Preventing Dementia: The Prevalence of Modifiable Risk Factors in People Attending Ireland's First Brain Health Clinic

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Medicine

Discipline of Medical Gerontology

School of Medicine

Trinity College Dublin

The University of Dublin

2025

Declaration of Authorship

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Acknowledgements

Ar scáth a chéile a mhaireann na daoine

I would like to thank my M.D. supervisor Professor Seán Kennelly for co-ordinating this research, for his mentorship and for giving me the invaluable opportunity to work in the Tallaght University Hospital Institute of Memory and Cognition (TIMC) where I have learned so much about cognition, exceptional patient centred care and service development. I wish to acknowledge the contribution of my colleagues in the work presented here. Thanks to Graham Knight, Fiona Tobin, Emma Nolan, Derek Wilde and Loredana Porumb who helped with the compilation of the Brain Health Database. Thank you also to Cathy McHale, Dr Aoife Fallon, Dr Laura Morrison, Dr Antoinette O'Connor and Dr Sean O'Dowd for all I have learned while working in TUH.

Thank you to my registrar colleagues who have supported me on this research journey and across my years of training. Thank you to Dr Helena Dolphin for sharing your biorender diagrams and to Dr Adam Dyer for sharing your research expertise and Dr Lucy Chapman for your help with formatting and for paving the way. Dr Emily Buckley shared her experience in writing a scoping review, while Dr Paddy Doyle has been an invaluable sounding board since I was an intern. A special thank you to Dr Aoife McFeely and Dr Naomi Davey for their kindness and camaraderie over the last number of years.

Thank you to my family who have supported and persevered with me on the winding road from mechanical engineering to geriatric medicine. Martin, thank you for all the time you spent editing this document and Mary thank you for minding both Úna and I. You both take such an interest in brain health and are an inspiration to me. Cormac thank you for always

looking after me, I promise this is the last degree! Finally, to Úna. Thank you for being the motivation to complete this work, for being a baby that sleeps so I could edit it, and most of all for the joy you have brought to all of our lives. It is a privilege to be your Mam.

Contents

List of Abbreviations

Abbreviation	Definition
A+	Aβ pathology
AAC	Auditory association cortex
ABPM	Ambulatory blood pressure monitor
ACE-III	Addenbrook's Cognitive Examination-III
AD	Alzheimer's Disease
AF	Atrial fibrillation
A-IADL-Q	Amsterdam Instrumental Activities of daily Living Questionnaire
AMPS	Assessment of Motor and Process Skills
ANP	Advanced Nurse Practitioners
ANU-ADRI	Australian National University Alzheimer's Disease Risk Index
APC	Alzheimer's Prevention Clinic
ApoA-1	Apolipoprotein A1
ApoB	Apolipoprotein B
APOE	Apolipoprotein E
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid-related imaging abnormalities oedema
ARIA-H	Amyloid-related imaging abnormalities haemorrhage
ARMD	Age related macular degeneration
AU-ARROW	Approach to Reduce dementia risk by protecting brain health with lifestyle intervention study
Aβ	Amyloid beta
BDNF	Brain-derived neurotrophic factor
BDSI	Brief Dementia Screening Indicator
BMI	Body Mass Index
CABG	Coronary artery bypass graft
CAIDE	Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CBI-R	Revised Cambridge Behavioral Inventory
CBT-I	Cognitive behavioural therapy for insomnia
CDR	Clinical Disease Rating
CDR	Clinical Dementia Rating
CDR-Sb	CDR sum-of-boxes
CEDAR	Comparative Effectiveness Dementia and Alzheimer's Registry
CRP	C-reactive protein
CSF	Cerebro-spinal Fluid
DASH	Dietary Approaches to Stop Hypertension
DaTscan	Dopamine transporter scan

Abbreviation	Definition
DCI	Detectible cognitive impairment
DCI-ND	Detectible cognitive impairment - neurodegenerative disease
DHA	Docosahexaenoic acid
DMTs	Disease Modifying Therapies
DOACs	Direct acting oral anticoagulants
DRS	Dementia Risk Score
EDA	Excessive daytime sleepiness
EMA	European Medicine Agency
Epa	Eicosapentaenoic acid
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EXAMINER	Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research
FAB	Frontal Assessment Battery
FCS-RT	Free and Cued Selective Recall Test
FDA	Food and Drug Administration
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FRS	Framingham Risk Score
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS-anxiety subscale
HADS-D	HADS-depression subscale
HbA1c	Glycosylated haemoglobin
HIIT	High intensity interval training
HSE	Health Service Executive
IC	Inferior colliculus
IHD	Ischemic heart disease
IPAQ	International Physical Activity Questionnaire
J-MINT	Japanese Multidomain Intervention Trial for prevention of dementia
KPI	Key performance indicator
LBD	Lewy body Disorder
LDL	Low density lipoprotein
LIBRA	Lifestyle for Brain Health
logMAR	Logarithm of minimum angle of resolution
Lp(a)	Lipoprotein (a) Mass
Lp-PLA2	lipoprotein-associated phospholipase A_2

Abbreviation	Definition
LSNS-6	Lubben Social Network Inclusion Scale 6
MAPT	Multidomain Approach for Preventing Alzheimer's Disease
MASS	Memory Assessment and Support Services
MBI	Mild Behavioural Impairment
MBI-C	Mild behavioural Impairment checklist
MCI	Mild Cognitive Impairment
MDT	Multi-disciplinary Team
MeSH	Medical Subject Headings
MET	Metabolic equivalent
MET	Metabolic equivalent
MGB	Medial geniculate body
MHRA	Medicines and Healthcare Regulatory Agency
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMSE	Mini-Mental State Examination
MPO	Myeloperoxidase
MTA	Medial temporal lobe atrophy
MTHFR	Methylenetetrahydrofolate reductase
MTL	Medial temporal lobe
NDO	National Dementia Office
NDO	National Dementia Office
NHS	National Health Service
NIA-AA	National Institute on Aging and the Alzheimer's Association
NIH	National Institutes of Health
NIHTB-CB	National Institutes of Health Toolbox Cognition Battery
NPI-Q	Neuropsychiatric inventory Questionnaire
NT-proBNP	N-terminal pro Brain Natriuretic Peptide
OSA	Obstructive Sleep Apnoea
PAC	Primary auditory cortex
PCI	Percutaneous coronary intervention
PET	Positron Emission Tomography
PHQ	Patient Health Questionnaire
PLMS	Periodic limb movement syndrome
PREDIMED	Primary Prevention of cardiovascular disease with a mediterranean diet
Pre-DIVA	Prevention of Dementia by Intensive Vascular care
PRISMA-Scr	Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews
PSQI	Pittsburgh Sleep Quality Index
RBANS	Repeatable Battery for Neuropsychological Status

Abbreviation	Definition
RBD	Rapid eye movement sleep behaviour disorder
RCT	Randomised control trial
RLS	Restless leg syndrome
RSMC	Regional Specialist Memory Clinic
SBP	Systolic blood pressure
SCD	Subjective Cognitive Decline
SD	Standard deviations
sdLDL	Small dense LDL
SSRI	Selective serotonin reuptake inhibitor
T+	Tau pathology
T2DM	Type 2 diabetes mellitus
TBI	Traumatic Brain Injury
TIMC	Tallaght University Hospital Institute of Memory and Cognition
TSH	Thyroid Stimulating Hormone
TUH	Tallaght University Hospital
UCLA	University of California, Los Angeles
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
WHR	Waist to hip ratio
WW-FINGERS	World-Wide FINGERS

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Abstract

Introduction:

Cognition exists on a spectrum which ranges from normal cognition, subjective memory complaints (SMC), mild cognitive impairment (MCI) and dementia. Dementia prevalence is rising globally, driven largely by changing population demographics. This poses a significant challenge to healthcare systems worldwide. Despite the rising dementia prevalence, the incidence of dementia is falling in Europe and North America over the last 25 years. This is potentially as an indirect result of improved management cardiovascular risk factors and societal and lifestyle changes. The prodromal period of dementia syndromes which begins in mid-life presents an opportunity to address modifiable risk factors for dementia. It is now acknowledged that on a population level around 45% of all causes of dementia are attributable to modifiable risk factors. Existing memory services must evolve to facilitate brain health interventions for patients with MCI or SMC by identifying and address their individual modifiable risk factors.

Aims:

1. To explore existing models for the delivery of brain health interventions and define a clinical service model for a Brain Health Clinic which is integrated into an existing memory service.
2. To quantify the prevalence of modifiable risk factors for dementia in a cohort of patients attending a Brain Health Clinic with a particular focus on cardiovascular risk factors, sensory risk factors and lifestyle factors such as physical activity, sleep and

psychosocial well-being. Does the risk factor profile differ between patients with SMC vs MCI?

3. To highlight the potential role of this brain health clinical service in identifying previously undiagnosed modifiable dementia risk factors in patients with MCI and SMC and the scope for intervention to reduce these risk factors on an individual level.

Methodology:

This thesis includes a prospective cohort study of patients attending the brain health service in Tallaght University Hospital Dublin between March 2022 and April 2024. Patients' consensus diagnosis of either MCI or SMC was recorded along with whether they had undergone testing for Alzheimer's Disease (AD) biomarkers. Risk factors were assessed through both biophysical assessments and self-reported questionnaires. Lifestyle risk factors physical activity levels, diet, sleep, depression, social isolation and loneliness were quantified using such as the International Physical Activity Questionnaire (IPAQ), mediterranean diet score tool, Pittsburgh Sleep Quality Index (PSQI), the Epworth sleepiness scale, the hospital anxiety and depression scale (HADS), the Lubben social network scale-6 and the University of California, Los Angeles (UCLS) three-item loneliness scale. The sensory risk factors of poor vision and hearing were screened for using the Peek Acuity smartphone app to generate a LogMAR score and the Siemens HearCheck^{TM} Screener respectively. Cardiovascular risk factors were assessed by measuring blood pressure, random lipid profile and glycosylated haemoglobin. Risk factor profiles were explored using descriptive statistics and compared across cognitive diagnosis and AD biomarkers.

Results:

In this prospective cohort study there were 118 patients (61% female, median age 71.9 years). Most patients had a MCI diagnosis (79.7%) and of these patients 81.9% were amnestic. Over half of patients in the cohort (n=49, 52.1%) had a lumbar puncture (LP) to assess for AD biomarkers with AD pathology detected in 21 cases. Hypertension was the most prevalent risk factor in patients attending the service, with 46% of patients with known hypertension found to have sub-optimally controlled blood pressure, while 23.7% of patients had newly identified hypertension. Poor sleep was reported by 59.3% of patients. Almost half of patients (48.6%) had low physical activity levels. A possible hearing impairment was identified in 32.6% of patients, with over one fifth of the patient cohort referred to audiology for formal hearing assessment. While there was a similar spread of risk factor profiles across the MCI and SMC patients, patients with SMC had significantly higher rates of loneliness while MCI patients had a significantly higher rate of type two diabetes and depression.

Discussion and conclusion:

This work is the first to describe a brain health clinic model which has been embedded in an existing memory service with the goal of educating patients with cognitive concerns about their dementia risk, while also quantifying their modifiable risk factor burden. This model enables patients to engage in a personalised prevention plan to improve their overall dementia risk. The wide range of cardiovascular, sensory and lifestyle risk factors which were found in this clinical patient cohort highlight both the risk factor burden in patients with cognitive complaints, but also the opportunity for intervention through

personalised prevention. This work outlines a framework which could be implemented in other memory clinical settings to longitudinally follow both cognition and risk factor burden in patients with cognitive concerns who do not meet the criteria for dementia.

Outputs

- Eimear Connolly, Graham Knight, Helena Dolphin, Aoife Fallon, Sean P. Kennelly; Brain Health Interventions in Clinical Practice: A Framework for Implementation and Provisional Results from Ireland's first Brain Health Clinic, AAIC 2024 – Poster Presentation
- Eimear Connolly, Aoife McFeely, Sean P. Kennelly; How are Brain Health Interventions Implemented in Clinical Settings Internationally? – A Scoping Review, IGS 2024 – Poster Presentation
- Eimear Connolly, Graham Knight, Cathy McHale, Aoife Fallon, Sean. P. Kennelly**:** The Prevalence of Lifestyle Risk Factor in Patients attending Ireland's First Brain Health Clinic, EUGMS 2024 – Poster Presentation
- Eimear Connolly, Graham Knight, Cathy McHale, Aoife Fallon, Sean. P. Kennelly**:** The Prevalence of Modifiable Vascular Risk Factors among Patients Attending Ireland's First Brain Health Clinic – An Opportunity for Intervention. EUGMS 20204 – Poster Presentation

Chapter 1. Introduction

1.1. Background

1.1.1. Defining Dementia, Mild Cognitive Impairment and Subjective Cognitive Decline

Dementia is an umbrella term that is used to describe a wide range of neurodegenerative disorders that differ in terms of their pathophysiology and their clinical phenotype. It presents as progressive decline across multiple domains of cognition that leads to impaired functional performance [1]. Despite advancing age being the main risk factor for the development of dementia, it is not an inevitable feature of normal ageing.

Alzheimer's Disease (AD) is estimated to account for 60-80% of all dementia cases, making it the most prevalent cause of dementia [2]. The diagnosis of AD has now advanced to include the pathophysiology of the disease [3, 4]. The clinical syndrome presents as a result of the accumulation of amyloid plaques and hyperphosphorylated tau neurofibrillary tangles [5]. These hallmark proteins of AD can now be detected *in-vivo* through Cerebro-Spinal Fluid (CSF) testing and Positron Emission Tomography (PET) imaging.

In 2023 the National Institute on Aging and the Alzheimer's Association (NIA-AA) diagnostic criteria were revised to incorporate the detection of these AD biomarkers in either CSF or PET imaging. Abnormal accumulation of amyloid and tau proteins in AD is thought to begin up to 20 years before the onset of symptoms [6]. This 20 year period of prodromal AD can be diagnosed prior to the advent of symptoms by detecting the presence of AD biomarkers [7]. This is graphically shown in Figure 1. This prodromal period can be viewed as a target for both emergent Disease Modifying Therapies (DMTs) and lifestyle modifications which may affect relevant risk factors.

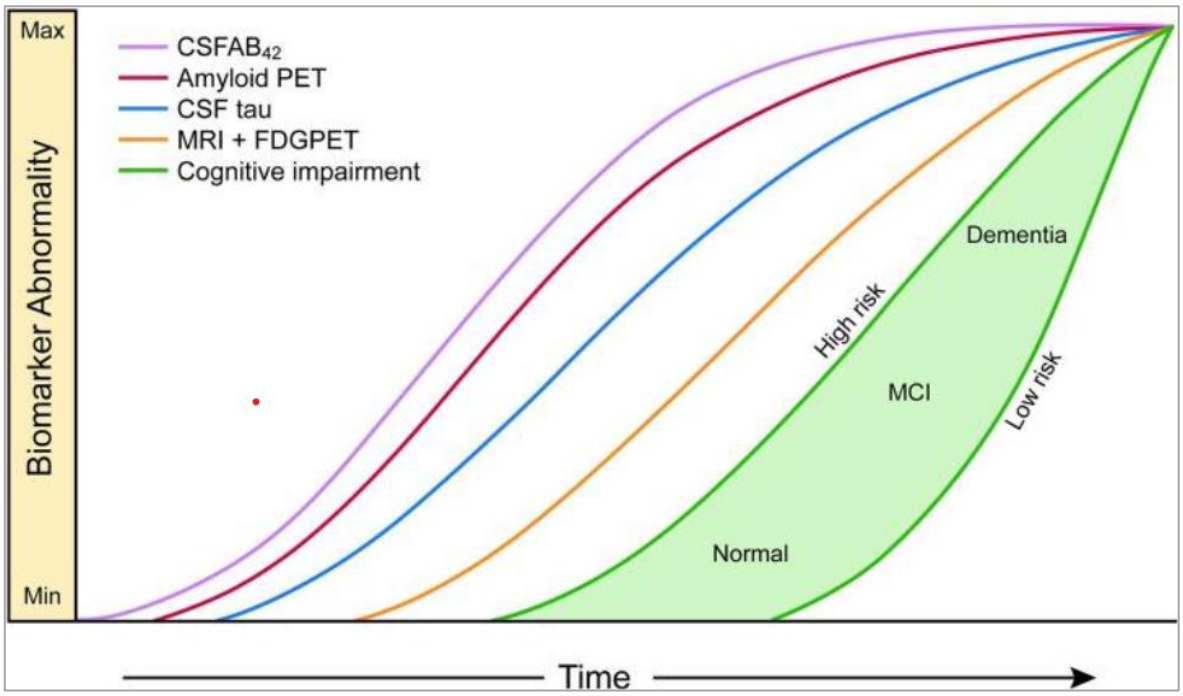

Figure 1: Dynamic biomarkers of AD pathological cascade model [8]

Cognition exists on a spectrum that includes normal cognition, Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and dementia [9]. SCD describes an individual who has a self-reported decline in cognitive capacity. However, no deficits in cognition can be detected on standardised cognitive tests adjusted for age, sex, and educational attainment [10]. SCD is often not associated with a subsequent progression to cognitive impairment or dementia. A meta-analysis of longitudinal data on SCD showed a decline to MCI in 27% of individuals and a decline to dementia of 14% over at least a 4 year time period [11]. Those with SCD do have an elevated risk of progression to dementia compared with the general population however, with an incidence of dementia of 20.1/1000-person year in patients with SCD compared with a 14.2/1000-person year incidence in those with previously normal cognition [12]. The risk of progression to dementia in the SCD population is greater in those with a known family history of dementia [13].

