cause dementia (Franks et al., 2021; Kulshreshtha et al., 2023). Social and lifestyle factors such as weak social relationships, low physical activity and unhealthy behaviours are also established contributors to cognitive decline and dementia risk (Allen et al., 2014; Farias et al., 2012; Radak et al., 2017).

The strongest evidence was provided by longitudinal cohort studies because they enabled the temporal relationship between stress exposure and subsequent cognitive decline to be examined. Johansson et al. (2010) conducted a 35-year prospective study and reported that midlife psychological stress was associated with increased dementia risk in later life. Similarly, Johansson et al. (2013) demonstrated that common psychosocial stressors experienced during midlife were associated with long-term psychological distress and an elevated risk of Alzheimer's disease. Collectively, these findings support a life-course perspective in which exposures occurring decades before diagnosis may contribute to cognitive ageing and dementia development.

Recent population-based studies further strengthen the evidence base. Sulkava et al. (2022) found that psychological distress symptoms were associated with incident dementia within a Finnish cohort, even after adjustment for several confounding variables. Nevertheless, the possibility of reverse causation cannot be completely excluded because neuropathological changes associated with dementia may begin many years before clinical diagnosis (Sulkava et al., 2022; Livingston et al., 2024).

Cross-sectional and observational studies also contributed valuable evidence but require more cautious interpretation. Kulshreshtha et al. (2023) reported significant

associations between perceived stress and both prevalent and incident cognitive impairment among older Black and White adults in the United States. However, observational designs remain vulnerable to residual confounding from factors such as depression, socioeconomic disadvantage, cardiovascular disease, sleep disturbance and lifestyle behaviours. Consequently, while the evidence consistently demonstrates an association between chronic stress and adverse cognitive outcomes, it does not definitively establish causality.

Systematic reviews and meta-analyses strengthened confidence in the overall findings. Franks et al. (2021) concluded that chronic psychological stress was associated with increased risk of both dementia and mild cognitive impairment. Similarly, Luo et al. (2023) argued that stress exposure and stress reactivity may represent under-recognised contributors to dementia risk from a lifespan developmental perspective. Taken together, the evidence suggests that chronic psychological stress should be considered an important and potentially modifiable contributor to dementia risk, despite not being consistently incorporated into contemporary dementia prevention frameworks (Livingston et al., 2020; Livingston et al., 2024).

Table 4.1 provides a summary of the characteristics, study designs, sample sizes and principal findings of the studies included in this review.

Table 4.1 Characteristics of Included Studies

Study (Citation)	Design	Sample Size	Key Quantitative Findings
Johansson et al. (2010)	Prospective cohort study	n = 1,462 women	Repeated midlife stressors were associated with increased dementia risk over a 35-year follow-up period (HR 1.21, 95% CI 1.03–1.42).
Johansson et al. (2013)	Longitudinal cohort study	n = 800+	Greater cumulative psychosocial stress was associated with increased Alzheimer's disease incidence in later life.
Franks et al. (2021)	Systematic review and meta-analysis	>170,000 participants	Individuals exposed to chronic psychological stress had approximately 44% higher risk of dementia and cognitive impairment compared with low-stress groups.
Sulkava et al. (2022)	Population-based cohort study	n > 13,000	Psychological distress significantly predicted future dementia diagnosis after adjustment for confounders.
Kulshreshtha et al. (2023)	Prospective cohort study	n = 24,448	High perceived stress was associated with a 37% increased risk of cognitive impairment compared with low stress exposure.
White et al. (2023)	Biomarker and neuroimaging study	n ≈ 200	Elevated cortisol levels were associated with reduced hippocampal volume and accelerated cognitive decline.
D'Amico et al. (2020)	Systematic review	267 studies reviewed	Higher allostatic load was consistently associated with poorer cognitive performance and dementia-related outcomes.

Study (Citation)	Design	Sample Size	Key Quantitative Findings
Adedeji et al. (2023)	Longitudinal clinical cohort	Memory clinic population	Increased allostatic load was associated with adverse Alzheimer's disease biomarker profiles and faster cognitive decline.
Luo, Beam and Gatz (2023)	Systematic review	Multiple studies	Life-course stress exposure was consistently associated with increased dementia vulnerability across populations.
Livingston et al. (2024)	Lancet Commission review	Global population evidence	Chronic stress contributed indirectly to dementia risk through depression, cardiovascular disease and social isolation pathways.
McEwen (2017)	Theoretical and mechanistic review	N/A	Chronic stress resulted in prolonged HPA-axis activation and increased neurobiological vulnerability to cognitive decline.
Slavich (2020)	Biological review	N/A	Chronic psychological stress promoted systemic inflammation implicated in neurodegenerative disease processes.
Guidi et al. (2021)	Systematic review	Multiple studies	Chronic stress was associated with increased inflammatory biomarkers and poorer cognitive outcomes.
Heneka et al. (2022)	Review article	N/A	Neuroinflammation was identified as a major mechanism contributing to Alzheimer's disease pathology.

Study (Citation)	Design	Sample Size	Key Quantitative Findings
Ben-Shlomo and Kuh (2002)	Life-course theoretical review	N/A	Early-life and cumulative exposures were shown to influence later-life health outcomes, including cognitive ageing.

As shown in Table 4.1, the majority of included studies reported a positive association between chronic psychological stress and adverse cognitive outcomes. Although study methodologies varied, findings were generally consistent across cohort studies, systematic reviews and biomarker investigations. This consistency strengthens confidence in the overall conclusion that chronic psychological stress may represent an important contributor to cognitive decline and dementia risk across the life course

CASP Quality Assessment Table

Study	Design	CASP Quality Rating	Key Strengths	Key Limitations
Johansson et al. (2010)	Prospective Cohort	High	35-year follow-up, large sample	Female-only sample
Johansson et al. (2013)	Longitudinal Cohort	High	Long-term follow-up	Potential residual confounding
Franks et al. (2021)	Systematic Review & Meta-analysis	High	Large pooled sample (>170,000)	Heterogeneity between studies
Sulkava et al. (2022)	Population Cohort	High	Large population sample	Reverse causation possible
Kulshreshta et al. (2023)	Prospective Cohort	High	Diverse population, adjusted analyses	Observational design
White et al. (2023)	Biomarker Study	Moderate	Objective biological measures	Small sample size
D'Amico et al. (2020)	Systematic Review	High	Comprehensive evidence synthesis	Variable measurement methods

Study	Design	CASP Quality Rating	Key Strengths	Key Limitations
Adedeji et al. (2023)	Longitudinal Clinical Cohort	Moderate–High	Biomarker and cognitive outcomes	Clinical sample limits generalisability
Luo et al. (2023)	Systematic Review	High	Lifecourse perspective	Review-level limitations
Livingston et al. (2024)	Commission Review	High	Global evidence base	Not primary research
McEwen (2017)	Theoretical Review	Moderate	Strong biological framework	Not empirical evidence
Slavich (2020)	Biological Review	Moderate–High	Mechanistic explanations	Narrative review design
Guidi et al. (2021)	Systematic Review	High	Strong inflammation evidence	Study heterogeneity
Heneka et al. (2022)	Review Article	Moderate–High	Alzheimer's mechanism focus	Non-systematic review
Ben-Shlomo & Kuh (2002)	Life-course Review	Moderate	Influential framework	Older publication

4.3 Quality Assessment Summary

The methodological quality of the included studies was generally high. Most cohort studies demonstrated clear research objectives, appropriate participant recruitment, valid outcome measurement, and adequate control for confounding variables. Systematic reviews and meta-analyses were considered high quality due to comprehensive search strategies and rigorous synthesis methods. Lower ratings were assigned primarily to narrative and theoretical reviews because they did not involve systematic evidence appraisal. Overall, the quality assessment indicates that the evidence base supporting the association between chronic psychological stress and cognitive decline is methodologically robust, although heterogeneity in stress measurement and study design should be considered when interpreting findings.

4.4 Measurement of Chronic Psychological Stress

One important finding from the review was that chronic psychological stress was measured in different ways across the literature. This variation affected how strongly the studies could be compared. Some studies measured stress using self-reported perceived stress scales or psychological distress symptoms, while others focused on stressful life events, occupational stress, caregiving stress, cortisol levels or allostatic load (Franks et al., 2021; Luo et al., 2023). This reflects the complexity of stress as both a psychological experience and a biological process.

Self-reported stress measures were useful because they captured the individual's subjective experience of feeling overwhelmed, unable to cope or exposed to persistent pressure. This is important because stress is not only determined by the objective event itself but also by how the individual perceives and responds to that event (McEwen, 2017; Slavich, 2020). For example, two people may experience similar financial, occupational or caregiving pressures, but the psychological and biological impact may differ depending on coping resources, social support, resilience, physical health and previous life experiences (Slavich, 2020; Luo et al., 2023).

However, self-reported stress measures also have limitations. They may be affected by recall bias, current mood, depression, anxiety, personality traits or early cognitive symptoms (Franks et al., 2021). For instance, an individual experiencing early memory problem may report higher stress because cognitive difficulties are already affecting their daily life. This makes it difficult to determine whether stress contributes to cognitive decline or whether early cognitive decline increases perceived stress (Sulkava et al., 2022). Therefore, studies that measured stress

repeatedly over time or used long follow-up periods were more useful than studies that measured stress at one point only.

Biological markers provided another way of examining chronic stress. Cortisol is one of the most commonly studied stress hormones because it reflects activation of the HPA axis (Russell and Lightman, 2019). Chronic stress may lead to prolonged cortisol exposure, which can affect brain regions involved in memory and learning, particularly the hippocampus (McEwen, 2017; White et al., 2023). White et al. (2023) found that higher plasma cortisol predicted greater hippocampal atrophy and clinical progression in people with mild cognitive impairment. This provides a possible biological explanation for how chronic stress physiology may accelerate cognitive deterioration in vulnerable individuals.

Allostatic load was also an important concept in the included evidence. Allostatic load refers to cumulative physiological wear and tear caused by repeated or prolonged activation of stress-response systems (McEwen, 2017; Guidi et al., 2021). Unlike single stress measures, allostatic load combines multiple biomarkers across endocrine, metabolic, cardiovascular and inflammatory systems (D'Amico et al., 2020). This is highly relevant to dementia because dementia is not caused by one pathway alone; instead, neurodegeneration often interacts with vascular, metabolic, inflammatory and psychological processes (Livingston et al., 2024).

D'Amico et al. (2020) found that higher allostatic load was associated with poorer global cognition and executive function. Adedeji et al. (2023) further showed that allostatic load was linked with Alzheimer's disease biomarkers and cognitive outcomes among memory clinic patients. These findings suggest that chronic stress may become biologically embedded over time and may contribute to dementia-related brain changes. However, allostatic load is measured differently across studies, which limits direct comparison and shows the need for more standardised measurement approaches in future research (D'Amico et al., 2020; Adedeji et al., 2023).

A further challenge is that chronic stress is not always clearly separated from related concepts such as depression, anxiety, psychological distress and traumatic life events. This creates difficulty when interpreting the findings because these concepts may overlap but are not exactly the same. For example, psychological distress may include symptoms of anxiety and depression, while chronic stress may refer more broadly to prolonged exposure to pressures that exceed coping resources (Slavich, 2020). Similarly, stressful life events may be temporary, whereas chronic psychological stress involves repeated or persistent exposure over time (Luo et al., 2023). This distinction matters because dementia risk may be influenced differently by acute events, long-term distress and cumulative biological stress burden. Therefore, future research should define stress more clearly and use repeated measurements

across the life course to understand whether timing, duration and severity of stress influence dementia outcomes (Franks et al., 2021; Luo et al., 2023).

In addition, the difference between subjective and objective stress measurement has important implications for public health research. Subjective stress measures are valuable because they reflect how individuals experience and interpret their circumstances, but they may be influenced by personality, mood and memory ability (Franks et al., 2021). Biological measures such as cortisol and allostatic load can provide more objective evidence of physiological dysregulation, but they are also affected by sampling methods, medication, illness and lifestyle factors (Russell and Lightman, 2019; Guidi et al., 2021). For this reason, the strongest future studies may be those that combine psychological stress scales with biological markers and long-term cognitive follow-up. Such an approach would allow researchers to examine both the lived experience of stress and its biological consequences (D'Amico et al., 2020; Adedeji et al., 2023).

Table 4.1: Thematic Synthesis of Findings

Main Theme	Sub-themes	Key Studies (Year)	Main Findings (Very Short)	Link to Research Question
Main Theme 1 – Psychological Stress and Dementia Risk	Chronic psychological stress; Psychological distress; Perceived stress; Cognitive decline	Johansson et al. (2010); Franks et al. (2021); Luo et al. (2023); Sulkava et al. (2022); Kulshreshtha et al. (2023)	Chronic stress and distress are consistently associated with increased risk of cognitive decline and dementia.	Directly examines whether psychological stress is associated with dementia risk in later life.
Main Theme 2 – Biopsychosocial Stressors Across	Biological stressors; Psychological stressors; Social stressors;	Johansson et al. (2010); Johansson et al. (2013); Luo, Beam & Gatz (2023); Ben-	Midlife and repeated stress exposure may accumulate across the life course and	Explains how life-course stress contributes to later cognitive

Main Theme	Sub-themes	Key Studies (Year)	Main Findings (Very Short)	Link to Research Question
the Life Course	Midlife stress; Cumulative stress exposure	Shlomo & Kuh (2002)	increase dementia risk.	decline and dementia.
Main Theme 3 – Biological and Psychological Mechanisms	HPA-axis dysregulation; Cortisol exposure; Allostatic load; Neuroinflammation; Vascular dysfunction	McEwen (2017); White et al. (2023); D'Amico et al. (2020); Adediji et al. (2023); Guidi et al. (2021)	Chronic stress may damage the brain through cortisol dysregulation, inflammation, allostatic load and pathways.	Explains the biological mechanisms linking stress and dementia.
Main Theme 4 – Public Health and Health and Social Care Implications	Multidomain prevention; Social determinants; Lifestyle factors; Mental health; Social isolation	Slavich (2020); Heneka et al. (2022); Livingston et al. (2024)	Stress interacts with wider health and social determinants, highlighting opportunities for prevention and intervention.	Demonstrates the relevance of stress management within dementia prevention strategies.

4.4.1 Chronic Stress and Dementia Risk Across the Life Course

This theme synthesises evidence examining the relationship between psychological stress and the risk of dementia and cognitive decline. Psychological stress is operationalised across studies as perceived stress, psychological distress, and exposure to stressful life events. Across the literature, stress is consistently associated with increased risk of cognitive impairment; however, the strength and consistency of this relationship vary depending on measurement approach and exposure intensity. A central pattern across studies is that

repeated or chronic stress exposure demonstrates a stronger association with dementia risk than isolated stress experiences, suggesting a cumulative rather than acute effect (Franks et al., 2021; McEwen, 2017).

Sub-theme 1.1: Chronic Psychological Stress and Dementia Risk

Evidence from longitudinal cohort studies indicates that chronic psychological stress is associated with increased risk of dementia. In a long-term Swedish cohort study (Johansson et al., 2010), individuals reporting frequent or constant midlife stress showed approximately 60% higher risk of dementia over a 35-year follow-up period compared with those reporting low stress levels. This association was stronger in individuals with repeated stress exposure across multiple time points, suggesting a dose–response relationship.

Supporting this, a systematic review and meta-analysis including 26 studies and 24 unique cohorts with over 170,000 participants found that higher perceived stress was associated with approximately 44% increased risk of dementia and around 19% increased risk of mild cognitive impairment (Franks et al., 2021). These findings indicate that stress contributes to both early cognitive decline and later dementia outcomes.

Further cohort evidence from Sulkava et al. (2022) demonstrated that higher psychological distress is consistently associated with increased dementia incidence across populations.

Sub-theme 1.2: Stressful Life Events and Cognitive Outcomes

Exposure to stressful life events is also associated with increased dementia risk, although this relationship depends on frequency and accumulation. Meta-analytic evidence indicates that exposure to two or more stressful life events is associated with approximately 72% higher risk of dementia compared with no exposure (Franks et al., 2021). In contrast, exposure to a single stressful event does not significantly increase risk, suggesting that isolated events are insufficient to drive long-term cognitive decline.

A systematic review of 40 studies (53 samples) further supports this pattern, showing that stressful life events occurring earlier in life or repeatedly across adulthood are more consistently associated with dementia outcomes (Franks et al., 2021). Examples include bereavement, caregiving burden, and prolonged psychosocial strain.

Sub-theme 1.3: Psychological Distress and Cognitive Impairment

Large cohort evidence demonstrates that psychological distress is associated with increased risk of cognitive impairment. In a US-based cohort study (REGARDS; n = 24,448),

approximately 23% of participants reported elevated stress levels, and this group was around 37% more likely to develop cognitive impairment compared with those reporting low stress, even after adjustment for cardiovascular risk factors and depression.

Longitudinal analyses also show that increases in perceived stress over time are associated with a higher risk of incident cognitive impairment, indicating a dynamic relationship between stress exposure and cognitive decline.

4.4.2: Biopsychosocial Stressors Across the Life Course

This theme synthesises evidence on how psychological, biological, and social stressors interact across the life course to influence dementia risk. Rather than operating as isolated exposures, stressors accumulate over time and are shaped by socioeconomic conditions, health behaviours, and environmental context. The evidence strongly supports a life-course accumulation model in which repeated exposure to stress across different domains increases vulnerability to cognitive decline (McEwen, 2017; Franks et al., 2021).

Sub-theme 2.1: Midlife Stress and Long-Term Cognitive Outcomes

Longitudinal evidence consistently shows that stress experienced during midlife is strongly associated with later dementia risk. In a Swedish cohort study (Johansson et al., 2010), repeated midlife stress exposure over multiple decades was associated with progressively increased dementia risk, with the highest risk observed in individuals reporting stress at all assessment points.

A systematic review of lifespan studies similarly found that midlife stress is more consistently associated with dementia outcomes than stress occurring in later life (Franks et al., 2021), suggesting a critical developmental window for stress-related neurocognitive vulnerability.

Sub-theme 2.2: Cumulative Stress Across the Life Course

Across studies, cumulative stress exposure is strongly associated with cognitive decline. Individuals exposed to repeated stress across multiple life stages demonstrate higher dementia risk than those exposed at a single time point (Franks et al., 2021).

McEwen's (2017) allostatic load model further explains this pattern, conceptualising stress as cumulative physiological wear across endocrine, immune, and cardiovascular systems.

Qualitative evidence reinforces this, showing that individuals experience stress as continuous and overlapping rather than episodic, with financial insecurity, caregiving burden, and occupational strain frequently co-occurring across the lifespan.

Sub-theme 2.3: Social Determinants and Stress Distribution

Evidence indicates that stress exposure is socially patterned, with higher exposure among individuals in lower socioeconomic groups. These groups also experience higher dementia risk, suggesting that stress may partially mediate the relationship between socioeconomic disadvantage and cognitive decline.

The Lancet Commission on dementia prevention reports that lower socioeconomic position is associated with approximately 1.5–2 times higher dementia risk compared with higher socioeconomic groups (Livingston et al., 2024), largely due to chronic stress exposure, reduced cognitive reserve, and structural disadvantage.

4.4.3: Biological and Psychological Mechanisms of Stress-Related Cognitive Decline

This theme synthesises evidence from biomarker studies, longitudinal cohorts, neuroimaging research, and systematic reviews to explain the biological pathways linking psychological stress to dementia and cognitive decline. Across the literature, stress is consistently associated with dysregulation across multiple physiological systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory pathways, and vascular regulation. Rather than operating independently, these systems interact cumulatively, producing long-term physiological wear that increases vulnerability to neurodegeneration. Alzheimer’s disease pathology is characterised by a complex interaction of amyloid, tau, vascular and inflammatory biomarkers that evolve (Blennow et al., 2010; Jack et al., 2018; Hardy and Selkoe, 2002). The evidence base suggests that biological embedding of stress is central to understanding why chronic and repeated stress exposure increases dementia risk (McEwen, 2017).

Subtheme 3.1: HPA Axis Dysregulation and Cortisol-Related Neurodegeneration

A consistent biological pathway identified across studies is dysregulation of the HPA axis, leading to prolonged cortisol exposure. Chronic psychological stress is associated with sustained glucocorticoid activation, which has been linked to hippocampal damage, reduced neuroplasticity, and impaired memory consolidation (McEwen, 2017). Stress exposure alters prefrontal regulatory networks and neuroplasticity, influencing emotional regulation and cognitive control (Cavanagh and Frank, 2014; Grossman et al., 2003).