Patients with MCI can be differentiated from those with SCD by their reduced performance on formal cognitive assessment. This is carried out with comprehensive neuropsychological assessment batteries which test multiple cognitive domains and have readily available comparative data for sex, age and educational attainment [14]. There is no defined cognitive score cut off to diagnose MCI, but standard deviation based cut offs are often used. Multiple studies advocate for -1 standard deviation below the normative mean applied across each domain of cognitive function to confer a diagnosis of either single-domain or multi-domain MCI [15]. It is estimated that MCI is prevalent in one third of the population over 65 years of age [16]. Progression from MCI to a dementia syndrome is characterised by a cognitive impairment so severe that it impacts on a person's ability to carry out their normal day to day function. Persons with MCI are not guaranteed to advance to dementia stage, however, close to 40% of individuals with MCI will progress and develop a dementia syndrome [17].

1.1.2. Memory Clinics and Dementia Care in an Irish Context

The assessment, diagnosis, and post-diagnostic care of patients with dementia falls under the remit of several different specialities worldwide including neurology, geriatric medicine, and psychiatry [18]. Memory clinics are tertiary referral specialist centres which diagnose and treat memory disorders including dementia [19]. The first memory clinics were set up in the United States of America (USA) in the 1970s and were largely focused on research and funded through drug trials [20]. The United Kingdom (UK) was to the forefront of the establishment of clinical memory services, with the first memory clinics implemented by the National Health Service (NHS) in the 1980s [21]. The need for specialist

centres was accelerated by the licencing of cognitive enhancing therapies for dementia in the mid-1990s and now there are over 200 memory clinics in the UK [22].

In an Irish context, a 2018 review by the National Dementia Office (NDO) found that memory clinics in Ireland lack uniformity in both their structure and the specialisms of health care professionals involved, and in the range of services that they provide to patients [23]. Furthermore, memory clinics in Ireland are not equitably located geographically. There are currently 25 memory clinics in Ireland, however these are situated in only 13 of 26 counties [24]. The NDO recently published a report entitled "Model of Care for Dementia in Ireland" which aims to outline a care pathway within the Irish health care system for people living with dementia and to standardise assessments and diagnosis for all patients with memory complaints. It sets out targets and practice recommendations to advance the care of people living with dementia in Ireland [25].

This model outlines a three-tiered service (see Figure 2) with primary-care led diagnosis for low complexity cases (Tier 1) and a wide network of local Memory Assessment and Support Services (MASS) where comprehensive assessment is performed by a multi-disciplinary team (MDT) (Tier 2). Here diagnosis ideally is formulated by the MDT at a clinical consensus meeting. More complex, atypical and young onset cases are referred onwards to the Regional Specialist Memory Clinic (RSMC) which should be staffed by an experienced, multidisciplinary team who perform a detailed diagnostic assessment process (Tier 3) [25].

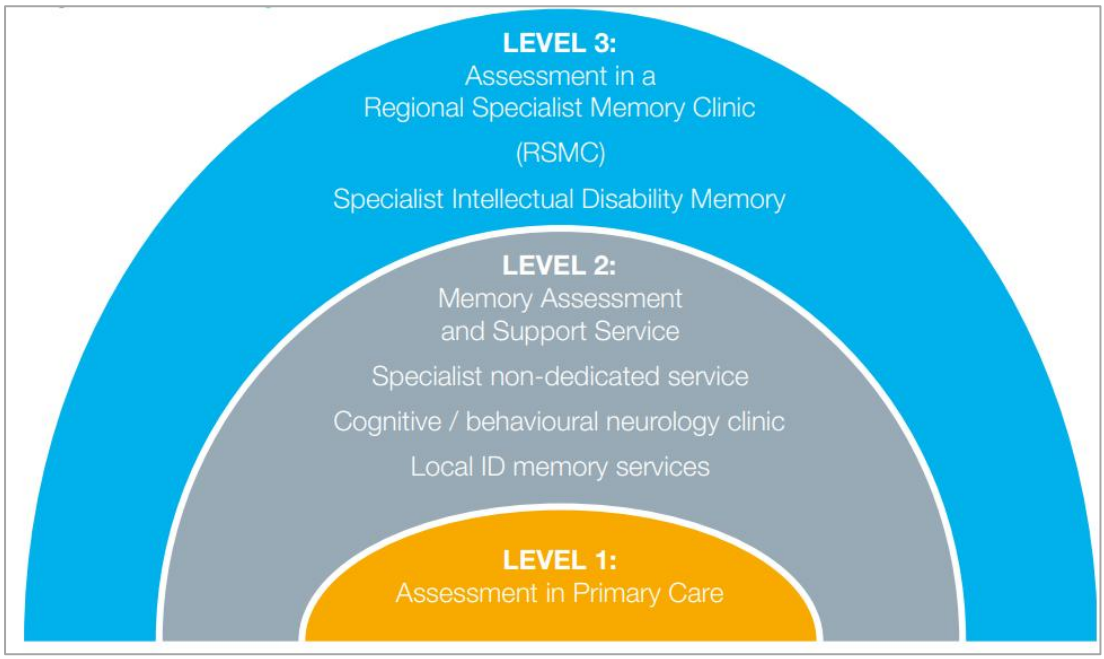

Figure 2: Three-tiered dementia diagnostic model of care, as illustrated by the NDO [25]

The level 3 specialist clinics act as diagnostic hubs for complex and atypical cases and where possible should filter patients back to their local memory clinics after diagnosis for post diagnostic support [26]. The NDO target a minimum of one MASS per 150,000 people and a minimum of five RSMCs nationwide [25]. To date in Ireland there are 10 MASS units [25] and four RSMCs have received funding under the Health Service Executive (HSE) National Service Plan 2021-2022.

1.1.3. Current and Future Treatment Options

Treatment options for patients with dementia can be classified into pharmacological based treatments, the current mainstay of which focuses on symptomatic improvement, or non-pharmacological therapies. These non-medication based therapies encompass a wide range of interventions delivered to either the patient themselves or their primary

caregivers and are rooted in a holistic, interdisciplinary, patient specific approach to care [27]. Examples of non-pharmacological interventions include cognitive stimulation therapy [28], reminiscence therapy [29], occupational therapy which aims to preserve independence, information delivered to cares such as training and support programmes, respite care, and assistive technology. Although certain non-pharmacological interventions have demonstrated cost-effectiveness, they fail to change the overarching course of the disease process [27].

Pharmacological treatments for dementia licenced for use in Europe are currently focused symptomatic benefit offered by cholinesterase inhibitors which prevent the breakdown of acetylcholine and increase cholinergic neurotransmission [30], however they do not slow underlying disease progression. Donepezil is one such drug in this class that is approved to treat the mild to moderate stages of AD dementia. A Cochrane review of its use reported that improvements in cognition and activities of daily living are modest, with no overall impact on quality of life of patients [31]. The side effect profile of cholinesterase inhibitors often limits their use. Cardiac conduction abnormalities leading to bradycardia and syncope and gastrointestinal side effects result in discontinuation of therapy in up to one third of individuals [32].

Disease modifying pharmacological therapy in dementia is advancing and there is a growing pipeline of potential DMTs entering clinical trials. As of January 1^{st,} 2024 there were 164 clinical trials ongoing assessing 127 unique agents with 32 of these drugs in Phase 3 testing [33]. Aducanumab, Lecanemab and Donanemab are disease modifying immunotherapies targeting amyloid beta (Aβ) that have completed phase 3 clinical trials [34-36]. These

agents target aggregated forms of Aβ, resulting in amyloid clearance and downstream slowing of disease progression. It is difficult to accurately assess the potential real-world clinical impact of DMTs, with a longer follow-up required to determine the magnitude and sustainability of cognitive change [37]. Consistent improvement across Clinical Disease Rating (CDR) scale and quality of life measures indicate a clinically meaningful benefit. Lecanemab was shown to have a statistically significant impact on CDR sum-of-boxes (CDR-Sb) at 18 months (a change of -0.45), while in the recent TRAILBLAZER-ALZ 2 phase 3 trial, Donanemab treatment also resulted in a significant slowing of progression by CDR-Sb score (change of -0.7) [38].

Despite the difficulties in predicting long term efficacy of these treatments, there is a cause for cautious optimism. The Food and Drug Administration (FDA) has approved Aducanumab, Lecanemab and Donanemab for patients with MCI or mild dementia due to AD. The European Medicines Agency (EMA) on 25th of July 2024 recommended against marketing authorisation for Lecanemab and reported that the clinical benefits of treatment were not large enough to outweigh the risks. This decision is currently being appealed by the manufacturer with a final recommendation pending [39]. However following a review of risks and benefits, the UK Medicines and Healthcare Regulatory Agency (MHRA) has approved a licence for Lecanemab for use in early stage AD [40] but currently it will not be reimbursable under the NHS.

The varied opinions of regulators in different jurisdictions highlights the challenges in the clinical delivery of DMTs. The clinical efficacy of these medications must be balanced against risk of adverse events [32]. The occurrence of amyloid-related imaging

abnormalities (ARIA), which can be segregated into either oedema (ARIA-E) or haemorrhage (ARIA-H), represent a major cause for concern as this side-effect can lead to cognitive decline, seizures and, on rare occasions, death – albeit the majority of DMT-related ARIA cases are asymptomatic and resolve spontaneously [38].

DMTs could have a transformative effect on AD care, with potential for a positive impact on the economic, social, and emotional burden attributable to AD progression. However, DMT delivery is not straightforward – currently-approved agents require biomarker proof of AD positivity, frequent intravenous infusions and regular MRI monitoring. The high cost of DMT procurement, administration and monitoring, combined with ageing demographic profiles and growing AD prevalence, represents a significant economic challenge; the hypothetical estimated cost of Lecanemab delivery across the EU was forecast to exceed 133 billion EUR per year [41].

The prodromal period of dementia which begins in midlife and is a target for DMTs also provides an opportunity to address dementia risk factors in middle age. In order to optimise a prevention and treatment strategy for dementia we must look towards a clinical model which combines accurate diagnostics, the ability to facilitate the delivery of emerging therapies should they be licenced, along with targeted risk factor modification.

1.1.4. A Move Towards Prevention

Alongside the development of disease modifying therapies for Alzheimer's disease, there has been significant strides made in the field of dementia risk factor identification. In 2017

the World Health Organisation (WHO) Global Action Plan on the Public Health Response to Dementia 2017-2025 was published. This document outlined 7 action areas to improve the lives of those living with dementia and their carers [42]. One of these action areas focuses on dementia risk reduction. This is an important focus of health policy as the estimated prevalence of dementia is projected to increase globally from 57.4 million cases in 2019 to 152.8 million cases of dementia by 2050 [43]. There is a significant economic and social cost associated with the rising prevalence of dementia. Here in Ireland dementia was estimated to cost over €1.69 billion per year in 2010, with 48% of this the opportunity cost of informal care provided by family members [44]. This figure is likely to increase with both the rising prevalence of dementia and the rising cost of living.

At a population level, it is acknowledged that around 45% of all causes of dementia are attributable to modifiable risk factors [45]. Given the predicted global demographic trends, successful targeting of these risk factors with a view to reduction of all cause dementias has the potential for significant economic and social benefits. It is important to note that despite the rising dementia prevalence, the incidence of dementia is falling in Europe and North America over the last 25 years. This is potentially as an indirect result of a sustained effort to manage cardiovascular risk factors and societal and lifestyle changes [46].

1.1.4.1. Risk Factors linked to Dementia

The Lancet Commission on Dementia Prevention [45] has identified 14 evidenced based modifiable risk factors for developing dementia. These are listed in Table 1 and shown in

Figure 3 in the life course model which also the population attributable fraction of each modifiable risk factor.

Table 1: Modifiable risk factors for dementia [45]

The Lancet Commission on Dementia Prevention list of Modifiable Dementia Risk Factors	
Hearing loss	Diabetes
Traumatic Brain Injury	Physical inactivity
Hypertension	Social Isolation
Alcohol Consumption in excess of 21 units per week	Depression
Obesity	Smoking
Poor educational attainment	Air Pollution
Untreated vision loss	High Low-density lipoprotein (LDL) cholesterol

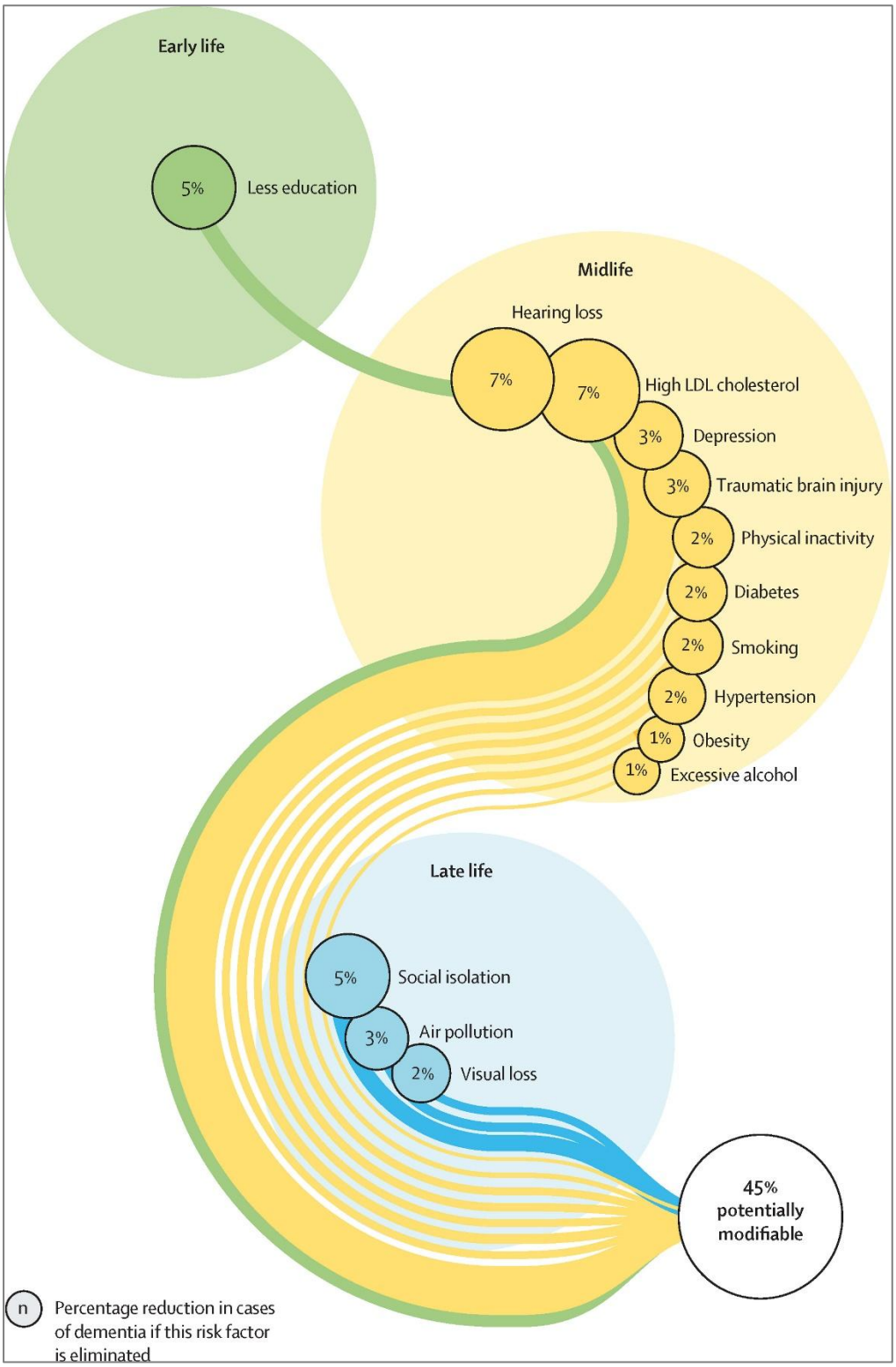

Figure 3: Population attributable fraction of potentially modifiable risk factors for dementia over a person's life course [45].