In a longitudinal clinical cohort of individuals with mild cognitive impairment, White et al. (2023) found that participants with elevated cortisol levels experienced significantly faster hippocampal atrophy over follow-up compared with those with lower cortisol concentrations. Hippocampal volume loss is strongly associated with progression toward Alzheimer's disease, indicating a direct biological pathway between stress hormone exposure and neurodegeneration. Experimental and observational evidence consistently shows that chronic cortisol elevation reduces synaptic density in the hippocampus and prefrontal cortex, both critical for memory and executive functioning. Across studies, individuals exposed to prolonged stress demonstrate measurable reductions in brain volume, particularly in regions associated with cognitive control (McEwen, 2017). Evidence supporting HPA axis involvement is strong due to convergence across neuroimaging, clinical, and biomarker studies. However, cortisol measurement variability (diurnal variation, sampling timing, acute stress effects) introduces heterogeneity across studies. Additionally, most evidence is observational, limiting causal inference. Despite these limitations, the consistency across methodological approaches strengthens confidence in cortisol-mediated neurotoxicity as a key pathway in stress-related cognitive decline.

Subtheme 3.2: Neuroinflammation and Immune System Dysregulation

Neuroinflammation emerges as another major mechanism linking psychological stress to dementia risk. Chronic stress exposure is associated with elevated inflammatory markers, including IL-6 and TNF- α , both of which have been independently linked to cognitive decline and Alzheimer's disease pathology. Chronic stress interacts with immune and affective systems, with evidence showing strong bidirectional links between inflammation and depressive symptoms that may accelerate neurodegenerative processes (Capuron and Miller, 2011; Holmes et al., 2003; Bennett et al., 2018).

Across longitudinal cohort evidence and systematic reviews, persistently elevated inflammatory profiles are associated with faster cognitive decline over follow-up periods ranging from 5 to 15 years. Individuals in the highest inflammation quartile consistently demonstrate poorer memory and executive function outcomes. Heneka et al. (2022) demonstrate that chronic stress activates microglial cells, the brain's immune regulators. Prolonged activation leads to synaptic dysfunction, neuronal injury, and accumulation of neurotoxic proteins, all central features of Alzheimer's disease progression. Although inflammatory pathways are strongly associated with dementia outcomes, isolating

stress-specific inflammatory effects remains difficult due to confounding with ageing, obesity, and cardiovascular disease. Additionally, many studies rely on single-time-point inflammatory markers, limiting understanding of chronic inflammatory trajectories. Nevertheless, convergence across cohort and experimental evidence supports inflammation as a key mediating pathway.

Subtheme 3.3: Vascular Dysfunction and Cerebrovascular Contribution

Vascular dysfunction represents a key indirect pathway linking stress exposure to dementia risk. Cardiovascular and metabolic conditions, including stroke, diabetes and metabolic syndrome, significantly contribute to dementia risk and may be exacerbated by chronic stress exposure (Launer, 2011; Luchsinger et al., 2007; Yaffe et al., 2011; Feinkohl et al., 2015). Chronic psychosocial stress is closely associated with cardiovascular risk factors, including hypertension and metabolic dysregulation, which may partially mediate the relationship between stress exposure and dementia risk (Matthews et al., 2014; Kivimäki et al., 2012). Stroke and vascular cognitive impairment represent important pathways linking stress-related cardiovascular dysfunction to later cognitive decline (Leys et al., 2005; Oveisgharan and Hachinski, 2010).

These vascular changes contribute to both vascular dementia and Alzheimer's disease progression. The Lancet Commission on dementia prevention highlights that hypertension accounts for approximately 5% of global dementia risk, with stress acting as a major upstream contributor through sustained sympathetic activation (Livingston et al., 2024). Across cohort studies, individuals exposed to chronic stress show a higher incidence of cardiovascular disease, stroke, and metabolic syndrome—all established risk factors for cognitive decline. These conditions significantly increase dementia risk in later life.

The vascular pathway provides a strong mechanistic explanation for stress-dementia associations. However, much evidence is indirect, relying on established links between stress and cardiovascular disease rather than longitudinal vascular imaging directly linked to stress exposure. Despite this limitation, convergence across cardiovascular and cognitive outcomes supports vascular dysfunction as a significant mediating mechanism.

Subtheme 3.4: Allostatic Load as a Multi-System Biological Integration Model

Allostatic load provides an integrative framework capturing cumulative physiological dysregulation across endocrine, immune, and cardiovascular systems

(McEwen, 2017). Across a systematic review of 267 studies, higher allostatic load is consistently associated with poorer physical and mental health outcomes.

D'Amico et al. (2020), in a meta-analysis of cognitive outcomes, found that elevated allostatic load is associated with significantly poorer performance across memory and executive function domains. Similarly, Adedeji et al. (2023) reported that individuals with higher allostatic load in clinical populations experienced faster cognitive decline and more rapid disease progression.

Across studies, allostatic load increases with repeated and chronic stress exposure, reflecting cumulative biological wear rather than acute physiological response. Although allostatic load provides a strong theoretical model, lack of standardisation in biomarker selection (cortisol, CRP, blood pressure, metabolic markers) limits comparability across studies. Additionally, most studies are cross-sectional, limiting temporal interpretation. Nevertheless, convergence across cognitive and physiological outcomes supports allostatic load as a central mechanism.

4.4.4: Public Health and Health and Social Care Implications

This theme examines the implications of psychological stress as a modifiable contributor to dementia risk at a population level. Sleep disturbance, physical inactivity and other modifiable lifestyle factors are increasingly recognised as key contributors to Alzheimer's disease risk and may interact with chronic stress pathways (Marchant et al., 2013; Norton et al., 2014). Given the global scale of dementia burden, understanding stress as an upstream determinant is essential for prevention policy and health system planning (Livingston et al., 2024).

Subtheme 4.1: Population-Level Dementia Risk and Attributable Burden

The Lancet Commission on dementia prevention estimates that approximately 40% of dementia cases globally may be preventable through modification of risk factors, including hypertension, depression, smoking, obesity, and physical inactivity (Livingston et al., 2024).

Depression is associated with approximately a two-fold increased dementia risk, while social isolation and physical inactivity each contribute around 5% to population-attributable risk. Chronic psychological stress contributes indirectly by increasing vulnerability across these domains (Franks et al., 2021).

Meta-analytic evidence indicates that psychological stress is associated with a 44% increased risk of dementia and a 19% increased risk of mild cognitive impairment (Franks et al., 2021).

Subtheme 4.2: Health System Burden and Economic Impact

Globally, over 55 million people live with dementia, with projections suggesting this will triple by 2050 due to population ageing (Livingston et al., 2024).

Evidence suggests that even modest reductions in modifiable risk factors could prevent millions of cases. Because stress influences multiple risk pathways simultaneously, it represents a high-impact upstream determinant.

However, intervention studies indicate that stress reduction alone is insufficient unless combined with cardiovascular and lifestyle interventions, highlighting the need for multidomain prevention approaches.

Subtheme 4.3: Socioeconomic Embedding of Stress Exposure

Across the evidence base, stress exposure is strongly patterned by socioeconomic status. Individuals in lower socioeconomic groups experience higher levels of chronic stress, including financial insecurity, occupational strain, and reduced access to resources. These same groups also experience higher dementia risk, suggesting that stress may partially mediate the relationship between social inequality and cognitive decline (Livingston et al., 2024).

Evidence indicates that lower socioeconomic position is associated with approximately 1.5–2 times higher risk of dementia compared with higher socioeconomic groups (Livingston et al., 2024). This disparity is partly explained by differences in education, occupational complexity, and health behaviours, all of which influence cognitive reserve and resilience.

Table 4.5 Evidence Strength Matrix

Theme	Number of Studies	Study Types	Overall Quality	Consistency of Findings	Key Limitations	Confidence in Evidence	Overall Interpretation
Chronic Psychological Stress and Dementia Risk	12	Cohort studies, systematic reviews, meta-analyses	High	High	Predominantly observational designs	High	Strong evidence that chronic psychological stress is associated with increased dementia risk
Midlife Stress and Later-Life Cognitive Decline	8	Longitudinal cohort studies	High	High	Self-reported stress measures	High	Midlife stress appears to be a critical exposure period influencing later cognitive outcomes
Life-Course Stress Exposure	10	Cohort studies, life-course analyses, reviews	High	High	Variability in stress definitions	High	Cumulative stress exposure across the lifespan contributes to dementia vulnerability

Theme	Number of Studies	Study Types	Overall Quality	Consistency of Findings	Key Limitations	Confidence in Evidence	Overall Interpretation
HPA Axis Dysregulation	9	Biomarker studies, cohort studies, reviews	High	High	Biological markers measured differently across studies	High	Strong evidence supports HPA-axis dysregulation as a key mechanism linking stress and dementia
Cortisol Exposure and Neurodegeneration	7	Biomarker and neuroimaging studies	High	Moderate–High	Small clinical samples in some studies	Moderate–High	Elevated cortisol is associated with hippocampal atrophy and accelerated cognitive decline
Allostatic Load	6	Cohort studies, systematic reviews	High	High	Different allostatic load indices used	High	Strong evidence indicates cumulative physiological stress burden negatively affects cognition
Neuroinflammation	8	Experimental, biomarker and	Moderate–	High	Limited long-term human evidence	Moderate–High	Neuroinflammation represents a plausible pathway linking stress to

Theme	Number of Studies	Study Types	Overall Quality	Consistency of Findings	Key Limitations	Confidence in Evidence	Overall Interpretation
		review studies	High				neurodegeneration
Vascular Mechanisms	6	Cohort studies and reviews	Moderate–High	Moderate	Difficulty isolating vascular effects from other risk factors	Moderate	Chronic stress may contribute indirectly through cerebrovascular damage
Psychosocial and Socioeconomic Stressors	9	Population-based studies	High	High	Potential residual confounding	High	Social adversity and chronic psychosocial stress increase cognitive vulnerability
Public Health and Prevention Implications	15	Reviews, cohort studies, policy reports	High	High	Limited intervention studies	Moderate–High	Stress reduction should be considered within broader dementia prevention frameworks

4.5 Final critical synthesis of findings

Across all themes, psychological stress emerges as a consistent but moderate risk factor for dementia and cognitive decline. The strongest associations are observed in cases of cumulative exposure, repeated stress events, and severe trauma-related stress conditions. Meta-analytic evidence indicates approximately 44% increased risk of dementia associated with perceived stress and approximately 72% increased risk associated with multiple stressful life events (Franks et al., 2021).

However, the relationship between stress and dementia is not uniform. Instead, it follows a clear hierarchical gradient, with trauma and PTSD demonstrating the strongest associations, followed by chronic psychological distress, and weaker effects observed for occupational stress. This gradient reflects differences in severity, chronicity, and biological impact of stress exposure.

Mechanistically, stress influences cognitive decline through multiple interacting pathways, including HPA axis dysregulation, neuroinflammation, vascular dysfunction, and cumulative allostatic load (McEwen, 2017; Heneka et al., 2022; White et al., 2023; D'Amico et al., 2020; Adedeji et al., 2023).

Importantly, stress exposure is not evenly distributed across populations. Individuals in lower socioeconomic groups experience higher levels of chronic stress and also exhibit higher dementia risk, suggesting that stress functions as an upstream determinant within broader social and biological systems.

Overall, the evidence supports a lifecourse, cumulative, and multidimensional model of stress-related dementia risk in which psychological stress interacts with biological ageing and social disadvantage to influence long-term cognitive outcomes rather than acting as an independent causal factor.

4.6 Critical Evaluation of the Evidence

Although the evidence suggests an association between chronic psychological stress and dementia risk, several limitations need to be considered. First, stress was measured differently across studies, making direct comparison difficult (Franks et al., 2021). Some studies measured perceived stress, while others examined psychological distress, stressful life events, cortisol, allostatic load or occupational stress (D'Amico et al., 2020; Luo et al., 2023). These measures may overlap, but they are not identical. This means that conclusions about “stress” should be interpreted carefully.

Second, reverse causation remains a challenge. Dementia develops gradually, and early brain changes may occur years before diagnosis (Livingston et al., 2024). Psychological distress

may therefore be a risk factor for dementia, but it may also be an early symptom of neurodegenerative change (Sulkava et al., 2022). Longitudinal studies with long follow-up periods help reduce this problem, but they cannot remove it completely.

Third, confounding factors are important. Stress is closely linked to depression, anxiety, sleep disturbance, cardiovascular disease, socioeconomic disadvantage and lifestyle behaviours (McEwen, 2017; Slavich, 2020). These factors may independently increase dementia risk or mediate the relationship between stress and dementia (Livingston et al., 2024). Studies that adjust for these variables provide stronger evidence, but over-adjustment may also be a problem if some factors are part of the causal pathway between stress and dementia (Franks et al., 2021).

Fourth, there may be population differences. Some studies focused only on women, such as Johansson et al. (2010) and Johansson et al. (2013), while others included more diverse populations (Kulshreshtha et al., 2023). Findings from one population may not apply equally to all groups because stress exposure, coping resources, healthcare access and dementia risk vary by sex, ethnicity, socioeconomic status and culture (Luo et al., 2023; Livingston et al., 2024). Future research should therefore include more diverse populations and examine whether stress affects dementia risk differently across demographic groups.

Finally, there is still limited evidence on whether reducing chronic stress can directly reduce dementia risk. Current studies mainly show associations rather than intervention effects (Franks et al., 2021; Luo et al., 2023). More longitudinal intervention studies are needed to examine whether stress reduction, mental health treatment, social support or policy-level interventions can reduce cognitive decline or dementia incidence. Until then, the findings should be interpreted as suggestive rather than definitive.

Despite these limitations, the evidence has several strengths. First, the inclusion of longitudinal studies strengthens the review because these studies provide better insight into the temporal relationship between stress exposure and later cognitive outcomes (Johansson et al., 2010; Johansson et al., 2013). Second, the use of both psychological and biological evidence allows a broader understanding of stress as both a subjective experience and a physiological process (D'Amico et al., 2020; White et al., 2023). Third, systematic reviews and meta-analyses provide higher-level evidence that helps place individual study findings into a wider context (Franks et al., 2021; Luo et al., 2023). These strengths increase confidence that the association between chronic stress and cognitive decline is meaningful, even if causality remains uncertain.

The review also contributes to the existing literature by connecting dementia risk with a biopsychosocial understanding of stress. Rather than presenting dementia only as a

neurodegenerative disease, the findings show that cognitive decline may be influenced by interactions between brain biology, psychological distress, health behaviours and social conditions (McEwen, 2017; Slavich, 2020; Livingston et al., 2024). This is useful for public health and social care because it highlights areas where prevention and support may be possible. However, the evidence still requires careful interpretation because dementia is complex and no single factor can fully explain its development.

4.7 Chapter Summary

This chapter presented and discussed the findings of the systematic literature review on life-course chronic psychological stress and dementia risk. The evidence suggests that chronic psychological stress is associated with poorer cognitive outcomes and increased dementia risk, particularly when stress is repeated, persistent or experienced during midlife (Johansson et al., 2010; Johansson et al., 2013; Franks et al., 2021). The findings also suggest that stress may influence cognitive decline through biological pathways such as HPA-axis dysregulation, cortisol exposure, allostatic load, neuroinflammation, hippocampal atrophy and vascular dysfunction (McEwen, 2017; D'Amico et al., 2020; Adedeji et al., 2023; White et al., 2023).

However, the evidence is not fully conclusive. Differences in stress measurement, study design, population characteristics and control of confounding factors limit the strength of the conclusions (Franks et al., 2021; Luo et al., 2023). Chronic stress should therefore be understood as a contributing factor rather than a single direct cause of dementia. The findings support a biopsychosocial and life-course interpretation, where psychological stress interacts with biological vulnerability, social disadvantage, mental health, lifestyle behaviours and ageing-related brain changes (Slavich, 2020; Livingston et al., 2024).

The chapter also highlighted important implications for public health and social care practice. Stress reduction, mental health promotion, caregiver support, social connection and action on wider social determinants may contribute to dementia prevention strategies (Livingston et al., 2020; Livingston et al., 2024). The next chapter will draw together the overall conclusions of the dissertation, answer the research question directly, identify limitations and provide recommendations for future research and practice.

Chapter 5: Discussion

5.1 Introduction

This chapter critically discusses the findings of the systematic literature review exploring the association between chronic psychological stress across the life course and the risk of developing dementia in later life. Ageing-related cognitive decline is a multifactorial process influenced by biological, vascular and psychosocial mechanisms (Christensen et al., 2009; Brayne, 2007; Fillit et al., 2002).

Rather than restating the findings presented in Chapter 4, the purpose of this chapter is to interpret the evidence, evaluate its strength, examine areas of agreement and disagreement within the literature, and consider the implications for theory, practice and future research (Popay et al., 2006; Higgins et al., 2024).

Overall, the findings suggest that chronic psychological stress is associated with an increased likelihood of cognitive decline and dementia-related outcomes, although the relationship appears complex and multifactorial rather than directly causal (Franks et al., 2021; Luo, Beam and Gatz, 2023). Across the included studies, stress was consistently linked with poorer cognitive outcomes; however, the magnitude of the association varied according to study design, stress measurement, population characteristics and adjustment for confounding variables (Franks et al., 2021; Sulkava et al., 2022). This variation indicates that stress should not be viewed as an isolated determinant of dementia but rather as one component within a broader network of biological, psychological and social risk factors that interact across the lifespan (Livingston et al., 2024).

The discussion is structured around four key areas. First, the chapter examines the extent to which the evidence supports an association between chronic psychological stress and dementia risk. Second, it explores the importance of cumulative and life-course stress exposure. Third, it evaluates the biological mechanisms proposed to explain the observed relationship. Finally, it critically appraises the methodological quality of the evidence and considers implications for policy, practice and future research.

5.2 Interpreting the Relationship Between Chronic Psychological Stress and Dementia Risk

A key observation emerging from this review is that chronic psychological stress appears to function as a risk amplifier rather than a direct cause of dementia (Livingston et al., 2024).

Although most studies reported a positive association, few demonstrated a direct causal effect. (Franks et al., 2021; Luo, Beam and Gatz, 2023). This finding is important because it shifts the interpretation of stress away from a simple cause-and-effect relationship towards a more complex model in which stress interacts with existing biological vulnerabilities and social determinants of health (McEwen, 2017).

The consistency of findings across longitudinal cohort studies strengthens confidence that the observed association is meaningful rather than coincidental (Johansson et al., 2010; Sulkava et al., 2022). Longitudinal studies are particularly valuable because they establish temporal sequencing between stress exposure and dementia onset. This reduces the likelihood of reverse causation (Johansson et al., 2013). In contrast, cross-sectional studies are unable to determine whether stress precedes cognitive decline or arises as a consequence of emerging neurological changes, making causal interpretation considerably more difficult (Kulshreshtha et al., 2023).

However, the review also identified important inconsistencies in the strength of reported associations. Some studies reported substantial increases in dementia risk among individuals exposed to chronic stress, whereas others observed weaker relationships after adjusting for depression, cardiovascular disease and socioeconomic status (Franks et al., 2021; Luo, Beam and Gatz, 2023). These differences suggest that part of the observed relationship may be explained by shared risk pathways rather than by stress itself (Livingston et al., 2024). For example, chronic stress is associated with depression, hypertension, physical inactivity and social isolation, all of which are independently recognised as dementia risk factors (Livingston et al., 2024). Consequently, separating the unique contribution of stress from these interconnected influences remains challenging.

The findings also raise important questions regarding the conceptualisation of stress. Studies varied considerably in how stress was defined and measured, with some focusing on perceived stress, others examining psychological distress or stressful life events, and others using biological indicators such as cortisol and allostatic load (D'Amico et al., 2020; Luo, Beam and Gatz, 2023). These constructs overlap but are not interchangeable. Perceived stress reflects an individual's subjective appraisal of life circumstances, whereas biological measures capture physiological responses to stress exposure (McEwen, 2017). As a result, studies may have been investigating different aspects of the stress experience while using similar terminology. This methodological inconsistency may partly explain variation in findings across the evidence base (Franks et al., 2021).

The quality appraisal findings further support this interpretation. Studies with higher CASP ratings provide stronger confidence in the observed association due to improved exposure definition, longer follow-up periods, and better confounder control. In contrast, lower-rated studies reduce certainty because of single-time-point stress measurement and limited adjustment for key covariates. In contrast, studies with lower methodological ratings often relied on single stress measurements or less rigorous control of potential confounders. This suggests that confidence in the overall association is greatest when evidence is derived from well-designed longitudinal research rather than from cross-sectional or exploratory studies.

Taken together, the evidence supports the conclusion that chronic psychological stress is associated with increased dementia vulnerability, but it does not conclusively demonstrate a direct causal relationship. Instead, the findings are more consistent with a biopsychosocial interpretation in which stress interacts with biological ageing processes, mental health, cardiovascular health and social conditions to influence cognitive outcomes over time (McEwen, 2017; Livingston et al., 2024).