It is estimated that over 40% of dementia cases worldwide may be attributable to potentially modifiable risk factors. When studied in 2014, the highest population attributable risk factor of a list of seven modifiable risk factors was found to be physical inactivity in Europe and the UK [47]. There is a growing awareness of the potential impact of targeting these modifiable risk factors at a political level, with key organisations such as the WHO, Alzheimer's Disease International, the World Dementia Council, and the International Research Network on Dementia prevention all making dementia risk reduction a priority area [48].

Increased political awareness of the importance of dementia prevention practices is reflected in national dementia policy documents. A 2019 scoping review examining the extent to which dementia prevention is considered in national policy [49] found that in the UK, dementia prevention is addressed in national policy documents, however evidence of implementation of these policies is inconsistent. In an Irish context, the National Dementia Strategy was published in 2014 by the NDO, with a midterm implementation review published in 2018 [23, 50]. The strategy's priority actions included the promotion of public awareness of modifiable lifestyle risk factors, and highlights the need for these risk factors to be "actively managed". This lead to the development of an education resource for Primary care teams, and information around modifiable risk factors has been published on an online platform [51]. However, these measures focus on public awareness campaigns, without focusing on addressing individuals' risk factors. The plan also proposes to implement a risk factor modification focus as part of a post diagnostic support pathway, however this has yet to come to fruition.

Preventative measures that target the aforementioned risk factors should be integrated into clinical practice, alongside biomarker lead diagnosis of MCI or AD to facilitate provision of disease modifying therapies when they are available, and optimisation of modifiable risk factors. The optimal way to provide risk factor modification advice and intervention is less clear. Frisoni et al highlighted the need for both primary preventions targeting cognitively normal individuals with modifiable risk factors through a population based approach in tandem with secondary prevention measures which target modifiable risk factors in individuals with AD pathology at high risk of developing dementia, integrating multidomain risk factor modification with DMT administration [52]. This will require structural changes in memory services internationally with new services such as Brain Health Clinics specialising in risk factor profiling and implementation of personalised risk reduction plans.

1.1.5. Multidomain Interventions targeting modifiable Risk Factors in Dementia

Initial research in the field of dementia prevention focused on identifying risk factors, with multiple studies highlighting the positive impact of modifying lifestyle factors on cognitive decline in the fields of exercise [53, 54], diet [55, 56] and vascular risk factors such as hypertension [57-59], hyperlipidaemia treatment and statin use [60, 61]. However randomised control trial (RCT) evidence was lacking in this area until the launch of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) in 2009. It was the first RCT to explore the effect of multi-domain interventions on cognitive performance. It targeted cognitively healthy adults at risk for AD with multiple interventions consisting of diet modification, exercise, cognitive training and monitoring of

vascular risk factors and reported significant benefits in the treatment arm with respect to the primary cognitive outcome [62].

The success of FINGER prompted the formation of a world-wide network (WW-FINGERS) to plan further similar trials and share data and expertise around the targeting of modifiable risk factors for dementia. Many other countries have followed the FINGER model and implemented their own similar studies including the American U.S POINTER study [63], the French Multidomain Approach for Preventing Alzheimer's Disease (MAPT) trial [64], the Dutch Prevention of Dementia by Intensive Vascular care (Pre-DIVA) [65], the Japanese Multidomain Intervention Trial for prevention of dementia (J-MINT) [66] and the Australian multi-domain Approach to Reduce dementia risk by protecting brain health with lifestyle intervention study (AU-ARROW) [67].

However, initial outcomes from these trials have been inconsistent. The Pre-DIVA study showed no benefit from a nurse-led intervention in general practice targeting cardiovascular risk factors for either dementia or cardiovascular disease incidence [68]. The MAPT trial showed no significant effect of any of its interventions (omega 3 polyunsaturated fatty acids and a multidomain intervention of group cognitive training, physical activity and nutrition education) compared to placebo in the primary outcome of change in cognitive test scores over 36 months. Subgroup analysis showed that significant effects favoured multidomain intervention with omega 3 in a subgroup at high risk for dementia based on the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score or in a subgroup with positive amyloid PETs, albeit the effect sizes were small [69].

The heterogenous nature of the participants, the diverse nature of the interventions in both their individual components and in their duration and intensity in the above multidomain intervention trials make them difficult to compare. There have been both systematic [70], narrative [71] and Cochrane reviews [72] looking at the efficacy of such multidomain intervention trials in dementia prevention. Castro et al looked at 15 trials published before November 2022 and found that participants with greater risk of dementia benefited more from multi-modal lifestyle changes, and highlighted the requirement for longer follow-up periods [70]. Only two RCTs in the Cochrane review by Hafdi et al looked at incident dementia as a primary end point [68, 73], with no evidence of a difference in incidence between the intervention and control groups. The review found that there was high certainty evidence that cognitive functioning was improved by a multi-domain intervention in Apolipoprotein E (APOE) e4 carriers, but not in non-carriers [72].

Evidence to date suggests that the efficacy of multidomain dementia risk reduction is promising if applied to high-risk populations but is not conclusive [74]. This suggests that targeting at-risk individuals is the optimal strategy for multi-domain prevention trials [75]. The use of biomarkers could be a means of identifying at risk individuals with prodromal AD for future trials. With regard to the interventions themselves, given the fact that multiple risk and protective factors for dementia co-exist and interact across the lifespan of a person to determine their overall dementia risk [76] the delivery of appropriate interventions for dementia prevention is complex. It is likely that a tailored, individualised prevention approach targeting multiple risk factors will be required.

1.1.6. Defining Brain Health

When looking at the concept of 'Brain Health' it is useful to start with the WHO definition of health, which was developed in 1948. The WHO constitution states that health "is a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity" [77]. The term brain health is commonly used both in medical literature and colloquially by the general population. It first appeared in the medical literature in 1989, and its use has increased exponentially since 2011 [78]. It is often used in a variety of contexts from mental health advocacy to improving modifiable risk factors for dementia.

Chen et al [78] sought to define brain health by performing a literature review and field analysis. They devised a definition of brain health as a "*lifelong, multidimensional, dynamic state consisting of cognitive, emotional and motor domains underpinned by physiological processes and can be objectively measured and subjectively experienced. It is influenced by eco-biopsychosocial determinants" [78].* Brain health can be both maintained, developed and improved as a person ages [79]. A WHO position paper in 2022 acknowledged brain health as an evolving concept, and defined brain health "*as the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders"* [80].

The term brain health is also applied directly to dementia prevention and dementia risk reduction. It focuses on the implementation of interventions to address the modifiable risk factors for dementia outlined in Section 1.1.4 in either cognitively unimpaired individuals or persons presenting with memory concerns. Section 1.1.7 outlines how brain health

interventions can be incorporated into clinical service models to implement dementia risk reduction strategies and Chapter 2 looks at how these brain health services have been implemented internationally.

1.1.7. Frameworks for implementation of Brain Health Interventions in a clinical setting

The structure of memory services in Ireland was discussed in Section 1.1.2. Memory clinics are structured to deliver comprehensive evaluation, diagnosis, pharmacological and non-pharmacological treatment initiation, and post-diagnostic support to patients presenting with cognitive concerns. They are currently not designed or in a position to provide care beyond that of reassurance and recommendations around a healthy lifestyle to persons who present with subjective cognitive concerns. Current memory services are not in a position to provide these patients with an estimate of their dementia risk and communicate this effectively, along with providing personalised strategies to patients to modify their dementia risk.

Several theoretical implementation models have been published with a view to allowing memory clinics to incorporate risk factor detection and modification into their current work practice. These frameworks outline ways to carry out brain health assessments and interventions in both memory clinic settings and in primary care [81-88] with target service users, structural frameworks, assessments, models of funding and potential interventions discussed.

1.1.7.1. Brain Health Services in a Memory Clinic Setting

Leroi et al [81] and the European Task Force for Brain Health Services [83, 84, 86-88] have, through separate consensus exercises, developed frameworks for the implementation of brain health services alongside existing memory services.

Target Service Users

Leroi et al outlined inclusion and exclusion criteria for patients referred to the service from either primary care, secondary care, or memory assessment services. The inclusion criteria consist of patients over 18 years with self or informant reported cognitive impairment with preserved function, or family history of a dementia disorder in a first degree relative, or an episode of delirium in the preceding 6 months [81]. The European Task Force identify individuals with subjective cognitive decline, functional cognitive disorders and the "worried well" for inclusion in their brain health framework [86]. The so called worried well are defined as individuals who do not report subjective cognitive decline and have normal cognitive test scores but who are concerned about their brain health because of a positive family history of dementia, because of professional reasons (such as working in a nursing home environment) or other life events [83].

Goals of a Brain Health Service

Both consensus exercises cited above quoted identifying both genetic and potentially modifiable risk factors for dementia in service users, while also identifying patients at risk of progression and implementing dementia risk reduction with multi-domain interventions as goals of the service [81, 83, 86]. In addition, the European Task Force also focused on dementia risk communication, and cognitive enhancement with cognitive and physical

training. They stated that education of the general public was outside the scope of a brain health service [86]. Leroi et al also highlighted the provision of resources around dementia risk and appropriate interventions to patients and their families as a goal of the service [81].

Suggested Structural Framework and Staffing

The implementation blueprint outlined by Leroi et al points towards a brain health clinic that spans both primary and secondary care memory assessment services [81]. This is outlined in Figure 4 and Figure 5 below. Initial assessments are performed in primary care, with detailed assessments and diagnostics performed in a memory clinic. Patients are then stratified into low, moderate, or high risk of progression to dementia depending on cognitive assessments and risk factor profile. Depending on an individual's risk classification, appropriate target risk factor intervention is implemented, and patients have ongoing longitudinal follow up in either primary care or in a brain health clinic in secondary care.

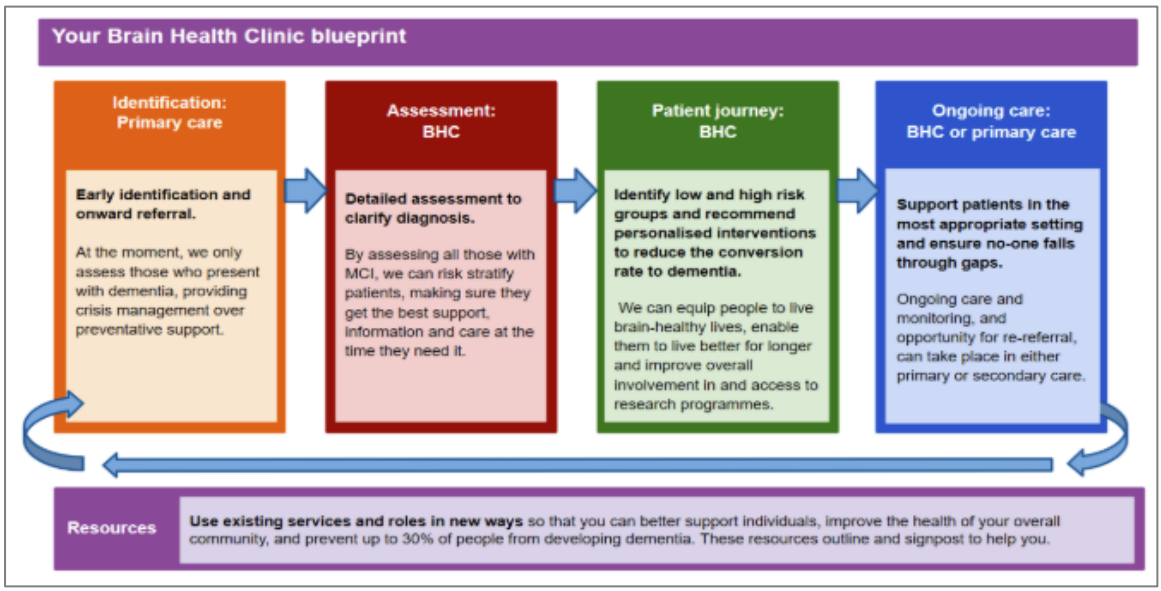

Figure 4: Suggested BHC implementation blueprint developed by Leroi et al [81]

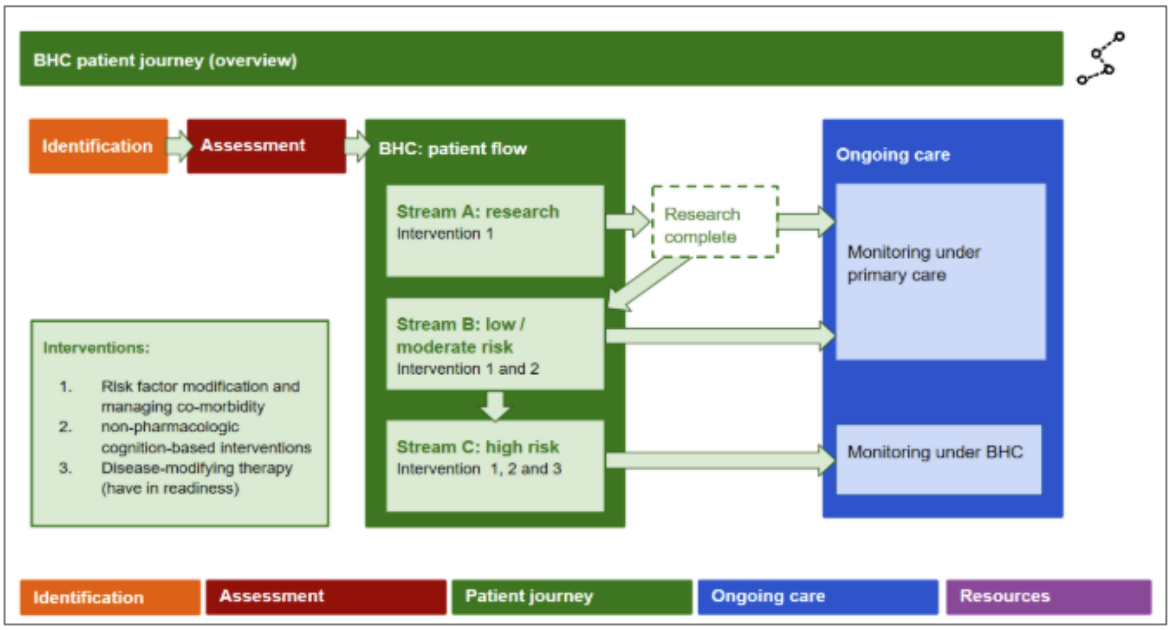

Figure 5: Blueprint for a patient journey through a BHC, developed by Leroi et al [81].

The European Task Force on Brain Health suggested a similar implementation framework whereby brain health services should leverage on the structure and function of existing memory services to access specialist clinicians with expertise in dementia, psychologists, and diagnostic imaging and AD biomarkers [83]. They proposed two distinct levels of brain health services. These would comprise of a basic service which would perform genetic, lifestyle and vascular risk assessment, and implementation of primary prevention protocols and cognitive enhancement training. The advanced service would offer neuroimaging including PET scanning and CSF biomarkers.

This brain health service could be either integrated into a memory clinic, operate as a standalone service or be delivered through primary care. Regardless of the clinical setting, the importance of collaboration between brain health services and memory clinics is strongly recommended by the working group. They advocate for a bi-directional referral

pathway between the memory clinic and the brain health service itself to facilitate risk factor identification for patients attending memory services, and onward referral for comprehensive diagnostics for patients who may be first linked with a brain health service. Embedding brain health services in memory clinics may make them more accessible to the general population and facilitate coverage of this service by health insurance providers or by national health services [86].

Staffing levels required to implement brain health services are also explored, with multidisciplinary teams at the heart of both implementation frameworks. These should include expertise in neuropsychology, medical experts in either neurology or gerontology, with further input from dieticians or physiotherapy highlighted as other potential members of the MDT [86].