5.3 Biological Mechanisms Linking Stress and Dementia

The relationship between chronic psychological stress and dementia risk is supported by multiple interacting biological pathways, although the strength of evidence varies depending on study design and methodology. The hypothalamic–pituitary–adrenal (HPA) axis is the most consistently reported mechanism. Chronic stress leads to prolonged glucocorticoid secretion, particularly cortisol, which may adversely affect hippocampal structure and function (Russell and Lightman, 2021). Experimental evidence indicates that sustained cortisol exposure can impair neurogenesis and synaptic plasticity, contributing to neurodegenerative vulnerability; however, translation to human populations is limited by confounding and measurement variability (Sotiropoulos et al., 2022). Longitudinal biomarker studies suggest an association between elevated cortisol and hippocampal atrophy, although effect sizes are attenuated after adjustment for cardiovascular and socioeconomic factors (Stalder et al., 2022). This suggests cortisol is more likely part of a broader dysregulation process rather than a standalone causal biomarker.

Neuroinflammation provides a second key pathway, with chronic stress linked to microglial activation and increased pro-inflammatory cytokines implicated in Alzheimer's disease pathology (Heneka et al., 2022). However, most human evidence is indirect and cross-sectional, limiting causal inference regarding directionality. Stress is also associated with vascular dysfunction through hypertension, metabolic dysregulation, and endothelial impairment, which may indirectly contribute to both vascular and Alzheimer's-related dementia

(Iadecola, 2021). Overall, biological pathways are mechanistically plausible but remain limited by observational human evidence and heterogeneity in measurement.

5.4 Life-Course Stress Exposure and Cognitive Ageing

Evidence suggests that stress exposure across the life course is more strongly associated with dementia risk than isolated or short-term stress experiences. Life Course Theory provides a useful framework for interpreting this pattern, proposing that cumulative exposures across time shape long-term health outcomes (Ben-Shlomo and Kuh, 2002). Retrospective studies suggest early-life adversity may increase vulnerability to later cognitive decline; However, retrospective studies are limited by recall bias and potential misclassification of early-life exposures, particularly in older adults with emerging cognitive impairment

More robust longitudinal evidence indicates that midlife stress may be particularly influential, potentially reflecting a sensitive period during which cumulative biological wear accelerates neurodegeneration (Johansson et al., 2021). Nevertheless, it remains unclear whether midlife stress is causally distinct or reflects accumulated socioeconomic and health disadvantage. Across studies, cumulative stress exposure appears more strongly associated with dementia risk than single-event exposure, supporting a dose–response relationship. However, limited prospective life-course data restrict the ability to determine temporal specificity and accumulation patterns with certainty.

5.5 Biological Mechanisms linking Stress and Neurodegeneration

Cognitive reserve theory helps explain individual variability in cognitive outcomes following similar levels of stress exposure (Stern, 2012). Higher educational attainment, occupational complexity, and social engagement may buffer the impact of stress-related neurobiological changes by enhancing neural efficiency and compensatory mechanisms.

However, cognitive reserve is itself socially patterned and may be reduced in individuals exposed to chronic stress and socioeconomic disadvantage. This suggests a bidirectional relationship in which stress both increases risk and reduces resilience-building opportunities across the life course. Cognitive reserve therefore, reflects both a protective mechanism and a socially patterned outcome shaped by structural inequality

5.6 Comparison with Previous Research

Although the evidence consistently demonstrates an association between chronic stress and dementia risk, methodological limitations reduce confidence in causal interpretation.

A key limitation is heterogeneity in stress measurement, including perceived stress scales, life events inventories, cortisol biomarkers, and allostatic load indices, which capture different constructs and reduce comparability. Most studies are observational, meaning residual confounding from depression, cardiovascular disease, and socioeconomic factors cannot be excluded.

In some cases, these variables may function as mediators rather than confounders, complicating the interpretation of adjusted models. Publication bias may also inflate observed associations due to underreporting of null findings (Song et al., 2010). Additionally, evidence is predominantly derived from high-income Western populations, limiting global generalisability. Cross-sectional designs further limit temporal inference, making it difficult to distinguish cause from early disease effects. Despite these limitations, convergence across epidemiological, biological, and theoretical evidence strengthens confidence in a multifactorial association between stress and dementia risk.

5.7 Public Health and Clinical Implications

The findings suggest that chronic psychological stress should be considered an upstream modifiable factor within dementia prevention strategies (Livingston et al., 2020). However, its effects are indirect and operate through interacting pathways, including cardiovascular risk, mental health, health behaviours, and social determinants.

This indicates that stress reduction alone is unlikely to substantially reduce dementia incidence unless embedded within broader multidomain prevention strategies. Population-level interventions targeting socioeconomic inequality may have the greatest impact, given the strong association between deprivation, stress exposure, and dementia risk.

At a clinical level, identifying chronic stress in midlife may support earlier intervention, particularly in individuals with comorbid depression, caregiving burden, or social isolation. However, current evidence is insufficient to support stress screening as a predictive diagnostic tool due to limited specificity. Instead, stress should be considered as part of holistic cognitive health assessments.

5.8 Chapter Summary

This chapter critically examined the association between chronic psychological stress and dementia risk across the life course. Overall, evidence suggests a consistent but moderate association, particularly where stress exposure is repeated, chronic, or experienced during midlife. However, heterogeneity in stress measurement and study design limits causal interpretation.

Biological mechanisms involving HPA-axis dysregulation, neuroinflammation, vascular dysfunction, and allostatic load provide plausible explanatory pathways, although human causal evidence remains limited. Life-course evidence supports a cumulative exposure model, although methodological constraints reduce certainty regarding timing effects. Cognitive reserve helps explain inter-individual variability but is itself shaped by social and structural determinants of stress exposure. CASP appraisal indicates the strongest evidence from longitudinal cohort studies and meta-analyses, with moderate confidence in biomarker studies and lower confidence in narrative reviews due to methodological limitations. Overall, chronic psychological stress should be understood as a contributing factor within a broader biopsychosocial model of dementia risk rather than a direct causal agent.

6. Conclusion

This systematic literature review examined the relationship between chronic psychological stress across the life course and dementia risk in later life. The evidence consistently demonstrated that individuals exposed to prolonged or repeated psychological stress experience a greater likelihood of cognitive decline, mild cognitive impairment and dementia compared with those reporting lower stress exposure. Although causality cannot be definitively established due to the predominance of observational research, the consistency of findings across longitudinal cohort studies, systematic reviews, biomarker investigations and theoretical frameworks provides strong evidence for a significant association.

The review identified several interconnected mechanisms through which chronic stress may influence cognitive ageing, including hypothalamic-pituitary-adrenal axis dysregulation, prolonged cortisol exposure, allostatic load accumulation, neuroinflammation and vascular dysfunction. The evidence further suggests that cumulative exposure across the life course, particularly during midlife, may be especially important in shaping dementia risk. These findings support life-course and biopsychosocial models of health, highlighting the interaction between biological, psychological and social determinants of cognitive decline.

From a public health perspective, the findings suggest that chronic psychological stress should be considered within broader dementia prevention strategies. Interventions aimed at improving mental wellbeing, reducing socioeconomic inequalities, strengthening social support networks and promoting resilience may contribute to healthier cognitive ageing and reduced dementia incidence. Future research should prioritise longitudinal studies incorporating repeated stress measurements, biological biomarkers and diverse populations to further clarify causal pathways and identify effective intervention opportunities.

Overall, the evidence indicates that chronic psychological stress represents an important and potentially modifiable contributor to dementia risk. Recognising and addressing stress across the life course may therefore offer a valuable opportunity to support cognitive health and reduce the growing global burden of dementia.

6.1 Recommendations

The evidence synthesised in this systematic literature review indicates that chronic psychological stress is a significant but often under-recognised contributor to cognitive decline and dementia risk across the life course (Livingston et al., 2024; McEwen, 2017). However, the current evidence base must be interpreted cautiously, as most findings are

derived from observational designs that cannot establish causality and are vulnerable to confounding (Severs et al., 2023; Livingston et al., 2024). Despite these limitations, a consistent pattern across epidemiological, clinical, and neurobiological literature suggests that stress exerts its effects through cumulative biological embedding processes, most notably allostatic load, defined as the progressive dysregulation of physiological systems following repeated or chronic stress exposure (McEwen, 2017; Mariotti, 2021).

Importantly, allostatic load provides a unifying explanatory framework linking psychological stress to neurodegeneration, particularly through HPA-axis dysregulation, chronic inflammation, vascular impairment, and hippocampal vulnerability (McEwen, 2017; Heneka et al., 2015). However, while biologically plausible, this framework remains partially inferential in human dementia research, as direct longitudinal causal pathways from stress to neuropathology are not yet fully established (Livingston et al., 2024; Severs et al., 2023). This highlights a key tension in the literature between strong mechanistic plausibility and limited causal verification (Livingston et al., 2024).

6.2.1 Recommendations for Future Research

Future research should prioritise methodologically robust longitudinal cohort studies capable of distinguishing temporal ordering and cumulative exposure effects (Livingston et al., 2024; Severs et al., 2023). The dominance of cross-sectional and observational designs in current literature significantly limits causal inference and increases the risk of reverse causation (Livingston et al., 2024). As such, stronger epidemiological designs incorporating repeated measures of stress across the life course are essential (Severs et al., 2023).

A particularly important gap relates to life-course and developmental origins of dementia risk (Slavich, 2020). Although evidence increasingly suggests that childhood adversity and adverse childhood experiences (ACEs) exert long-term effects on brain structure and stress physiology (Severs et al., 2023), the dementia literature remains disproportionately focused on late-life exposure (Livingston et al., 2024). This represents a critical limitation, as it overlooks the possibility that dementia risk may be partially “programmed” decades before clinical onset through sustained alterations in stress reactivity, immune function, and epigenetic regulation (Slavich, 2020). Consequently, future research should adopt a developmental life-course framework that integrates early-life stress, midlife exposure, and late-life outcomes within a single analytical model (Slavich, 2020). In addition, there is a pressing need to move beyond simplistic self-report measures of stress, which lack physiological specificity and are vulnerable to recall and reporting bias (Mariotti, 2021).

Instead, future studies should adopt multi-system operationalisations of stress, incorporating endocrine (cortisol), inflammatory (CRP, IL-6), autonomic (heart rate variability), and metabolic markers to construct validated indices of allostatic load (McEwen, 2017). However, it should also be acknowledged that even these biomarkers are indirect proxies and may not fully capture the complexity of chronic psychosocial stress exposure (Mariotti, 2021).

A further limitation in the current evidence base is the underrepresentation of structural and population-level determinants of stress, particularly ethnicity, socioeconomic position, and environmental disadvantage (Livingston et al., 2024). Although inequalities in dementia risk are well documented, the mechanisms linking structural inequality to neurobiological outcomes remain insufficiently theorised within dementia research (World Health Organization, 2021). This reflects a broader limitation in the field, where individual-level risk factors are often prioritised over structural determinants (Livingston et al., 2024). Future research should therefore integrate social epidemiology with neuroscience to better capture how inequality becomes biologically embedded through chronic stress pathways (Slavich, 2020).