Assessments Performed

Potential assessments performed in a brain health clinic can be grouped into clinical and lifestyle risk factor assessment, cognitive assessment, behavioural and functional assessments, biomarker assessments and genetic profiling. Leroi et al [81] outlined the need for clinical and lifestyle risk factor profiling to examine vascular health markers such as hypertension and diabetes, hearing and vision, depression, social isolation and diet and physical activity levels. No specific assessment tools are outlined. The European Task force elaborate on this by defining how to best asses each individual risk factor and these assessments are detailed in Table 2 below.

Table 2: List of risk factor assessment methods compiled from the European taskforce for Brain Health Services [83, 84]

Risk Factor	Potential Assessment Methods
Low educational attainment	Calculation of years in education
Hearing loss	Pure tone audiometry, whispered voice test
Hypertension	Physician measurement, ambulatory blood pressure monitoring
Obesity	Body Mass Index (BMI) or waist circumference
Depression	Hospital Anxiety and Depression Scale (HADS) or Patient Health Questionnaire (PHQ)
Physical inactivity	Accelerometers, smart watch app, self-reported questionnaire
Diabetes	Fasting plasma glucose levels or glycosylated haemoglobin (HbA1c)
Social Isolation	Lubben Social Network Scale or the Duke Social Support Index

Depending on the structure of the brain health clinical service, cognitive assessments may be performed prior to referral to the brain health clinic or as part of the assessment process. Leroi et al specified the Repeatable Battery for Neuropsychological Status (RBANS), the Free and Cued Selective Recall Test (FCS-RT) and the National Institutes of Health (NIH) Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER) as potential neuropsychological assessment batteries which would help identify an amnestic cognitive profile indicative of possible AD pathology. Behavioural and functional assessments are also addressed by Leroi et al, with the Mild behavioural Impairment checklist (MBI-C) to assess for neuropsychiatric symptoms and the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) proposed as possible assessment tools to screen for behavioural symptoms and detect deficits in complex IADL tasks [81].

Both frameworks advocate for APOE e4 testing. APOE e4 is an APOE variant associated with a heightened risk of developing dementia (51-95% in homozygous patients and 22-90% in heterozygous patients [83]) which can be tested for with a blood sample. Biomarkers for neurodegeneration including an MRI scan to look for medial temporal lobe atrophy (MTA) scores, and PET imaging are also mentioned as possible assessment tools in brain health services depending on the clinical impression. Lumbar punctures to assess for AD pathology in CSF are also proposed as part of the assessment battery used in brain health services in certain circumstances, depending on the cognitive and risk factor profile of the patient. While not currently clinically validated, blood-based biomarkers have been shown to excellent sensitivities and specificities for detecting AD pathology in a memory clinic setting [89]. Blood-based biomarkers have the potential to replace CSF testing in brain health settings over the coming years.

A cumulative risk score to calculate overall dementia risk is another assessment proposed by Frisoni et al. This working group advocate for the use of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) score. This can be used as a basis for risk factor communication in brain health services. This score incorporates APOE e4 carrier status along with 10 of the modifiable risk factors identified by the Lancet commission for dementia prevention [90] to assess long-term risk of dementia in middle aged adults.

Potential interventions

Multimodal lifestyle risk factor modifications such as targeting vascular risk factors and other lifestyle changes with medication rationalisation and non-pharmacologic cognition based interventions such as brain training and cognitive stimulation are suggested as

potential interventions in the brain health clinical blueprint outlined by Leroi et al [81]. Solomon et al [87] also highlighted that interventions should be multimodal and advocated for activities to be group based to maximise social interaction. The authors also proposed combining dementia risk reduction interventions with existing chronic disease prevention programmes in line with the 2019 WHO guidelines for risk reduction.

1.1.7.2. Brain Health Services in a Primary Care Setting

Vellas et al [85] and Godbee et al [82] discuss dementia prevention in a primary care setting. Both feel primary care is the optimal location for identifying at risk patients and implementing targeted interventions for dementia prevention. This is due to a primary care physicians' detailed knowledge of their patients social and past medical history and their access to chronic disease management programs. Vallet et al proposed two target patient population groups namely adults over 55 years of age with subjective cognitive concerns, and the older-old aged over 85 with physical and cognitive frailty [85].

A potential implementation framework for brain health interventions in a primary care setting is proposed by Vellas et al and is shown in Figure 6 below. It suggests that longitudinal cognitive monitoring be performed in primary care with onward referral to specialist memory centres for detailed assessment to include AD biomarkers. In the first target group namely adults aged over 55 years with SCD, an individualised multidomain intervention encompassing nutrition, exercise and cognitive stimulation should be delivered by primary care physicians. For the second target group of cognitively frail older adults it is proposed that primary care physicians will address potential hearing and vision impairment, mood disorders and polypharmacy that may be contributing to cognitive

symptoms. A multidomain intervention targeting diet, exercise and cognitive stimulation should also be implemented.

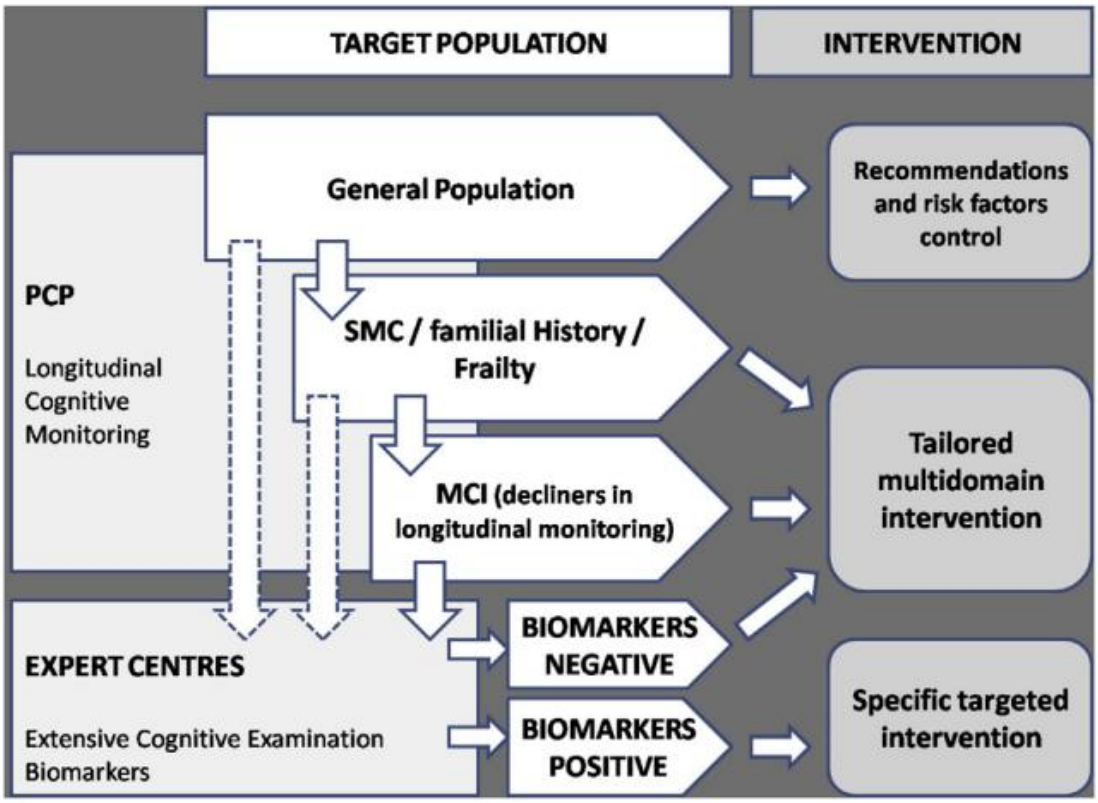

Figure 6: Potential framework for implementing preventative approaches and cognitive monitoring in a primary care setting, developed by Vellas et al [85].

The barriers to providing brain health interventions for dementia prevention in primary care was explored in the scoping review performed by Godbee et al [82]. Primary care physicians suggested a lack of resources, the non-reimbursable nature of preventive health care and a lack of knowledge as reasons why brain health is not currently routinely promoted in primary care. Strategies to resolve these issues proposed by Godbee et al included changing the current reimbursement structures in primary care, education sessions to educate primary care physicians around dementia prevention and conducting consensus discussions around promoting brain health.

Brain health interventions to promote dementia risk reduction is an evolving field. The optimal intervention strategy and the setting in which to apply this strategy are not yet known, with ongoing research in this field likely to shape brain health services over the coming years. Access to diagnostic imaging, genetic testing and AD biomarkers will be essential to accurately estimate an individual's risk, and existing memory services seem best placed to provide this diagnostic process. As a result, most brain heath implementation frameworks suggest brain health services be in some way linked to existing memory clinics. It is likely that primary care physicians will also have a role to play in terms of chronic disease management, but it is essential that this is appropriately resourced to ensure that dementia risk reduction strategies are practicable.

1.2. Study Aims

This research thesis focuses on brain health in terms of dementia risk reduction and comprises three main study aims outlined below.

4. Explore existing models for the delivery of brain health interventions and define a clinical service model for a Brain Health Clinic which is integrated into an existing RSMC.
5. Quantify the prevalence of modifiable risk factors for dementia in a cohort of patients attending a Brain Health Clinic within a memory service with a particular

focus on cardiovascular risk factors, sensory risk factors and lifestyle factors such as physical activity, sleep and psychosocial well-being.

   a. Does the risk factor profile differ between patients with SMC vs MCI?
   b. Does the risk factor profile differ between patients with evidence of AD pathology versus those who don't?

6. Highlight the potential role of this brain health clinical service in identifying previously undiagnosed modifiable dementia risk factors in patients with MCI and SMC and the scope for intervention to reduce these risk factors on an individual level.

Chapter 2. Scoping Review of Brain Health Clinics Internationally

2.1. Introduction

The optimal way to target the modifiable risk factors risk factors for dementia in clinical practice has yet to be established. Section 1.1.7 details the theoretical implementation frameworks published in this area. These frameworks provide clinicians with a potential guide on how to provide brain health interventions in both general practice and in a memory clinic setting. Given that this is an emerging area of practice, the most effective way to implement dementia risk reduction in a clinical setting has yet to be determined. This chapter will explore what clinical models are currently in operation to deliver brain health interventions.

2.1.1. Previous reviews around the clinical implementation of brain health practices to target dementia risk reduction

Previous scoping reviews in this area explored the clinical implementation of dementia risk reduction in primary care [82, 91] and have also looked at dementia prevention policies and their implementation using England as a case study [49]. From a primary care point of view, current clinical guidelines for dementia risk reduction were synthesized by Godbee et al who found that they lacked specificity [91]. While this scoping review recommended clusters of actions to effectively implement dementia risk reduction, it did not highlight any examples of currently implemented brain health clinics in primary care. Godbee et al subsequently went on to explore attitudes towards implementation of dementia risk reduction in primary care with resource availability among the reasons cited for lack of confidence in promoting dementia risk reduction in primary care [82]. Again, there is no

mention of current real-world dementia prevention clinics in action in this review. Collins et al found that while dementia prevention is identified in national, regional and local policies in the UK, the evidence of implementation of these policies at a clinical level is limited [49].

2.1.2. Aims and Objectives

The aim of this review is to identify the current models that have been successfully implemented for providing brain health interventions in a clinical setting. It will focus on existing international clinical services and exclude theoretical frameworks for implementation that do not reflect an implemented clinical model of care. For the purposes of this review a clinical setting is defined as a permanent established clinical service offering a suite of assessments and interventions by a healthcare professional.

The specific objectives of this scoping review:

1. Identify the structural models of brain health clinics internationally. Are they integrated with memory clinics and what staffing levels are required to implement these services? How are patients recruited into these clinical services?
2. What risk factors are targeted in these clinics and how are they measured?
3. What targeted interventions are performed?
4. What outcome measures are recorded to assess effectiveness of interventions?
5. Are patients followed longitudinally, and if so, how frequently?

This review will look to add to the knowledge base around the provision of dementia risk reduction interventions in clinical practice and highlight any gaps that my exist in the current literature around this globally important subject.

2.2. Review Methodology

2.2.1. Scoping Review Framework

A scoping review methodology was chosen in order to explore brain health implementation in clinical practice. It differs from a systematic review methodology in that a scoping review is set up to identify different types of evidence that is available in a given field, to identify key factors related to a concept and to potentially identify and analyse knowledge gaps [92]. On the other hand a systematic review focuses on a well-defined research question and looks to produce answers from a narrow range of study types, which are assessed for quality and bias [93]. The scoping review method allows for the inclusion of a broad range of literature from various sources outside of the confines of a systematic review, and this methodology allowed the consideration of a range of materials from of both conventional and grey literature for inclusion in this review.

This review was conducted in using the descriptive, analytical framework as proposed by Arksey and O'Malley [93]. The following 5 stage iterative process was followed: identify the research question; identify the relevant studies; study selection; chart the data; collate, summarize, and report the results. The PRISMA-Scr (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews) reporting checklist was used to formally report on the literature included in the review in a transparent manner [94]. Given the nature of the review question and its scoping methodology, results are presented in a qualitative rather than a quantitative manner, without reference to specific qualities of the literature reviewed [95]. A narrative synthesis will be conducted with thematic analysis and a summary table of results used to display the results where

possible. The results may be used to highlight gaps in the body of existing literature in this area.

2.2.2. Search Strategy and Information Sources

A two-pronged approach to identifying relevant records was employed for the purpose of this review. Firstly, a search of peer reviewed literature was undertaken. This was done by initially performing a limited search of relevant databases (MEDLINE, Embase, CINHAL, Psychinfo) to identify relevant articles. The index terms which were used to describe these articles were then used to guide the development of an exhaustive search strategy for MEDLINE, Embase, CINAHL and PsychInfo. The key themes of dementia, prevention, and brain health clinic were then developed into a set of key words which were expanded using Medical Subject Headings (MeSH) terms and combined using Boolean operators 'OR' and 'AND'. The review team collaborated with a medical librarian to finalise this search strategy, and the key words used along with results from each database are detailed in Section 12.1 Appendix A. Data from this search was extracted to Endnote 20, and duplicates were removed.

In addition to the search databases mentioned above, grey literature was also included given the broad nature of the research question. National dementia policy documents were considered as part of the review search strategy. These policy documents have the potential to provide details of implemented dementia prevention strategies at a national level. These policy documents were published on the Alzheimer's Disease International webpage for dementia plans [96]. This website search was completed on October 12th,

2023. Finally, backward citation chaining was utilized by reviewing the references for any evidence deemed eligible for inclusion.

2.2.2.1. Eligibility Criteria

This scoping review considered descriptive papers including observational study designs, case studies, individual case reports and descriptive cross-sectional studies for inclusion. Published opinion papers and policy documents were also be considered. The purpose of this review is to identify existing clinical services implementing brain health interventions. Therefore, this work did not focus on experimental study designs assessing the benefits of single or multimodal interventions.

Experimental study designs such as randomized controlled trials, non-randomized controlled trials, or analytical observational studies such as prospective or retrospective cohort studies which explore the effectiveness of specific interventions for research purposes only were excluded from the final results. However, these studies were included in the review if they included a description of an existing clinical service model, wither as the setting for the experimental study, or as a control in a trial design. Longitudinal studies were considered if they were performed in a clinical setting, and not solely in a research context.

If there was any ambiguity around whether the intervention was ongoing beyond the period described in the studies, the corresponding author was contacted for clarification. Works which focused solely on the analysis of relevant modifiable risk factors without description of a feasible implementable clinical model to address them were also excluded

from this review. Theoretical frameworks for the potential implementation of brain health clinics were not considered for inclusion.

Reports considered for inclusion were not limited to peer reviewed academic literature or specific study designs. Academic letters and policy documents were considered eligible for inclusion, and conference abstracts were reviewed and considered for inclusion if there was sufficient information in the abstract to answer the research questions. We included reports from the above listed sources that contained information related to the provision of brain health interventions in a clinical setting. A clinical setting could be either linked to an existing clinical memory service, general practice or set up de novo to recruit members of the public with subjective memory concerns or an interest in health promotion.

As dementia care falls under the remit of a wide variety of medical specialties including neurology, gerontology, psychiatry, general practice and is also of interest to public health specialists services implemented by all specialities and scopes of practice were included. Information published in the 10-year period between September 2013 and September 2023 was considered for inclusion. The 10 year cut off period was implemented as 2013 saw the publication of The Global Impact of Dementia 2013-2050: Policy Brief for Heads of Government [97] which highlighted the need to prioritise research that identified options for prevention of the disease. Studies published in any language were initially included in the screening of titles and abstracts. If an English translation of the full text was not available, they were discarded at the point of full document review. This was due to both financial and time constraints of the scoping review.

Inclusion Criteria:

- Publications related to the delivery of Brain Health interventions in a clinical setting. For the purposes of this review a clinical setting is defined as a permanent established clinical service offering a suite of assessments and interventions by a healthcare professional.
- Publications that looked at the effectiveness of a brain health intervention if the intervention was part of an existing and established clinical setting. To be considered for inclusion, the clinical service had to exist beyond the interventional period. From these studies information around the description of the clinical service was extracted, and the effectiveness or otherwise of the trialled intervention was not commented upon.
- Works published between 2013 and September 2023 were considered.

Exclusion Criteria:

- Any service or clinical intervention delivered only for research purposes or where the clinical intervention was delivered only on a temporary basis and not a part of established permanent service.
- Descriptive studies related to risk factors for dementia
- Lifestyle modification interventions for general chronic disease management without specific mention of dementia risk reduction or prevention
- Implementation frameworks without a description of an existing clinical service
- Full text of the paper or policy document is not available in English.
- Other scoping, systematic or narrative reviews
- Work published before 2013

2.2.2.2. Selection of Sources of Evidence

The review team consisted of three researchers. Two team members individually screened the titles of all publications identified by the database search strategy. Following a title screen, abstracts were then screened by both reviewers. Works were excluded based on the aforementioned eligibility criteria. The remaining papers underwent an independent full text review by both researchers. The same two team members also reviewed all policy documents. The review team met regularly throughout the selection process and disagreements around data for inclusion in the review were resolved by the senior reviewer. These meetings were also an opportunity to clarify any ambiguities in the inclusion and exclusion criteria. This selection process was documented in the form of a Prisma diagram.

2.2.2.3. Data Extraction and Processing

Data from the databases Embase, PsycINFO, CINAHL and Medline was extracted to Endnote 20 and this was used to manage the screening process and categorise and manage abstracts and full text versions of references from these sources. Microsoft excel was used to collate data extracted from the policy documents search.

A framework was developed in Microsoft Excel for the purpose of data extraction. This was developed by the research team and data was extracted by one reviewer using the developed framework. The data extracted from each resource is detailed below.

Data extracted:

- Article/Resource Title

- Author/year of publication/Publication location
- Information Source Type e.g. National Dementia Policy Document, narrative article, randomised controlled trial etc.
- Clinic/Service Location
- Clinic Structure
- Risk Factors Targeted
- Assessments completed
- Interventions implemented
- Follow up process

2.2.3. Synthesis of Results

The results synthesis process involved collating included sources and conducting a narrative synthesis and a thematic analysis of the relevant extracted data. The data outlined in Section 2.2.2.3 was tabulated and this was followed by a descriptive piece which discussed common themes, highlighting any potential gaps in the literature. The final results were presented in the form of a narrative description of emergent themes, and a table summarising pertinent information.

2.3. Results

2.3.1. Screening and Selection

A comprehensive search across OVID MEDLINE, Embase, PsychInfo and CINHAL databases from 01/01/2013 to 23/08/2023 returned 2988 records, while 47 records were identified from the search of National Dementia Policy Documents. Following the removal of 926 duplicate records, the refinement procedure using the inclusion and exclusion criteria

outlined in Section 2.2.2.1 narrowed the results to 5 papers from the database while no National Dementia Policy Documents met the eligibility criteria. This selection process is depicted in a PRISMA flow diagram in Figure 7.

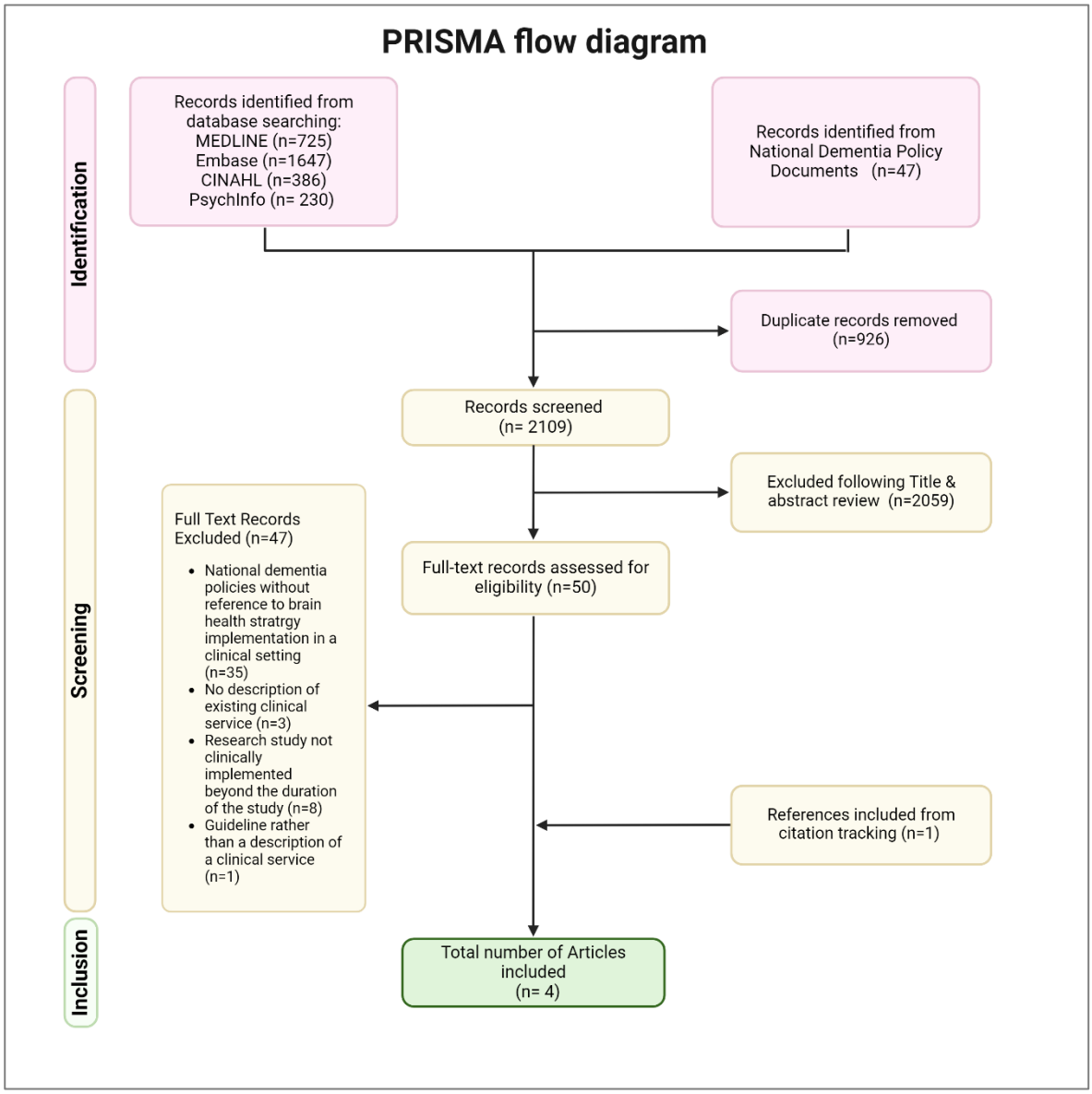

Figure 7: Prisma Flow diagram of Source selection from Scoping Review

2.3.2. Summary of Included Articles

The systematic search returned four published articles which referred to two separate clinical services offering brain health interventions while no implemented clinical services were described in the national dementia policy documents reviewed. The details of the four articles selected and the two clinical services they describe are displayed in Table 3 below. The data extracted about each clinical service is outlined in Table 4.

Table 3: Characteristics of Articles included in the scoping review and the clinical services they describe

Clinical service described	Publication Title	Lead Author	Year Published	Publication Location	Article Type
Alzheimer's Prevention Clinic (APC) at Weill Cornell Medicine and New-York Presbyterian, USA **And APC and Research Centre in San Juan, Puerto Rico.**	The clinical practice of risk reduction for Alzheimer's disease: A precision medicine approach [98]	Richard S. Isaacson	2018	Alzheimer's & Dementia	Narrative Article
	The Alzheimer's Prevention Clinic at Weill Cornell Medical College / New York - Presbyterian Hospital: Risk Stratification and Personalized Early Intervention [99]	Alon Seifan	2015	JPAD: The Journal of Prevention of Alzheimer's Disease	Narrative Article
	Nutritional interventions for Alzheimer's prevention: a clinical precision medicine approach [100]	Matthew W. Schelke	2016	Annals; the New York Academy of Sciences	Narrative Article
Brain Health Scotland	The Scottish Brain Health Service Model: Rationale and Scientific Basis for a National Care Pathway of Brain Health Services in Scotland [101]	Craig W. Ritchie	2021	JPAD: The Journal of Prevention of Alzheimer's Disease	Narrative Article

Table 4: Data extracted regarding the clinical services included in the scoping review

Clinical service described	Clinic Structure	How are patients Recruited?	Risk Factors Targeted	Summary of Assessments performed	Potential Interventions Implemented	Follow-up Process
Brain Health Scotland [101]	• Separate from existing memory clinic model for symptomatic dementia diagnosis • Patients stratified based on risk status of neuro-degenerative disease • Facilitates onward referral to memory service if needed	- Community walk-in service (self-referral); - Referral from healthcare provider based on identified risk factors and/or Subjective cognitive concerns	- Lifestyle assessment - Alcohol - HTN - Obesity - Physical inactivity - Smoking - Depression anxiety - Sleep	**All risks:** Lifestyle assessment; **Intermediate to High risk:** Cognitive assessment, Blood tests, Assess comorbidities; **High Risk:** Neuroimaging and CSF	Personalised prevention plans developed in partnership with the patient and develop personal goals	<u>Lower risk:</u> encouraged to revisit the service as needed; <u>Intermediate risk:</u> review in 12-24 months; <u>High risk:</u> review in 3-9 months based on need
Alzheimer's Prevention Clinic (APC) at Weill Cornell Medicine and New-York Presbyterian USA [48-50]	• Linked to the Weill Cornell Memory Disorders Programme • Patients with family history of AD or patients seeking to lower their AD risk. Referral pathway not clear	- Patients with a family history of AD; - Patients looking to lower their AD risk can self-refer via the clinic website	- Insulin resistance - Dyslipidaemia - oxidative stress - physical inactivity - sleep - cognitive ability - social engagement	Neuroimaging & CSF, B12 folate, vitamin D, Omega 3 index, APOE status, Advanced lipid Panel, The Rapid Assessment of Physical Activity	• Treat OSA • Medications: statin, anti-hypertensives • Regular/intense physical exercise • Counselling, • Adult education, • mindfulness	Cognitive assessment and risk factor assessment at baseline and at 6monthly follow up

2.3.3. Thematic Analysis

This section will discuss specific elements of each clinical service which were explored in the articles included in this review and highlight and further themes which emerged from this scoping review.

2.3.3.1. Clinic Structure

The clinic structures of Brain Health Scotland and the APC are summarised in Table 5 below.

Table 5: A comparison of brain health clinic structures in APC and Brain Health Scotland

	Brain Health Scotland	**Alzheimer's Prevention Clinic (APC)**
Referral Sources	Walk-in self-referrals for people: - with subjective cognitive concerns, - wishing to learn about modifiable risk factors	- Self-referral - Local Primary Care Physicians - Offer service to family members of patients attending linked Memory Clinic
Affiliations with existing memory clinical service	- Suspected dementia cases referred onwards to a memory service	- Complex cases discussed at memory clinic multidisciplinary case conference.
Staffing requirements	Not discussed	Clinical team includes: - Board certified neurologist/internist - Family nurse practitioner - Access to neuropsychologists, preventative cardiologist, old age psychiatrist
Follow-up Period	Based on risk stratification: - Low risk: reviewed again as required - Intermediate risk: follow-up at 12-24 months - High risk: follow up in 3-9 months	- First review at 4-6 weeks (to discuss blood results) - Subsequent review at 6 months (repeat cognitive assessments and review of goals and compliance with intervention) - Asymptomatic patients remain in the clinic for 1-2 years

Both clinical services identified in this review offer both self-referral options and accept onward referrals from other healthcare providers. The brain health clinical pathway devised by Brain Health Scotland is separate from traditional memory clinics focused on diagnosing symptomatic patients and offering post diagnostic supports to these patients. They take self-referrals from patients with subjective cognitive concerns or those with no cognitive concerns who wish to learn about their modifiable risk factor burden. They do however have a link to existing memory clinics to facilitate onward referral to this diagnostic service when needed. Similarly, the Alzheimer's Prevention Clinic (APC) in Cornell and Puerto Rico are separate from their traditional memory clinical services but do offer review to family members of patients who have been diagnosed with a dementia syndrome in their memory services.

In Brain Health Scotland's brain health clinic patients can self-refer to the first stage of the service. At this clinic they undergo risk factor profiling, lifestyle assessment, and their level of risk for neurodegenerative disease is stratified into lower risk, intermediate risk, higher risk or suspected dementia (see Section 2.3.3.2). Lower risk patients are given tailored lifestyle advice, encouraged to join dementia research programmes and advised to present again to the service on an as needed basis. Intermediate and higher risk patients who self-present, along with those referred by a healthcare provider are assessed at stage 2 of the clinical framework. Here they undergo an assessment of co-morbidities, a clinical history is taken, and a clinical examination is performed along with blood tests and a cognitive assessment. Intermediate risk patients are given a personalised prevention plan, invited to join a research registrar, and followed up in 12-24 months. Higher risk patients are offered

neuroimaging and the opportunity to undergo CSF biomarkers. If these patients have a suspected dementia following this assessment, they are referred to a local memory service for formal diagnosis and post diagnostic supports. Otherwise, patients are given a personalised prevention plan and reviewed in 3-9 months [101].

In the APC patients are most commonly self-referred, with the next most common referral pathway being from local primary care providers and word of mouth. Patients are split into "prevention" candidates and treatment candidates. Prevention referrals are screened by asking patients to answer two questions namely "Do you have any memory loss or other cognitive complaints?" and "Do you have a family history of AD?". Potential patients must answer no to the former and yes to the latter question to be considered a prevention candidate, otherwise they are considered treatment candidates [98].

Prior to their initial assessment visit to the APC, patients must complete an electronic pre-visit questionnaire which includes cognitive assessments (The Face Name Associated Memory Test [102], Cognitive Function Test [103] and Neurotrack [104]). Patients must also complete two online education sessions which promote behaviours which may reduce AD risk [98].

Following completion of the online questionnaire patients at APC have an initial in person clinical assessment which involves one hour of standardized cognitive testing [99] followed by neurological evaluation and undergo a number of assessments detailed in Section 2.3.3.3 along with targeted education around relevant risk factors. Fasting bloods are taken on the day after the initial clinic visit. Patients are then reviewed at a second visit which

occurs 4-6 weeks following the first visit. At this visit blood results are available and more targeted recommendations can be made based on these results (See Section 2.3.3.4.). Prior to the next follow up appointment 6 months after their initial appointment, patients must identify their personal goals and report their adherence to these stated goals. At the 6-month follow-up visit treatment plans are refined, and cognitive testing is repeated. One of the challenges to this clinical framework is the uncertainty around how long to follow asymptomatic at risk patients and at present they are recommended to remain in the clinic for 1-2 years with subsequent ongoing primary care follow up of identified risk factors [98].

The staffing levels required to run the Brain Health Scotland clinic was not discussed in the review article. Staffing requirements in the APC are briefly explored by Isaacson et al. The initial visit is described as being carried out by a member of the clinical team with extensive training in the practice of AD risk reduction and in New York this team is said to include a board-certified neurologist and/or a family nurse practitioner. In the Puerto Rico APC reference is made to a board-certified internist rather than a neurologist [98]. It is not clear what other staff members, both clinical and non-clinical staff, are required to run these clinics. Reference is made to complex cases being discussed at a multidisciplinary case conference which is attended by a team of neurologists, neuropsychologists, and other specialties where appropriate including preventative cardiology, nutritionists, geriatric psychiatrists and visiting experts [98]. The role these other specialists play in the overall structure of the Alzheimer's Prevention Clinic is unclear from the available resources.