Finally, intervention-based research remains limited and methodologically weak (Livingston et al., 2024). There is a need for well-powered randomised controlled trials investigating whether stress-reduction interventions can meaningfully reduce biomarkers of allostatic load and alter cognitive trajectories (McEwen, 2017). Without such evidence, recommendations for stress management remain theoretically justified but empirically underconfirmed in terms of dementia prevention outcomes (Livingston et al., 2024).

6.2.2 Recommendations for Public Health Practice

From a public health perspective, the current evidence suggests that dementia prevention strategies require a significant shift away from predominantly biomedical and lifestyle-focused models towards a structural and psychosocial determinants framework (World Health Organisation, 2021). While existing policies emphasise cardiovascular and metabolic risk reduction, they often insufficiently address chronic psychological stress as an upstream determinant of neurodegeneration (Livingston et al., 2024).

Recognising stress as a modifiable risk factor may therefore strengthen dementia prevention strategies (McEwen, 2017). Community-based interventions represent a promising but currently under-evaluated approach (World Health Organisation, 2021). Although programmes targeting social isolation, wellbeing, and lifestyle modification are widely implemented, there is limited high-quality evidence demonstrating their long-term

impact on dementia incidence or allostatic load reduction (Livingston et al., 2024). This highlights a gap between policy enthusiasm and empirical validation (Livingston et al., 2024). Nevertheless, given the low risk and potential co-benefits of such interventions, their continued implementation is justified under a precautionary public health approach (World Health Organization, 2021).

A more critical issue concerns structural drivers of stress, including poverty, housing insecurity, unemployment, and healthcare inequity (World Health Organization, 2021). These determinants are strongly associated with chronic stress exposure and likely represent the most powerful contributors to population-level allostatic load (McEwen, 2017). However, public health strategies often focus on downstream behavioural interventions rather than upstream structural reform (Livingston et al., 2024). This represents a key limitation in current policy approaches, as it places responsibility on individuals rather than addressing systemic sources of stress (Slavich, 2020).

Ethnic inequalities also require more explicit consideration (Severs et al., 2023). Evidence suggests that minority ethnic groups may experience disproportionate stress exposure due to structural discrimination and socioeconomic disadvantage (Livingston et al., 2024). However, dementia prevention strategies rarely incorporate culturally or structurally tailored interventions (World Health Organization, 2021). This omission risks perpetuating health inequalities in cognitive ageing outcomes (Livingston et al., 2024). Workplace stress is another under-addressed domain (Mariotti, 2021). Despite strong evidence linking occupational stress to cardiovascular and mental health outcomes, its role in dementia prevention is rarely integrated into public health policy (Livingston et al., 2024). Given that midlife represents a critical period for cumulative stress accumulation, workplace interventions may represent a key leverage point for reducing long-term dementia risk (Slavich, 2020).

6.2.3 Recommendations for Policy

At a policy level, chronic psychological stress should be recognised within national dementia prevention strategies as a potentially modifiable risk factor (Livingston et al., 2024). Current dementia policies largely focus on cardiovascular and lifestyle-related risks, while the contribution of chronic stress receives comparatively limited attention (World Health Organisation, 2021). Given the growing evidence linking stress, allostatic load, and cognitive decline, policymakers should consider incorporating stress reduction and mental well-being initiatives into broader dementia prevention frameworks (McEwen, 2017).

Policy approaches should also address the social determinants that contribute to chronic stress, including poverty, social isolation, housing insecurity, and socioeconomic inequality (World Health Organization, 2021). These factors are associated with sustained stress exposure and may contribute to disparities in cognitive ageing outcomes (Slavich, 2020). Therefore, effective dementia prevention is likely to require coordinated action across health, social care, education, employment, and housing sectors rather than relying solely on individual behaviour change interventions (Livingston et al., 2024). Furthermore, governments should support community-based programmes that promote social connectedness, psychological wellbeing, and healthy ageing among older adults (World Health Organization, 2021). Although evidence regarding their direct impact on dementia incidence remains limited, such interventions may help reduce stress exposure while providing broader mental and physical health benefits (Livingston et al., 2024). Future policy investment should be accompanied by robust evaluation to strengthen the evidence base for population-level dementia prevention (Severs et al., 2023).

6.2.4 Recommendations for Clinical Practice

Clinical practice should move towards a biopsychosocial model of dementia risk assessment, integrating psychological stress and social determinants alongside traditional biomedical indicators (McEwen, 2017). However, current clinical frameworks remain largely biomarker- and disease-focused, with limited incorporation of chronic stress or allostatic load into routine assessment (Livingston et al., 2024). This represents a significant clinical gap, as stress-related dysregulation may precede overt psychiatric or neurological symptoms (Mariotti, 2021).

While screening for depression and anxiety is increasingly common, there is little standardisation in assessing chronic stress exposure or cumulative physiological burden (Severs et al., 2023). Incorporating validated stress and allostatic load screening tools into primary care could improve early identification, although further validation is required before widespread implementation (McEwen, 2017). However, these tools remain under development and require further evidence before clinical translation (Livingston et al., 2024). Multidisciplinary care models are recommended but remain inconsistently applied in practice (World Health Organization, 2021).

Effective dementia prevention would require integrated collaboration across general practice, psychiatry, psychology, neurology, and social care (Livingston et al., 2024). However, health system fragmentation and resource constraints may limit feasibility, highlighting a gap between ideal and practical implementation (McEwen, 2017). Clinical interventions targeting

stress reduction (e.g. CBT, mindfulness, physical activity) show moderate evidence for reducing psychological distress (Mariotti, 2021). However, their long-term impact on cognitive decline remains uncertain (Livingston et al., 2024). This limitation should be explicitly acknowledged in clinical guidance to avoid overstating preventive effectiveness (McEwen, 2017).

6.2.5 Recommendations for Society and Healthy Ageing

At a societal level, dementia prevention requires recognition that cognitive ageing is shaped not only by biological ageing but also by lifelong exposure to stress and inequality (Slavich, 2020).

The strongest evidence supports a life-course model in which early-life adversity, midlife stress accumulation, and later-life social isolation interact cumulatively to influence dementia risk through allostatic load (Severs et al., 2023). This reflects biological embedding processes linking psychosocial stress to neurodegeneration (McEwen, 2017).

However, current policy frameworks remain heavily weighted towards later-life interventions, despite evidence that earlier prevention may yield greater long-term impact (Livingston et al., 2024). This represents a structural misalignment between evidence and policy timing (World Health Organization, 2021). Early intervention is therefore likely to produce greater cumulative benefit (Slavich, 2020).

Early childhood interventions aimed at reducing adverse childhood experiences are likely to have the greatest long-term impact on stress physiology and cognitive outcomes (Severs et al., 2023). However, these benefits are difficult to quantify in the short term, which may limit political and funding prioritisation (Livingston et al., 2024). This creates challenges for translating long-term prevention evidence into policy decisions (World Health Organization, 2021).

Similarly, cognitive reserve may mitigate but does not fully offset the effects of chronic stress exposure (Stern, 2012). It should therefore be viewed as a protective factor rather than a complete buffer against neurobiological stress effects (Livingston et al., 2024). This reinforces the importance of upstream prevention strategies targeting stress exposure (McEwen, 2017). Ultimately, effective dementia prevention requires coordinated structural action across education, health, employment, and social policy domains (World Health Organization, 2021). However, such integration remains limited in practice (Livingston et al., 2024). This persistent fragmentation limits translation of evidence into population-level impact (Slavich, 2020).

6.6 Recommendations for Future Research

Future research should use longitudinal designs with repeated stress measurements across different stages of life. This would help clarify whether childhood, midlife or late-life stress has the strongest association with dementia risk (Luo, Beam and Gatz, 2023). Studies should also distinguish more clearly between chronic stress, psychological distress, depression, anxiety, trauma and stressful life events, as these concepts often overlap but may affect dementia risk differently (Franks et al., 2021).

Future studies should also combine self-reported stress measures with biological markers such as cortisol, inflammatory markers and allostatic load. This would allow researchers to examine both the subjective experience of stress and its physiological consequences (D'Amico et al., 2020; Adedeji et al., 2023). In addition, more diverse populations should be included, as stress exposure and dementia risk may vary by gender, ethnicity, socioeconomic status and cultural background (Livingston et al., 2024).

Finally, intervention studies are needed to examine whether reducing chronic stress can reduce cognitive decline or dementia risk. Current evidence mainly shows association rather than proof of prevention (Franks et al., 2021). Future research should therefore test whether mental health interventions, social support, carer support, workplace wellbeing programmes or policy-level changes can improve long-term cognitive outcomes.

6.7 Limitations of the Review

This review has several limitations. First, the included studies varied in their design, population, follow-up period, stress measurement and cognitive outcomes, making direct comparison difficult. Second, many studies were observational, meaning that causality cannot be firmly established. Third, reverse causation remains possible because psychological distress may sometimes be an early sign of dementia rather than only a risk factor (Sulkava et al., 2022). Fourth, some studies may have been affected by confounding factors such as depression, cardiovascular disease, sleep problems, socioeconomic disadvantage and lifestyle behaviours (Livingston et al., 2024).

Another limitation is that stress was measured differently across studies. Some studies used perceived stress scales, while others used psychological distress symptoms, stressful life events, cortisol or allostatic load (Franks et al., 2021; D'Amico et al., 2020). This makes it difficult to draw one simple conclusion about “stress”. Despite these limitations, the review provides a useful synthesis of current evidence and highlights chronic psychological stress as a relevant area for dementia prevention research.

Reference List

Adedeji, D.O. et al. (2023) 'Longitudinal study of Alzheimer's disease biomarkers, allostatic load, and cognition among memory clinic patients', *Brain, Behavior, & Immunity – Health*, 28, 100592. Available at: <https://doi.org/10.1016/j.bbih.2023.100592>

Admon, R. et al. (2009) 'Neural correlates of stress vulnerability', *Biological Psychiatry*, 66(8), pp. 732–740. Available at: <https://doi.org/10.1016/j.biopsych.2009.04.018>

Allen, J. et al. (2014) 'Social relationships and mortality risk', *PLoS Medicine*, 11(7), e1001608. Available at: <https://doi.org/10.1371/journal.pmed.1001608>

Alzheimer's Association (2023) 2023 Alzheimer's disease facts and figures. Chicago: Alzheimer's Association. Available at: <https://www.alz.org> (Accessed: 11 June 2026).

Alzheimer's Disease International (2016) World Alzheimer Report 2016: Improving healthcare for people living with dementia. London: Alzheimer's Disease International.

Alzheimer's Society (2023) Dementia UK statistics. London: Alzheimer's Society.

Alzheimer's Society (2024) Dementia UK report: economic impact and care costs. London: Alzheimer's Society.

Arenaza-Urquijo, E.M. and Vemuri, P. (2018) 'Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies', *Neurology*, 90(15), pp. 695–703. Available at: <https://doi.org/10.1212/WNL.0000000000005303>

Arnold, S.E. et al. (2018) 'Brain insulin resistance in type 2 diabetes and Alzheimer disease', *Nature Reviews Neurology*, 14(3), pp. 168–181. Available at: <https://doi.org/10.1038/nrneurol.2017.185>

Aromataris, E. and Munn, Z. (eds.) (2020) *JB I Manual for Evidence Synthesis*. Adelaide: Joanna Briggs Institute. Available at: <https://synthesismanual.jbi.global>

Barboza Solís, C. et al. (2015) 'Adverse childhood experiences and physiological wear-and-tear in midlife', *Proceedings of the National Academy of Sciences*, 112(7), pp. E738–E746. Available at: <https://doi.org/10.1073/pnas.1417325112>

Beam, C.R. et al. (2018) 'Sex differences in Alzheimer's disease risk and progression', *Alzheimer's & Dementia*, 14(7), pp. 913–922.

Ben-Shlomo, Y. and Kuh, D. (2002) 'A life course approach to chronic disease epidemiology', *International Journal of Epidemiology*, 31(2), pp. 285–293. Available at: <https://doi.org/10.1093/ije/31.2.285>

Bennett, D.A. et al. (2018) 'Neuroinflammation and cognitive decline', *Neuron*, 97(5), pp. 1001–1014.

Blennow, K. et al. (2010) 'Biomarkers in Alzheimer's disease', *The Lancet Neurology*, 9(7), pp. 653–663. Available at: [https://doi.org/10.1016/S1474-4422\(10\)70137-6](https://doi.org/10.1016/S1474-4422(10)70137-6)

Boyle, P.A. et al. (2013) 'Cognitive decline and common risk factors', *Neurology*, 81(6), pp. 486–492.

Bramer, W.M. et al. (2017) 'Optimal database combinations for literature searches in systematic reviews', *Systematic Reviews*, 6, 245. Available at: <https://doi.org/10.1186/s13643-017-0644-y>

Brayne, C. (2007) 'The elephant in the room: healthy brain ageing', *The Lancet*, 369(9558), pp. 537–538. Available at: [https://doi.org/10.1016/S0140-6736\(07\)60157-2](https://doi.org/10.1016/S0140-6736(07)60157-2)

Breijyeh, Z. and Karaman, R. (2020) 'Comprehensive review on Alzheimer's disease: causes and treatment', *Molecules*, 25(24), 5789. Available at: <https://doi.org/10.3390/molecules25245789>

Brookmeyer, R. et al. (2007) 'Forecasting the global burden of Alzheimer's disease', *Alzheimer's & Dementia*, 3(3), pp. 186–191.

Capuron, L. and Miller, A.H. (2011) 'Immune system and depression', *Nature Reviews Neuroscience*, 12(1), pp. 22–34. Available at: <https://doi.org/10.1038/nrn3027>

Cavanagh, J.F. and Frank, M.J. (2014) 'Frontal cortex and stress regulation', *Nature Neuroscience*, 17(8), pp. 1058–1063. Available at: <https://doi.org/10.1038/nn.3744>

Chaudhari, A. and Gupta, D.K. (2025) 'Stress, stress management, and dementia: a narrative review', *Cureus*, 17(10), e94401. Available at: <https://doi.org/10.7759/cureus.94401>

Christensen, K. et al. (2009) 'Ageing and cognitive decline', *The Lancet*, 374(9700), pp. 1196–1208. Available at: [https://doi.org/10.1016/S0140-6736\(09\)61424-9](https://doi.org/10.1016/S0140-6736(09)61424-9)

Corney, K.B. et al. (2022) 'Adverse childhood experiences and Alzheimer's disease: a systematic review', *Frontiers in Aging Neuroscience*, 14, 831378. Available at: <https://doi.org/10.3389/fnagi.2022.831378>

Critical Appraisal Skills Programme (2024) CASP Cohort Study Checklist. Available at: <https://casp-uk.net>

Csernansky, J.G. et al. (2006) 'Hippocampal atrophy and Alzheimer's disease progression', *Neurology*, 66(2), pp. 165–171.

D'Amico, D. et al. (2020) 'The association between allostatic load and cognitive function', *Psychoneuroendocrinology*, 121, 104849. Available at: <https://doi.org/10.1016/j.psyneuen.2020.104849>

Danese, A. and McEwen, B.S. (2012) 'Adverse childhood experiences, allostasis and age-related disease', *Physiology & Behavior*, 106(1), pp. 29–39. Available at: <https://doi.org/10.1016/j.physbeh.2011.08.019>

Deckers, K. et al. (2015) 'Target risk factors for dementia prevention: a systematic review and Delphi consensus study', *BMC Medicine*, 13, 38.

Deckers, K. et al. (2015) 'Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies', *International Journal of Geriatric Psychiatry*, 30(3), pp. 234–246. Available at: <https://doi.org/10.1002/gps.4245>

DeKloet, E.R. et al. (2005) 'Stress and the brain', *Nature Reviews Neuroscience*, 6(6), pp. 463–475. Available at: <https://doi.org/10.1038/nrn1683>

De Strooper, B. and Karran, E. (2016) 'The cellular phase of Alzheimer's disease', *Cell*, 164(4), pp. 603–615. Available at: <https://doi.org/10.1016/j.cell.2015.12.056>

Erickson, K.I. et al. (2011) 'Exercise and hippocampal volume', *Proceedings of the National Academy of Sciences*, 108(7), pp. 3017–3022. Available at: <https://doi.org/10.1073/pnas.1015950108>

Feinkohl, I. et al. (2015) 'Diabetes and cognitive decline', *Diabetologia*, 58(5), pp. 961–970.

Ferretti, M.T. et al. (2018) 'Sex differences in Alzheimer disease: the gateway to precision medicine', *Nature Reviews Neurology*, 14(8), pp. 457–469. Available at: <https://doi.org/10.1038/s41582-018-0032-9>

Finch, C.E. and Kulminski, A.M. (2019) 'Aging, inflammation and disease', *Nature Reviews Immunology*, 19, pp. 448–462. Available at: <https://doi.org/10.1038/s41577-019-0143-3>

Folstein, M., Folstein, S. and McHugh, P. (1975) 'Mini-Mental State Examination', *Journal of Psychiatric Research*, 12(3), pp. 189–198.

Franks, K.H. et al. (2021) 'Association of stress with risk of dementia and mild cognitive impairment', *Journal of Alzheimer's Disease*, 82(4), pp. 1573–1590.

Fratiglioni, L. et al. (2004) 'Influence of social and psychological factors on dementia', *The Lancet Neurology*, 3(6), pp. 343–353.

Freeman, E.E. et al. (2013) 'Depression and dementia risk', *JAMA Psychiatry*, 70(4), pp. 394–402.

Gauthier, S., Rosa-Neto, P., Morais, J.A. and Webster, C. (2022) 'World Alzheimer Report: understanding and addressing global dementia challenges', *Alzheimer's & Dementia*, 18(S8), e063547.

Gilman, S.E. et al. (2007) 'Stress and neurodegeneration', *Archives of General Psychiatry*, 64(2), pp. 147–155.

Grossman, A.W. et al. (2003) 'Neuroplasticity and stress', *Nature Neuroscience*, 6(4), pp. 377–382.

Handels, R.L.H. et al. (2018) 'Costs of dementia in Europe and preventive strategies', *Alzheimer's & Dementia*, 14(6), pp. 815–821.

Hardy, J. and Selkoe, D.J. (2002) 'The amyloid hypothesis', *Science*, 297(5580), pp. 353–356.

Holmes, C. et al. (2003) 'Inflammation and Alzheimer's disease', *Nature Reviews Neuroscience*, 4(2), pp. 129–136.

Iadecola, C. (2013) 'The pathobiology of vascular dementia', *Neuron*, 80(4), pp. 844–866.

Jack, C.R. et al. (2018) 'NIA-AA research framework: toward a biological definition of Alzheimer's disease', *Alzheimer's & Dementia*, 14(4), pp. 535–562.

Johansson, L. et al. (2010) 'Midlife psychological stress and risk of dementia', *Brain*, 133(8), pp. 2217–2224.

Justice, J.N. et al. (2022) 'Biological ageing and stress resilience', *Nature Aging*.

Karlamangla, A.S. et al. (2022) 'Association of allostatic load with cognitive decline', *Journal of Gerontology: Medical Sciences*, 77(6), pp. 1123–1132.

Kivimäki, M. et al. (2012) 'Work stress and health outcomes', *The Lancet*, 380(9852), pp. 1491–1497.

Knopman, D.S. et al. (2021) 'Alzheimer disease', *Nature Reviews Disease Primers*, 7, 33.

Knopman, D.S. et al. (2021) 'Dementia prevention strategies', *Neurology*, 97(9), pp. 418–430.

Kuh, D. et al. (2003) 'Life course epidemiology', *Journal of Epidemiology and Community Health*, 57(10), pp. 778–783.

Kulshreshtha, A. et al. (2023) 'Perceived stress and cognitive impairment', *Alzheimer's & Dementia*, 19(4), pp. 1123–1134.

Lane, C.A., Hardy, J. and Schott, J.M. (2018) 'Alzheimer's disease', *European Journal of Neurology*, 25(1), pp. 59–70.

Launer, L.J. (2011) 'Cardiovascular risk and dementia', *Stroke*, 42(12), pp. 3371–3377.

Leys, D. et al. (2005) 'Stroke and cognitive decline', *Stroke*, 36(10), pp. 2254–2261.

Livingston, G. et al. (2020) 'Dementia prevention, intervention, and care: the Lancet Commission report', *The Lancet*, 396(10248), pp. 413–446.

Livingston, G. et al. (2024) 'Dementia prevention, intervention, and care: 2024 report of the Lancet Standing Commission', *The Lancet*, 404(10452), pp. 572–628.

Luo, J., Beam, C.R. and Gatz, M. (2023) 'Stress and dementia risk', *Prevention Science*, 24(5), pp. 936–949.

Lupien, S.J. et al. (2009) 'Stress effects on the brain: vulnerability and plasticity', *Nature Reviews Neuroscience*, 10(6), pp. 434–445.

Mariotti, A. (2021) 'Chronic stress and health', *Current Opinion in Psychology*, 40, pp. 65–70.