2.3.3.2. Patient Risk Stratification

Both clinical services refer to stratifying patients in terms of their risk of developing a neurodegenerative disorder. The APC have classified patients based on their cognitive profiles, family history and clinical history and exam. The first grouping are patients with normal cognition on screening tests and these patients are further subdivided into low moderate or high risk based on their family history, risk factor profiles, presence of non-cognitive symptoms, presence or absence of PD features and "expected AD or PD biomarkers" [99]. Patients undergo APOE genetic analysis (with pre and post-test genetic counselling) and those who have genetic susceptibility to the development of AD are treated as high risk and their risk factors are managed in a more aggressive manner than those without a genetic AD risk.

Patients attending the APC with detectable deficits on cognitive screening are referred to as detectible cognitive impairment (DCI). These patients are defined as having detectible cognitive deficits but not sufficient to meet the criteria for MCI. If these patients have any non-cognitive symptoms they are further classified as being due to a neurodegenerative disease (DCI-ND) or otherwise non-specified DCI. DCI-ND is then further subclassified based on the predicted underlying pathology, either AD, alpha-synuclein or atypical neurodegenerative diseases. This classification is aided by biomarkers for amyloid, tau or alpha-synuclein however the precise biomarker testing offered to patients is unclear. Whether the follow up period is longer for patients with DCI versus normal cognition or whether they are streamlined into a memory service is also unclear from the available literature.

In the Brain Health Scotland framework patients are also classified as lower risk, intermediate risk and higher risk for neurodegenerative disease and also grouped into having suspected dementia if applicable. Ritchie et al reference the development of a risk prediction algorithm which will utilize shared data between patients' hospital and GP records and use risk factor and biomarker data to predict disease progression. This algorithm has yet to be fully developed and is not currently in use in clinical practice. While patients are stratified based on risk and their care pathway in the clinical service depends on this risk classification, the precise way in which this is calculated is not clearly outlined in the article.

Brain Health Scotland have also stratified conditions based on a red, amber and green traffic light system which defines the scope of disorders that can be managed within the brain health clinical service. Red conditions are those whose management are beyond the scope of the service and include incidental findings of brain tumours, stroke or significant mental illness including suicidal ideation. The care of amber conditions can be shared between the brain health service and other specialised clinics. These conditions include alcohol use disorders, Parkinson's disease, multiple sclerosis, epilepsy, diabetes and cardiovascular disease. Green conditions can be manged within the brain health service alone and include functional cognitive disorders and neurodegenerative dementias however these patients are referred onwards to a specialist memory clinic for post diagnostic support [101].

2.3.3.3. Assessments Performed

The details of patient assessments performed in the APC are outlined in detail by Isaacson et al [98-100] while the specific assessments performed at the Brain Health Scotland pilot clinic are less clear. Assessment of patients at the APC is based on an "ABC" framework, namely anthropometrics, cognition and blood biomarkers [98]. All patients at the APC undergo a thorough clinical history which explores educational attainment including class rank and major career achievements, current and past lifestyle patterns which focus on sleep, diet, hobbies, stress management techniques and exercise and the duration spent seated at a desk for a prolonged time-period. Other risk factors explored in clinical history include depression and hearing loss. Protective factors such as cognitively engaging activities are also explored in clinical history with patients asked about learning new skills such as languages or instruments [98]. In the Brain Health Scotland service model, the importance of screening for and managing depression and anxiety is highlighted, but the specific screening questionnaires used are not defined.

Non-cognitive symptoms often associated with neurodegeneration such as mood, motor and sleep function are explored in the APC clinic and in the Brain Health Scotland clinic where neuropsychiatric and behavioural symptoms have been grouped into the concept of Mild Behavioural Impairment (MBI) and screened for routinely [101]. History of head trauma and duration of loss of consciousness along with history of engaging in contact sports is explored. Dental hygiene is addressed by exploring the frequency of dental visits and a standard past medical history to include information about medications and supplements used, smoking and alcohol history is also obtained [98]. Regarding past medical history, in the Brain Health Scotland framework Ritchie et al highlight the

importance of screening for comorbidities such as atrial fibrillation, hypertension, heart failure, diabetes and traumatic brain injury [101]. In the Cornel APC, a detailed family history is elicited from patients, with questions focusing on presence of cognitive or neurological impairment in any relatives including the earliest age of identifiable symptoms [98].

Objective measurements taken in the APC include BMI and waist to hip ratio (WHR) while body fat percentage and total body water are measured using bioelectrical impedance vector analysis. These measurements are always done fasting, and ideally by the same person to ensure validity over time. Fasting bloods are taken to assess standard (Total cholesterol, LDL, triglycerides) and advanced lipid profiles (apolipoprotein B (ApoB), small dense LDL (sdLDL), Lipoprotein (a) Mass (Lp(a)), Apolipoprotein A1 (ApoA-1)). A coronary calcium scan is also performed in certain instances to aid risk stratification [98].

In the APC bloods are also assessed for inflammatory markers including fibrinogen, c-reactive protein (CRP), lipoprotein-associated phospholipase A_2 (Lp-PLA2) and myeloperoxidase (MPO). Metabolic blood tests taken include HbA1c, fasting glucose, fasting insulin and adiponectin. Nutritional biomarkers vitamin D, thyroid stimulating hormone (TSH), N-terminal pro Brain Natriuretic Peptide (NT-ProBNP), Cystatin C, homocysteine, omega-3 (DHA and EPA), vitamin B12, folate and vitamin B6 [98] are measured.

Gait speed is highlighted in the Brain Health Scotland clinical framework as a predictor of incident dementia, while this is not included in the APC clinical assessment. Grip strength

and its dementia risk is also highlighted by Ritchie et al but it is unclear whether this and gait speed have been incorporated into their clinical assessment. The potential method for measuring gait speed in the brain health clinic is not explicitly stated.

Genetic risk factors are mentioned by both clinical services. Specifically, APOE variants and methylenetetrahydrofolate reductase (MTHFR) gene mutations are assessed in the APC, and patients are uniformly consented and receive genetic counselling prior to ordering these blood tests. Patients are also advised to consider life assurance prior to undergoing genetic testing [99]. Ritchie et al discuss the importance of genetic testing for the APOE variant to determine personal risk [101], however from this article it is not clear whether it is being screened for in their pilot brain health clinic or not.

Cognitive testing is performed in both services. A “cognitive assessment” is referred to in the Brain Health Scotland framework, and while the authors highlight that the majority of people accessing brain health services will not have cognitive symptoms detectable on traditional assessments such as the Mini-Mental State Examination (MMSE), which is optimised for use in symptomatic populations, the nature of the assessments performed in the clinical service is not specified [101].

In APC a neuropsychological profile is administered at the initial visit and at 6-monthly intervals. It incorporates elements of the computer-administered National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) [105]; namely the Rey Auditory Verbal Learning Test (new learning and memory), Dimensional Change Card Sort (executive ability), the Flanker Inhibitory Control/Attention (executive ability and attention) and the

Pattern Comparison Processing Speed and Oral Symbol Digit (processing speed) [106] along with the Picture Vocabulary and Oral Reading Recognition measures (language and verbal knowledge) [107]. Other cognitive tests administered include the Mini-Mental State Examination [108], the Trail-Making Test Part B [109] and oral word production under categorical constraint (animals) to assess semantic fluency [110]. Patients at APC also undergo a standardized smell test using the NIH Toolbox Brief Odor Identification Test [111].

2.3.3.4. Specific Interventions Discussed

The description of the Scottish brain health service model by Ritchie et al [101] does not include specific information around the interventions offered in this service. It refers to implementing a personalised risk reduction and prevention plan that includes "interventions and secondary prevention approaches". However, the authors report that the specific details of such prevention plans will be elaborated upon in further publications.

In contrast the interventions offered at the Alzheimer's Prevention Clinic across sites at Cornell in New York and Puerto Rico are extensively reported on in supplemental materials supplied with the 2018 article by Isaacson et al describing the service [98]. The tailored interventions offered to patients attending this clinical service are split into three distinct categories namely patient education and counselling, pharmacological interventions, and non-pharmacological interventions. The interventions offered to each patient differ based on their risk stratification as discussed in Section 2.3.3.2.

Patient Education and Counselling

Isaacson et al report that most of each clinic visit is focused on one-to-one counselling by the treating clinician [98]. This involves extensive education around the specific interventions which will be recommended depending on patient risk factors. All patients attending the APC are instructed to complete an online course which consists of 10 lessons on dementia prevention. The topics covered as part of this online educational course include the stages of AD, diagnostic strategies along with detailed instruction on nutrition, physical exercise and food supplements.

Pharmacological and Non-Pharmacological Interventions

The specific pharmacological and non-pharmacological interventions offered to patients attending the APC are detailed in their published research. These are described in Table 6 below.

Table 6: Interventions offered in response to risk factors identified in patients attending the APC

Risk Factor	**Intervention Offered**
Hyperlipidaemia	- Omega-3 - plant sterol supplement - referral to preventative cardiologist
Elevated HbA1c	- Cocoa flavonoids [98] - Referral to preventative cardiologist
Smoking	Smoking cessation advice
High BMI	Patients are advised to reduce their body fat percentage by 2-3% over a 6–12-month time-period while increasing lean mass by around 1% over this same time.
Depression	- Low dose selective serotonin reuptake inhibitor (SSRI), escitalopram the preferred drug of choice - Referral to psychologist for counselling

Risk Factor	Intervention Offered
Sleep	- Target between seven and a half to eight hours of sleep per night - Melatonin or Trazadone [98]. - Sleep Hygiene Advice: avoiding electronic devices 30-40 minutes prior to bed and avoiding caffeine after 2pm - Referral for Cognitive behavioural therapy for insomnia (CBT-I)
Diet	- Dietary recommendations are tailored to each individual patient attending the clinic - All follow the general concepts of the Mediterranean diet with lower carbohydrate intake or - Time-restricted eating or intermittent fasting - Foods high in Omega-3 are promoted along with lean poultry, low fat yogurt with live cultures and less than 2 portions of red meat per week along with the use of 1 teaspoon of olive oil per day
Physical Activity	- High intensity interval training (HIIT) - Resistance training - 3 and 4 sessions per week of between 45-60 minutes - If motivation is an issue, it is suggested that patients hire a personal trainer
Cognitive stimulation	- Brain HQ developed by Posit Science [112] - Learn a new language, musical interment or taking up a new hobby in a group setting)
Other	- Oral hygiene improvements - Vitamin D supplementation and 10-15 minutes of sunlight per day

Risk Factor	Intervention Offered
	- B-Complex multivitamin in the event of elevated serum homocysteine levels

Isaacson et al acknowledge that while multiple cardiovascular risk factors are assessed in the APC and an extensive lipid profile, blood pressure and HBA1c are all measured during the clinical visit, it is "uncommon" for doctors in this clinic to prescribe medications to target these risk factors [98]. Isaacson et al acknowledge that the management of hypertension, hyperlipidaemia, diabetes and other medical conditions that increase AD risk are primarily overseen by the primary care doctors. Instead of prescribing medication to reduce these risk factors they report that patients are given a copy of their clinical assessments and encouraged to discuss more comprehensive management of these risk factors with their primary care doctor or preventative cardiologist [98].

2.3.3.5. The Importance of Public Health Messaging and Awareness

Brain Health Scotland aims to reduce the incidence of dementia in Scotland through combined public health messaging and clinical approaches [101]. In association with Alzheimer's Scotland, they aim to engage in education programs, awareness raising and policy development to target modifiable risk factors for dementia. The APC in Cornel, alongside its individually tailored prevention clinic, also engages in an educational program which delivers local and online education interventions which aim to increase awareness of dementia and its risk factors [99]. Improving public awareness and providing access to resources around dementia reduction were outlined as priorities in The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships 2013-2018 [113]

and as a result Isaacson et al as part of their clinical framework also aim to improve public awareness of dementia and its risk factors.

2.3.3.6. The Importance of Integrating Clinical Services with Ongoing Research

Both clinical services outline the importance of integrating research and ongoing clinical practice in brain health clinics. All patients presenting to the APC are given the opportunity to enrol in the Comparative Effectiveness Dementia and Alzheimer's Registry (CEDAR) Project. As part of this project, patients consent to their clinical data being stored. This establishes a well-characterised cohort of individuals with risk factors for AD or other dementia subtypes who are invited to enrol in clinical trials as they take place [99].

Brain Health Scotland also feel that brain health services will play a significant role in AD research, advocating that they are the natural environment to enable the integration of well-established methods of disease detection alongside novel and emerging approaches in clinical practice. This belief is a key driver of the Scottish Brain Health and Dementia Research Strategy which was launched in 2021 [101]. Ritchie et al [101] argue that the combined efforts of academic research and clinical brain health models will allow proof of concept of the brain health clinical model and will demonstrate the impact of early disease detection, intervention, and personalised prevention. They also highlight that brain health clinics could create a pool of well- characterised patients who would be ideal candidates for clinical trials.

2.4. Discussion

The results of the scoping review documented in Figure 7 highlight the paucity of available information about clinically implemented brain health interventions, with only two clinical services identified from 3,035 results screened. The articles included in the review contained differing amounts of information about their clinical services. The APC in Cornell has been operational since 2013 and as a result has more published information about the assessments performed. The brain health Scotland clinical framework outlined by Ritchie et al was first implemented in December 2023 so met inclusion criteria for the review but as a result of being operational for only short months the specifics of the assessments performed and the interventions offered to people attending the service is limited.

While there is detailed information in articles relating to the APC [98-100] regarding blood tests performed and specific interventions offered, it is less clear whether specific assessment tools are used to quantify risk factor burden beyond the specifics of the clinical history detailed by Isaacson et al. There are a number of validated tools for quantifying the level of the modifiable risk factors assessed in both of these clinical services, for example anxiety and depression [114-116] , physical activity level [117-120], sleep quality [121-124], social inclusion [125] and Mediterranean diet [126, 127]. From the available resources included in this scoping review it is unclear whether any of these screening tools to quantify specific modifiable risk factor burden were used which would make mirroring of these clinical services in other settings difficult.

Articles relating to both clinical services reference the use of neuroimaging and AD biomarkers, but it is unclear where these fit in either clinical pathway, or what patient

cohort are offered access to these tests. Further information on the role of biomarkers in this setting would be useful to assess the transferability of these clinical structures to other jurisdictions.

The clinical model in use at the APC requires patients to complete two online learning modules and complete a questionnaire prior to attending the clinic, which is accepted will attract people to the clinic who are more likely to engage in preventative medicine. The model also directs patients back to their primary care doctor to have medications initiated for hypertension and hyperlipidaemia, or onwards to a preventative cardiologist. This model of care is attuned towards people with readily available access to healthcare and with a high degree of premorbid health literacy. Some of the potential lifestyle interventions suggested such as hiring a personal trainer, purchasing a standing desk, or taking regular vacations may not be feasible interventions for those in lower socio-economic groups. This clinical model therefore runs the risk of not providing a service to those in lower socio- economic groups who have a higher risk of developing dementia and cognitive dysfunction [128].

Brain Health Scotland highlights the need to provide equitable access to brain health services and references targeting at risk populations with outreach educational programmes, but it is not clear from the article how the pilot brain health clinics are funded or if private insurance is required to access diagnostic tests if they are deemed necessary. Some of the assessments performed in the APC such as body fat percentage and total body water measurement with bioelectrical impedance vector analysis or coronary calcium scans are unlikely to be available in state provided healthcare models such as primary care

practices or public hospitals. The funding of this clinical model is not clear, with reference being made to philanthropic donations and health insurance claims, with the latter sometimes hindered by health insurance companies' unwillingness to reimburse claims made in respect of asymptomatic individuals. The use of expensive diagnostic tests and the reliance on health insurance reimbursement and philanthropic donations to provide this Alzheimer's Prevention Clinic limits its generalisability to other publicly funded hospital structures.

2.4.1. Strengths and limitations

This is the first review of brain health interventions implemented in a clinical service. The scoping review framework allowed for consideration of information from grey literature outside the confines of a systematic review which is a strength of this study. Despite this there are likely other clinical services implementing brain health interventions which were not captured by the search. Isaacson et al refer to an Alzheimer's Risk Assessment and Intervention Clinic at the University of Alabama in Birmingham, an Alzheimer's Prevention Programme at Cedars Sinai Medical Centre in Los Angeles, and the Comprehensive Centre for Brain Health Dementia Prevention Initiative at Florida Atlantic University in Boca Raton, Florida [98] however there was not sufficient information about their clinical services to include them in the review.