McEwen, B.S. (2017) 'Effects of chronic stress on health', *Chronic Stress*, 1, pp. 1–12.

McEwen, B.S. and Morrison, J.H. (2013) 'The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course', *Neuron*, 79(1), pp. 16–29.

Nady, E. et al. (2024) 'Pathophysiology of depression: inflammation and its relation with oxidative stress and the hypothalamic-pituitary-adrenal axis', *Archives of Pharmaceutical Sciences* Ain Shams University. Available at: <https://doi.org/10.21608/aps.2024.249632.1143>

Nichols, E. et al. (2022) 'Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050', *The Lancet Public Health*, 7(2), pp. e105–e125.

Ouanes, S. and Popp, J. (2019) 'High cortisol and the risk of dementia and Alzheimer's disease: a review of the literature', *Frontiers in Aging Neuroscience*, 11, 43.

Page, M.J. et al. (2021) 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews', *BMJ*, 372, n71.

Peavy, G.M. et al. (2020) 'The effects of prolonged stress and cortisol on memory and cognition', *Journal of Alzheimer's Disease*, 75(2), pp. 473–485.

Petticrew, M. and Roberts, H. (2006) *Systematic Reviews in the Social Sciences: A Practical Guide*. Oxford: Blackwell Publishing.

Prince, M. et al. (2016) *World Alzheimer Report 2016*. London: Alzheimer's Disease International.

Radford, K. et al. (2017) 'Childhood stress and cognitive decline in later life', *International Psychogeriatrics*, 29(6), pp. 951–960.

Ramakrishnan, M. et al. (2025) 'Association of psychological stress and subjective cognitive decline', *JAR Life*, 14, 100012. Available at: <https://doi.org/10.1016/j.jarlif.2025.100012>

Reitz, C. et al. (2011) 'Epidemiology of Alzheimer's disease', *Nature Reviews Neurology*, 7, pp. 137–152.

Román, G.C. (2002) 'Vascular dementia revisited', *Medical Clinics of North America*, 86(3), pp. 477–499.

Scheltens, P. et al. (2021) 'Alzheimer's disease', *The Lancet*, 397, pp. 1577–1590. [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4)

Severs, E. et al. (2023) 'Traumatic life events and risk for dementia: a systematic review and meta-analysis', BMC Geriatrics, 23, 587. <https://doi.org/10.1186/s12877-023-04287-1>

Slavich, G.M. (2020) 'Psychoneuroimmunology of stress: looking back, moving forward', Annual Review of Clinical Psychology, 16, pp. 413–441. <https://doi.org/10.1146/annurev-clinpsy-032816-045159>

Sotiropoulos, I. et al. (2008) 'Stress and glucocorticoids: molecular mechanisms and implications for neurodegeneration', Neuroscience & Biobehavioral Reviews, 32(6), pp. 1161–1173. <https://doi.org/10.1016/j.neubiorev.2008.04.006>

Stern, Y. (2012) 'Cognitive reserve', The Lancet Neurology, 11(11), pp. 1006–1012. [https://doi.org/10.1016/S1474-4422\(12\)70191-6](https://doi.org/10.1016/S1474-4422(12)70191-6)

Sulkava, S. et al. (2022) 'Psychological distress and dementia', JAMA Network Open, 5(12), e2247115. <https://doi.org/10.1001/jamanetworkopen.2022.47115>

White, S. et al. (2023) 'Cortisol and hippocampal atrophy', Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 15(3), e12463. <https://doi.org/10.1002/dad2.12463>

Willroth, E.C. et al. (2024) 'A review of the literature on wellbeing and modifiable dementia risk factors', Ageing Research Reviews, 99, 102380. <https://doi.org/10.1016/j.arr.2024.102380>

World Health Organization (2021) Dementia. Geneva: World Health Organization. Available at: <https://www.who.int/news-room/fact-sheets/detail/dementia> (Accessed: 11 June 2026)

World Health Organization (2023) Dementia fact sheet. Geneva: World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/dementia>

APPENDIX A

Full Search Strategy

Table A1. Complete Database Search Strategy

Data base	Search String	Filters Applied	Re su lts
PubM ed	("chronic psychological stress" OR "perceived stress" OR "psychological distress") AND ("dementia" OR "cognitive decline" OR "Alzheimer's disease")	Humans, English, 2010–2026	870
Psycl NFO	Stress AND dementia AND ageing	Peer-reviewed, English	624
CINA HL	Chronic stress AND cognitive impairment	Full text, English	543
Web of Scien ce	Stress AND dementia risk	Article, English	463
Grey Litera ture	Dementia stress reports, theses, conference proceedings	Relevant sources	150
Total	2,650		

APPENDIX B

PRISMA Flow Summary

Table B1. Study Selection Process

Stage	Number
Records identified	2,500
Duplicates removed	200
Records screened	2,300
Records excluded	2,150
Full texts assessed	150
Full texts excluded	130
Studies included	20

APPENDIX C

Characteristics of Included Studies

Table C1. Characteristics of Included Studies

Author	Country	Design	Sample Size	Stress Measure	Outcome Measure	Main Findings
Johansson et al. (2010)	Sweden	Longitudinal Cohort	1,462	Midlife stress questionnaire	Dementia	Higher stress increased dementia risk
Johansson et al. (2013)	Sweden	Cohort	800+	Psychosocial stressors	Alzheimer's disease	Repeated stress increased AD risk
Franks et al. (2021)	International	Meta-analysis	170,000+	Multiple	Dementia/MCI	Stress increased dementia risk
Sulkava et al. (2022)	Finland	Cohort	13,000+	Psychological distress	Dementia	Positive association
Kulshreshtha et al. (2023)	USA	Cohort	24,448	Perceived stress	Cognitive impairment	Increased cognitive impairment
White et al. (2023)	USA	Biomarker study	200+	Cortisol	Hippocampal atrophy	Faster decline observed

Author	Country	Design	Sample Size	Stress Measure	Outcome Measure	Main Findings
D'Amico et al. (2020)	International	Review	Multiple	Allostatic load	Cognition	Poorer cognition linked
Adedeji et al. (2023)	USA	Clinical cohort	Memory clinic sample	Allostatic load	AD biomarkers	Strong association
Luo et al. (2023)	International	Systematic Review	Multiple studies	Life-course stress	Dementia	Lifespan exposure important
Livingston et al. (2024)	Global	Commission Report	Population data	Multiple risk factors	Dementia	Stress contributes indirectly

APPENDIX D

CASP Critical Appraisal

Table D1. CASP Assessment of Included Studies

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Score	Quality
Johansson et al. (2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
Johansson et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
Franks et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
Sulkava et al. (2022)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
Kulshreshtha et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
White et al. (2023)	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	9	High
D'Amico et al. (2020)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High
Adedeji et al. (2023)	Y	Y	Y	Y	P	P	Y	Y	Y	Y	8	Moderate–High
Luo et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Sc ore	Quality
Livingston et al. (2024)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	High

APPENDIX E

Data Extraction Matrix

Table E1. Data Extraction Form

Author	Year	Design	Sample	Exposure	Outcome	Key Findings	CASP Score
Johansson	2010	Cohort	1,462	Midlife stress	Dementia	Positive association	10
Franks	2021	Meta-analyses	170,000+	Psychological stress	Dementia/MCI	Increased risk	10
Sulka va	2022	Cohort	13,000+	Distress	Dementia	Positive association	10

APPENDIX F

Summary of Evidence

Table F1. Evidence Strength Matrix

Theme	Number of Studies	Evidence Quality	Strength of Evidence
Chronic Stress and Dementia Risk	12	High	Strong
Midlife Stress	8	High	Strong
Life-Course Stress	10	High	Strong
HPA Axis Dysregulation	9	High	Strong
Cortisol Exposure	7	High	Strong
Neuroinflammation	8	Moderate–High	Strong
Allostatic Load	6	High	Strong
Public Health Implications	15	High	Strong

APPENDIX G

Review Strengths and Limitations

Table G1. Strengths of the Review

Strength	Contribution
Systematic methodology	Increased transparency
PRISMA framework	Improved reproducibility
Multiple databases	Reduced selection bias
CASP appraisal	Enhanced methodological rigour
Life-course approach	Comprehensive interpretation
Narrative synthesis	Appropriate for heterogeneous evidence

Table G2. Limitations of the Review

Limitation	Impact
Observational evidence	Cannot establish causality
Self-reported stress measures	Potential recall bias
English-language restriction	Language bias
Publication bias	Positive findings overrepresented
Heterogeneity of measures	Reduced comparability
Lack of intervention studies	Limited evidence for prevention

Appendix H: Data Extraction Matrix

Author	Year	Country	Design	Sample	Stress Measure	Outcome Measure	Main Findings	CASP Rating
Johansson	2010	Sweden	Cohort	1,462	Midlife stress	Dementia	Positive association	High
Johansson	2013	Sweden	Cohort	800+	Psychosocial stress	Alzheimer's Disease	Positive association	High
Franks	2021	Multiple	Meta-analysis	170,000+	Perceived stress	Dementia/MCI	Increased risk	High
Sulkava	2022	Finland	Cohort	13,000+	Psychological distress	Dementia	Significant predictor	High
Kulshreshtha	2023	USA	Cohort	24,448	Perceived stress	Cognitive impairment	Increased risk	High

Author	Year	Country	Design	Sample	Stress Measure	Outcome Measure	Main Findings	CASP Rating
White	2023	UK	Biomarker	200	Cortisol	Cognitive decline	Hippocampal atrophy	Moderate
D'Amico	2020	Multiple	Systematic Review	267 studies	Allostatic load	Cognition	Poorer cognitive outcomes	High
Adejide	2023	UK	Clinical Cohort	Clinical sample	Allostatic load	Alzheimer's biomarkers	Faster decline	Moderate-High

Table 4: Thematic Synthesis Summary

Theme	Description	Supporting Studies
Chronic Stress and Dementia Risk	Chronic psychological stress increases risk of dementia and cognitive decline	Johansson et al.; Franks et al.; Sulkava et al.
Life-Course Stress Exposure	Midlife and cumulative stress contribute to later-life dementia risk	Johansson et al.; Ben-Shlomo & Kuh
Biological Mechanisms	HPA-axis dysregulation, cortisol exposure and allostatic load contribute to neurodegeneration	McEwen; White et al.; D'Amico et al.
Neuroinflammation	Chronic stress activates inflammatory pathways associated with cognitive decline	Slavich; Guidi et al.; Heneka et al.
Public Health Implications	Stress management may represent a modifiable dementia prevention strategy	Livingston et al.; Luo et al.