Furthermore, conference abstracts identified potential clinical services in Italy [129] and Orange County in California [130] and both authors were contacted to determine if these clinical models were existing services. No reply was received and due to the lack of information in the conference abstracts available both were excluded. The exclusion of

information sources outside of the English language has led to the omission of some international brain health clinics such as the clinical model in Cologne, Germany [131]. An English translation of its' abstract suggested it would meet the criteria for inclusion in this review however the full text was not available in English, so it was excluded. There were 11 National Dementia Policy documents excluded due to lack of English translations available and this is a limitation of the search.

2.4.2. Future work

Neither of the clinical services identified in this scoping review are embedded within an existing memory service. There is a lack of published information on how to implement a clinical service that targets assessment and development of a personalised prevention plan for patients referred to an existing memory clinic with a subjective cognitive disorder or a mild cognitive impairment. In the Irish National Dementia Strategy, the need to both improve the awareness of modifiable dementia risk factors and provide a pathway to actively manage modifiable lifestyle risk factors as part of a care plan for people presenting to memory services was emphasised [50].

While theoretical frameworks exist for the implementation of brain health interventions within memory services [81, 83] there is a lack of real-world clinical experience of the implementation of these services. It would be beneficial to have more published articles relating to brain health services which are embedded in a memory clinic setting, allowing clinicians to consider the resource implications and potential structural adjustments required to implement a similar clinical model in their local service.

2.5. Conclusion

The evaluation of existing brain health clinics internationally is essential for developing similar services locally. This review has shown that there is a lack of available information in both published literature and in national dementia policy documents regarding existing fully implemented brain health clinics that target modifiable risk factors of dementia. Neither of the services highlighted by the search strategy are embedded within public memory services.

There is a need for more readily available literature discussing an implemented, operational brain health service which is integrated into an existing memory service to provide risk factor assessment and personalised intervention plans to patients attending a public memory service. This would help grow a network of operational clinics with the potential for resource sharing.

Chapter 3. A Description of Ireland's first Brain Health Clinical Service

3.1. Introduction

Several theoretical implementation frameworks for brain health clinics are outlined in Section 1.1.7. The scoping review in Chapter 2 highlights the lack of published literature describing brain health clinics as they are currently implemented. This chapter will outline the brain health clinic model currently implemented in Tallaght University Hospital. It will describe how the clinic is integrated into a Regional Specialist Memory Clinic (RSMC).

3.2. A description of the Tallaght University Hospital Institute of Memory and Cognition (TIMC) clinical service

3.2.1. Clinic Structure and staffing

The structure of memory services in Ireland and the model of care outlined by the National Dementia Office (NDO) for the provision of care to patients with memory complaints is discussed in Section 1.1.2 above. Tallaght University Hospital (TUH) is home to the Tallaght University Hospital Institute of Memory and Cognition (TIMC). It is one of the designated RSMCs in Ireland providing a diagnostic hub for atypical and young onset cases referred from general practitioners and hospital clinicians in centres from around Leinster region (Catchment population c1,000,000), while it also provides a level 2 Memory Assessment and Support Service (MASS) to patents from its own hospital catchment area (Population c500,000).

The clinic is staffed in accordance with the NDO's staffing guidelines for RSMCs and current staff members are detailed in Table 7 below. The service also has access to the expertise of a neuro-radiologist. Referrals are received from both primary, secondary and tertiary care.

Table 7: Staffing levels in the TUH RSMC

Staff Member	**Number**
Consultant Geriatrician	2
Consultant Neurologist	2
Advanced Nurse Practitioner (ANP)	3
Principal Neuropsychologist	1
Clinical Specialist Occupational Therapist (OT)	2
Senior Social Worker	1
Senior Speech and Language Therapist	1
Clinical Dietician	0.5
Clerical Staff	2

3.2.2. Consensus Diagnostic Process

Patients undergo initial neuropsychological testing with the Addenbrook's Cognitive Examination-III (ACE III) [132], Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [133] and Frontal Assessment Battery (FAB) [134]. An informant historian completes a Clinical Dementia Rating (CDR) score [135] and if there is any ambiguity around the presence of functional impairment an objective functional assessment, an Assessment of Motor and Process Skills (AMPS) [136] is performed by a specialist OT. Neuro-behavioral and psychiatric symptoms are explored with the Revised Cambridge Behavioral Inventory (CBI-R) informant questionnaire [137] and the

Neuropsychiatric inventory Questionnaire (NPI-Q) [138]. During this initial assessment by an ANP or a specialist OT, patients also undergo a depression screen, an assessment of polypharmacy while sleep symptoms, vision or hearing deficits and any previous history of delirium are explored.

Following this initial review patients undergo blood tests and structural neuroimaging in the form of CT or MRI while if required patients can be referred for advanced imaging in the form of PET scans or dopamine transporter scans (DaTscan). Patients with a clinical phenotype consistent with AD and who have no contraindications such as dual antiplatelet or anticoagulant use or recent spinal surgery are offered biomarker testing in the form of a lumbar puncture to assess CSF biomarkers. Results of neuropsychological assessments, neuroimaging, biomarkers if applicable and informant histories are then discussed at a weekly multidisciplinary consensus meeting attended by all staff in TIMC where a working diagnosis is formulated based on all available clinical information.

Following the MDT consensus diagnostic meeting patients are invited to clinic for diagnosis disclosure. Patients are counselled on their diagnosis and commenced on medications if indicated. Patients who receive a diagnosis of dementia are then offered post diagnostic support, while patients with MCI or SMC are referred to the Brain Health Clinic (detailed in Section 3.3 below) for assessment of their risk factors with a view to optimizing them. A flow diagram of a patients' journey through the TIMC service is outlined in Figure 8 below.

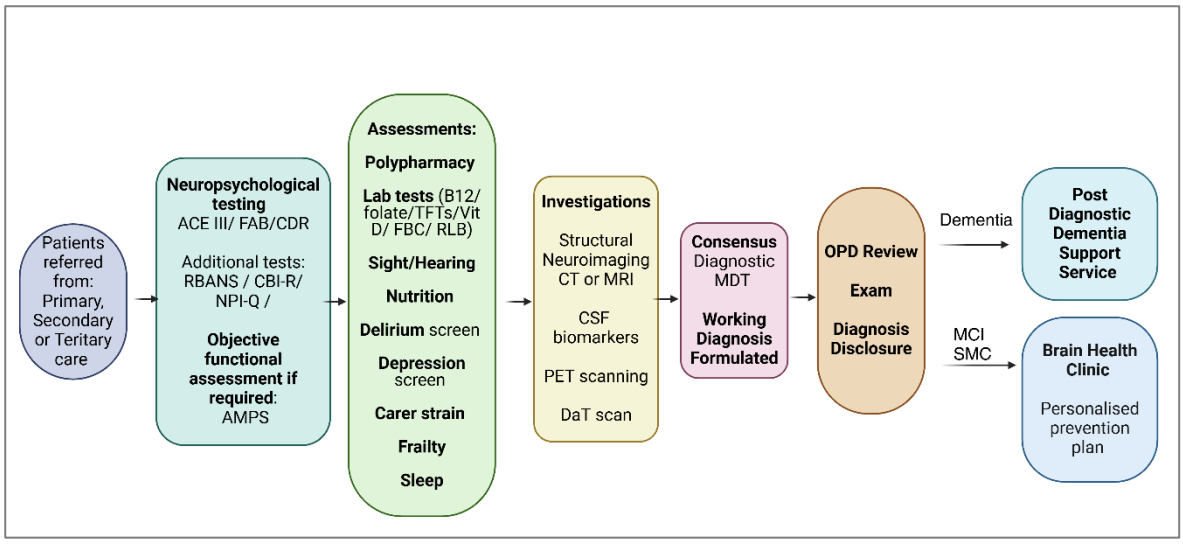

Figure 8: Patient Journey through TMIC clinical services. Created on https://BioRender.com

3.3. TIMC Brain Health Clinic Framework

The Brain Health Clinic was first established in 2020. Patients referred to TIMC and diagnosed with either MCI or SMC are referred to the Brain Health Clinic following disclosure of their diagnosis. The purpose of this clinic is to identify an individual patient's risk factors for dementia and aim to improve their overall risk factor burden through education around their risk factors and creating a personalized prevention plan to address any identified risk factors. Patients on the brain health clinical pathway are followed longitudinally over a 54-month period. This follow up period was chosen as the conversion rate from MCI to dementia has been shown to decline after 5 years in clinical and population based studies [139]. Patients' neuropsychological assessments are repeated at 18 months, 36 months and 54 months following their initial visit to the BHC. The 18-month interval for repeat assessment was chosen to accommodate the available clinical resources, while the virtual consultations at 9 monthly intervals allows repeat assessments to be expedited if there was a clinical concern for a significant deterioration. The clinic is staffed

by an ANP and a Specialist Registrar in geriatric medicine and has the support of an administration staff member from the memory service.

Should there be any concerns regarding a change to their working diagnosis following repeat neuropsychological assessments, patients are re-discussed at a consensus MDT meeting and if required, are reviewed in the memory clinic to receive their new diagnosis. These patients are then discharged from the brain health clinic and their ongoing care is provided on the post diagnostic support clinical pathway. A flowchart outlining the patent follow-up process in the Brain Health Clinic can be seen in Figure 9.

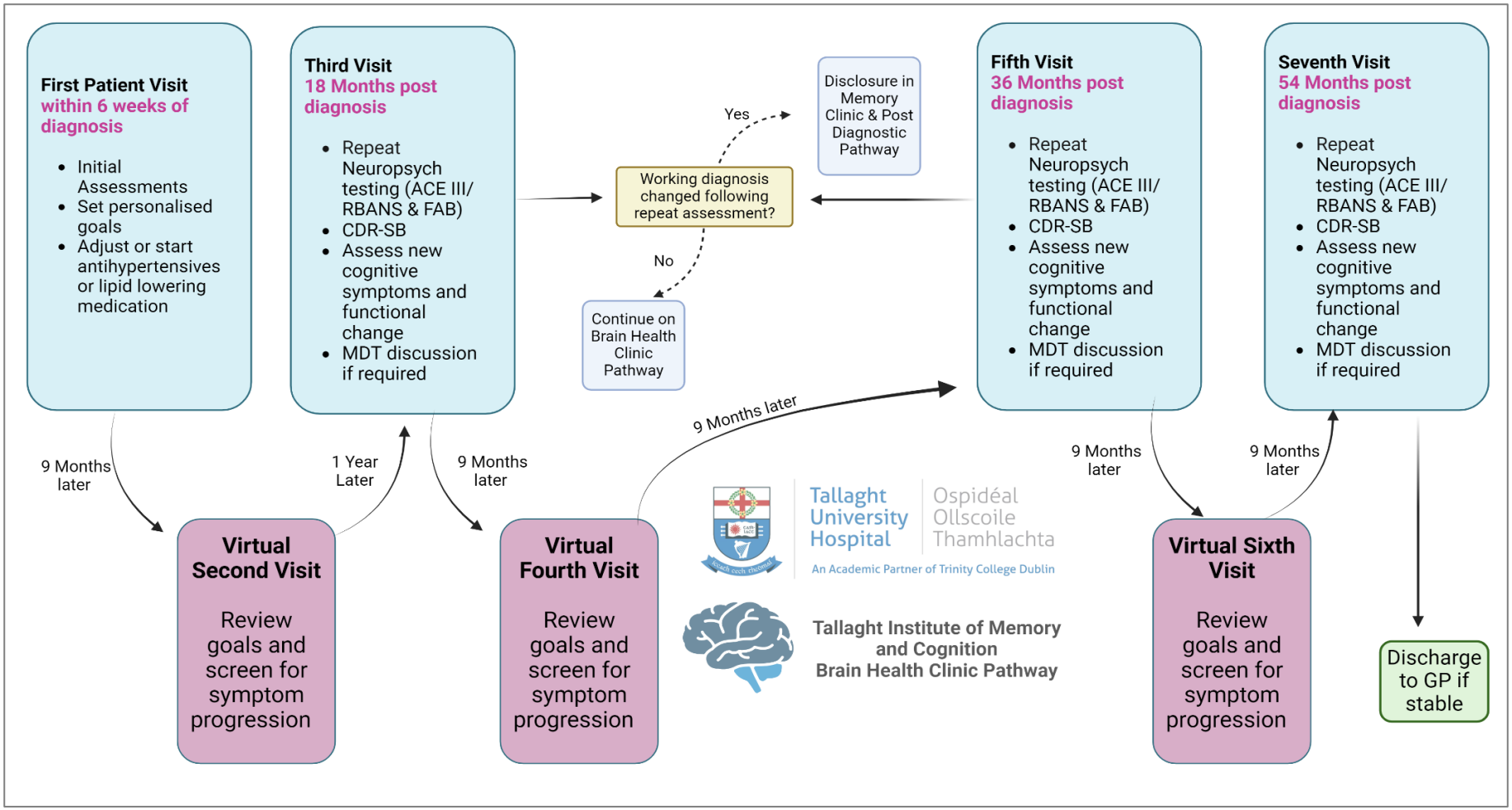

Figure 9: TIMC Brain Health Clinic pathway. Created in https://BioRender.com

3.3.1. Risk Factor Assessments Performed in TIMC BHC

The risk factors screened for, along with the assessment tools used to assess them are detailed in Table 8 below. The rationale for analysing each risk factor along with tools used to measure each risk factor will be further explored in the results chapters of this thesis. While genetic risk factor assessment in the form of APOE4 testing is advocated for in the theoretical clinical frameworks outlined in Section 1.1.7. it is not currently incorporated into the suite of assessments offered at the BHC. On balance the resource burden required to provide this test was weighed up against the information to be gained from it and it was decided not to clinically test for APOE4 status. To provide this risk factor assessment going forward would require training of clinic staff on the communication of genetic risk. However, given the importance of APOE4 status in determining risk of ARIA in patients receiving DMTs it is likely that APOE4 testing will be incorporated into memory services over the coming years.

Table 8: Risk factor assessments carried out in BHC

Risk Factor	**Assessment tool used**
Hypertension	Physician measurement, ambulatory blood pressure monitoring
Hyperlipidaemia	Fasting lipid profile
Diabetes	HbA1c (mmol/mol)
Obesity	BMI (kg/m^2)
Smoking status	Patient self-report (current, ex or never smoker)
Alcohol intake	Patient self-report (units/week)
History of head trauma	Patient self-report (yes/no)
Low Educational Attainment	Patient self-report – number of years in full time education
Hearing loss	Siemens HearCheck^{TM} Screener – handheld screening audiometer [140]
Impaired vision	Peek Acuity application (LogMAR) [141]
Physical Activity level	International Physical Activity Questionnaire (IPAQ) [119]
Diet	Mediterranean Diet Score [142]

Sleep Quality	Pittsburgh Sleep Quality Index (PSQI) [143]
Obstructive Sleep Apnoea (OSA)	Epworth Sleepiness Scale Score [144]
Depression	Hospital Anxiety and Depression Scale [145]
Social Isolation and Loneliness	Lubben Social Network Inclusion Scale 6 (LSNS-6) [146] UCLA Three item loneliness scale [147]

The above risk factor assessments are performed at patients' first, third, fifth and eighth visits to the clinic. A personalized prevention plan is developed with each individual patient based on the results of these assessments. This plan can include pharmacological interventions in the form of antihypertensive, oral hypoglycaemics or statin prescriptions, social interventions such as referrals to local community groups, referral to a group exercise classes, smoking and alcohol cessation advice, referral for formal audiology or sleep studies if required, signposting to primary care counselling, sleep hygiene tips and referral to a dietician if indicated. Compliance with the personalized prevention plan is followed up virtually nine months following the first clinic visit and again at 27 and 45 months.

3.4. Conclusion

This chapter outlines a framework for embedding a brain health clinic within an existing memory service. It outlines the frequency of patient visits, and frequency of repeat cognitive and risk factor assessments. The specific tools used to quantify the relevant risk factors measured have been outlined above and the rationale behind risk factor measurement will be explored further in Chapter 6 to Chapter 9. The brain health clinic framework described in this chapter will be used as the site for this study into the prevalence of modifiable risk factors for dementia in patients with MCI or SMC attending a memory service which is outlined in the subsequent chapters of this thesis.

Chapter 4. Brain Health Clinic Assessments and Methodology

4.1. Introduction

This is a prospective cohort study of patients attending a brain health service integrated into an existing memory service. This chapter details all elements of the patient assessment that they undergo while attending the brain health service along with how this data was collected and analysed with a view to quantifying the prevalence of modifiable risk factors for dementia in this patient cohort, highlighting previously undertreated or undiagnosed risk factors and emphasising the potential for intervention in a brain health clinic setting. The methodology described in this chapter will form the basis for the compilation and analysis of data described in the subsequent results chapters.

4.2. Study population

The TUH memory service receives referrals from GP practices within the hospital's catchment area, from other specialties within the hospital, and also receives referrals from other Level 2 MASS services in hospitals around the Leinster Region. Patients were referred to the brain health clinic from the TUH memory service upon receiving a diagnosis of MCI or SMC. There is no age cut off for referral to the brain health service and patients are offered appointments as close to diagnosis as possible, ideally within six weeks.

The Brain Health Clinic has undergone an iterative process since it was first established in 2020, with the assessment proforma evolving over time to capture a wider range of risk factors as emerging evidence unfolded. The current assessment proforma is in place since

2022 and patients considered for inclusion in this study have attended the brain health clinic for their first clinical assessment since this time.

4.3. Data collection

Data was collected at the first patient visit which was 60 minutes in duration. Data were recorded to capture demographic features such as age, sex, and past medical history and number of medications. Clinical assessments were performed by ANP and the database was completed prospectively at the time of the assessment by the author.

4.3.1. Medical Co-Morbidities

The number of co-morbidities was calculated from the list of a patients past medical history in their medical records and this was corroborated by patient self-report. The presence of absence of a known risk factors hypertension, atrial fibrillation, hyperlipidaemia, diabetes, history of previous head trauma, previous stroke or TIA, epilepsy, depression or anxiety, and ischemic heart disease were documented as present of absent in the database. Alcohol use was recorded via patient self-report in units per week.

4.3.2. Polypharmacy

The number of medications a patient was taking was also documented from this referral letter and this list was confirmed with the patient. If a patient was taking a tablet which was a combination of more than one drug, the number of individual medications in the combination tablet were counted. If patients were prescribed an inhaler which was a combination of medications, this was classified as one medication. As required medications

were not included in the calculation of the total number of medications documented for each patient. Polypharmacy was defined as taking five or more medications [148].

4.3.3. Socio-economic status

There is a well-documented link between socio-economic disadvantage and poor health outcomes [149]. This is also true when looking at dementia. A systematic review by Bodryzlova et al found that there is a significant association between belonging to a disadvantaged social class and higher risk of developing dementia over time [150]. As a result, it was deemed important to use a measure of socioeconomic status in this study.

The Pobal HP Deprivation Index [151] was used as a surrogate marker of a patient's socio-economic status. This index is compiled by Pobal at five yearly intervals following the publication of the national census. It uses objective information from the census in three domains (demographic vitality, social class composition and labour market situation) made up of 10 data points from the census which include educational attainment, occupational status, proportion of lone parents and unemployment rates. These data points are modelled to create a deprivation/affluence score for every small area in Ireland [152] which can be viewed on the Pobal website in the form of an interactive map shown in Figure 10.

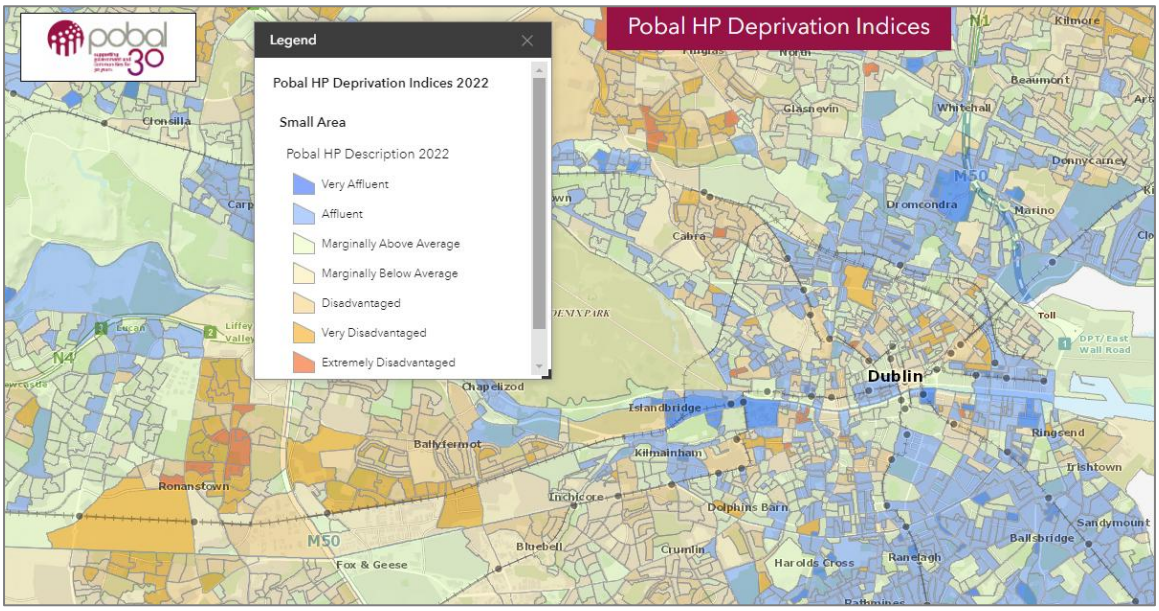

Figure 10: Pobal HP Deprivation Indices interactive map [153].

Patients' index score was calculated by inputting their address into the interactive map. They were classified on a scale from one to eight ranging from very affluent to extremely disadvantaged as shown in the legend in Figure 10.

4.3.4. Diagnostic Data

4.3.4.1. Formulating a Consensus Diagnosis

The consensus diagnostic process used in TIMC is outlined in Section 3.2.2 above. A multidisciplinary consensus diagnosis is formulated for each patient following their initial neuro-psychological assessment which includes an ACE-III [132], an RBANS [133] and a FAB [134]. The RBANS scores are adjusted for age and educational attainment [154]. Patients attending the brain health clinic will have a diagnosis of either SMC or MCI. Patients with MCI are further subdivided as having either amnestic or non-amnestic, single or multidomain MCI based on their test scores.

These diagnoses are formulated at the consensus MDT meeting based on a patient's neuropsychological testing, functional status with clinical judgement of the MDT also used. MCI is diagnosed when there is a concern (subjective or objective) regarding a change in cognition, with impairment evident in one or more cognitive domains without a loss of functional abilities. In people with an MCI diagnosis, neuropsychological test scores are typically at least 1 standard deviation (SD) below the mean for age and educationally matched peers [155]. Patients were classified as amnestic if they had deficits in memory cognitive domains of more than 1 SD below the mean, and non-amnestic if they did not meet these criteria.

MCI was then further grouped into single or multidomain impairments based on the number of cognitive domains (memory, visuospatial/constructional, language, attention) in which patients had scores of 1 -1.5 SD below the mean. Patients presenting with a subjective concern around change in their memory but who did not meet the criteria for MCI were classified as SMC. This diagnostic data was recorded when patients attended the brain health clinic and recorded in the database as amnestic or non-amnestic, single or multi domain MCI or SMC.

4.3.4.2. Defining Amyloid Pathology

Patients with appropriate clinical phenotypes and no clinical contraindications to undergoing a LP (such as anticoagulant use; history of spinal surgery etc) were given the option to pursue cerebrospinal fluid (CSF) sampling for AD biomarkers. This is done where possible to pursue a clinical-biological diagnosis using the AT(N) classification (A: Amyloid +/-, T: Tau +/-, N: neurodegeneration +/-) system which was outlined by the National

Institute of Aging and Alzheimer's Association (NIA-AA) research criteria [3]. Validated, available biomarkers (CSF and PET CT imaging) can be used to classify patients based on their biomarker profile using these criteria. Table 9**Error! Reference source not found.** below outlines how amyloid (A), tau (T) and neurodegeneration (N) are measured.

Table 9: How A+, T+ and N+ are defined by the NIA-AA [3].

Biomarker	Method of classification
A+	• Decrease in amyloid beta-42 (AB-42) in CSF • Amyloid deposition on PET CT
T+	• Elevated phosphorylated tau (p-tau) on CSF • PET CT
N+	• Elevated CSF total Tau • MRI imaging showing atrophy • FDG PET showing hypometabolism

Due to limited availability of Amyloid PET CT scans during the timeframe of this study and the non-availability of Tau PET CT scans, CSF samples were used. N+ was not recorded as not all patients had access to MRI or PET imaging at the time of diagnosis. CSF samples were taken as part of the diagnostic work up and CSF samples were analysed either on the Roche Elecsys® Immunoassay using a Cobas E801 analyser or using the Fujirebio Innotest® as part of routine clinical practice: Aβ42 levels ≤ 1030 pg/mL (Elecsys®)/≤ 712.0 pg/mL (Fujirebio) on CSF diagnostic testing were considered indicative of Aβ pathology (A+) whilst p-tau 181 levels of ≥ 27 pg/mL (Elecsys®)/ ≥ 58.6 pg/mL (Fujirebio) were considered as indicative of tau pathology (T+).

Our practice was to classify patients as biomarker positive AD if they were A+T+ or were A+T- with a positive p-Tau181/Ab42 ratio of > 0.023. The p-Tau181/Ab42 ratio is used as

studies have shown the use of ratios when interpreting CSF AD biomarkers improve diagnostic accuracy, performing better than single markers [156], with CSF Aβ1-42/1-40 and CSF p-tau/Aβ1-42 ratios performing equivalently [157]. LP results were recorded in the database where applicable and patients were documented having positive AD biomarkers if they were A+T+ or A+T- with a positive p-tau/Aβ1-42 ratio. An accurate clinical-biological diagnosis is important give that patients with positive biomarkers indicating AD pathology have been previously shown to have higher conversion rates from MCI to dementia than those with a negative AD biomarker profile (A-T-) [158].

4.3.5. Patient Assessments

At their nurse lead clinical assessment patients were asked about smoking history (current, ex or never smoker), their alcohol intake and any previous history of head trauma and this was prospectively recorded. The duration of a patient's symptoms prior to receiving their diagnosis in the memory clinic was recorded in months. The time in months from a patient receiving their diagnosis of SMC or MCI in the memory clinic and their first visit at the brain health clinic was also recorded in the database. The following questionnaires were used to quantify risk factors across a number of areas.

4.3.5.1. International Physical Activity Questionnaire (IPAQ)

The IPAQ is a seven question self-assessment questionnaire which explores a person's activity level over the seven days prior to the assessment. Activities lasting less than 10 minutes in duration are not scored. It has been previously validated in 10 European Union (EU) countries [159] and provides internationally comparable data on health-related physical activity. Results were recorded as a continuous variable namely MET (metabolic

equivalent) minutes per week, with one MET equating to a person's resting energy expenditure. For calculating the continuous variable of MET minutes per week, walking is considered 3.3 METs, moderate physical activity 4 METs and vigorous physical activity 8 METS. The MET value is then multiplied by the number of minutes spent in each activity state and again by the number of days per week that the activity was undertaken to give a score in MET minutes/week [160]. An individual's activity levels were then categorized into high, moderate or low based on their IPAQ score (MET minute/week) as shown in Table 10.

Table 10: Low, moderate and high levels of physical activity as per IPAQ score [160, 161]

Activity level category	**IPAQ Cut off score in MET minutes/week**
Low	<600 MET Minutes/week.
Moderate	600-3000 MET Minutes/week
High	≥ 3000 MET minutes/week

4.3.5.2. Mediterranean Diet Score Tool

The Mediterranean Diet Score Tool used was the score adapted by Alison Hornby and Katherine Paterson [142] from the Primary Prevention of cardiovascular disease with a mediterranean diet (PREDIMED) study [162]. It is a 14-item questionnaire administered during the brain health clinic appointment and is scored from zero to 14. Higher scores indicate greater compliance with a mediterranean diet. A copy of the administered questionnaire can be found in Appendix B: Assessment Tools.

4.3.5.3. Pittsburgh Sleep Quality Index (PSQI)

Sleep quality of each patient was measured using the PSQI, a self-rated seven component questionnaire which assesses sleep quality and disturbances over a one-month period. A total score was calculated buy summing the seven component scores across subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction [143]. A global PSQI score > 5 was considered indicative of poor sleep quality [163].

4.3.5.4. Epworth Sleepiness Scale

The Epworth Sleepiness Scale was used to measure a patient's general level of excessive daytime sleepiness (EDS). It is a self-reported questionnaire with the person rating how likely they are to fall asleep in certain situations. A score of 10 or greater was used to characterize EDS [144].

4.3.5.5. Hospital Anxiety and Depression Scale (HADS)

The HADS self-assessment instrument [145] was used to measure symptoms of anxiety and depression. It consists of 14 items, seven for the anxiety subscale (HADS-A) and seven for the depression subscale (HADS-D) with each item scored on a response scale ranging between 0-3. Six items that are reverse scored are adjusted for and all responses are added to obtain the two subscale results [164]. Each patient's individual score was documented in the database. A combined score of 0-7 indicated no anxiety/depression, a score of 8-10 indicated moderate anxiety and depression, with a score of 11-21 indicating severe anxiety/depression [145]. A cut off score of 8 or above on HADS-A and HADS-D was used

to define anxiety/depression as this had been previously shown to achieve an optimal balance of sensitivity and specificity [165].

4.3.5.6. University of California, Los Angeles (UCLA) Three Item Loneliness Scale

The UCLA three item loneliness scale [147] was used to measure loneliness in the patient cohort attending the Brain health clinic. Questions were asked during the patient interview. The questionnaire consists of 3 questions with the scores for each response added together to give a possible range of scores from 3-9 with higher scores indicating greater degrees of loneliness. A cut off score of 5 was used, with patients who scored 3-5 were classified as "not lonely" while patients with a score of 6-9 were classified as "lonely" [166].

4.3.5.7. Lubben Social Network Scale-6 (LSNS-6)

The LSNS-6 was used to gauge social isolation by measuring the frequency and number of social contacts a person has with friends and family and the perceived social support received from these sources. This six-item scale was administered to patients attending brain health clinic, with the LSNS-6 total score an equally weighted sum of the six items in the questionnaire. A score was calculated for each patient and recorded. A cut off score of 12 or lower was used to delineate a patient being "at risk" for social isolation [146].

4.3.6. Biophysical Measurements

4.3.6.1. Weight and Height

Weight was measured with a digital scale accurate to 0.1kg. Height was recorded using a stadiometer accurate to the nearest 0.01m. These measurements were used to calculate BMI by the standard definition of weight/height^2 expressed in units of m/kg^2.

4.3.6.2. Blood Pressure Measurement

Office based blood pressure was assessed in the clinic using an electronic sphygmomanometer. Measurements were recorded in a seated position, after the patients had been sitting for 5 minutes. Hypertension was defined as a reading of systolic blood pressure (SBP) ≥ 130 mmHg [167] or diastolic blood pressure of ≥ 85 mmHg. If BP met criteria for hypertension in the brain health clinic, a 24hr ambulatory blood pressure monitor (ABPM) was performed to examine further.

4.3.6.3. Vision Check

Visual acuity was measured in the brain health clinic using the Peek Acuity smartphone app. This app has been validated against the Early Treatment Diabetic Retinopathy Study (ETDRS) Logarithm of minimum angle of resolution (logMAR) chart in a Kenyan cohort of 600 patients over a 6 year period. The Peek Acuity app was shown to be comparable in accuracy to the logMAR chart [141]. The test is performed in the clinic with the patient in a seated position. If a patient wears distance glasses day to day (including bifocals), then they are advised to wear them for the duration of the test. Reading glasses should not be worn. A two-metre distance is measured and marked on the floor. The assessor stands at this point and holds the device at the patient's eye level, ensuring that the smartphone device is not tilted.

The Peek Acuity test uses an E shape (see Figure 11 below) that points in different directions and changes in size to measure eyesight. The patient is asked to gesture in the direction they think the E is pointing and the examiner swipes the screen in the direction that the

patient points. If the patient is unable to see the E, the examiner shakes the device until a new E appears. This process is continued until the test ends and a score is generated [168]. One eye is measured at a time with the patient instructed to cover the other eye with the palm of their hand prior to beginning the test.

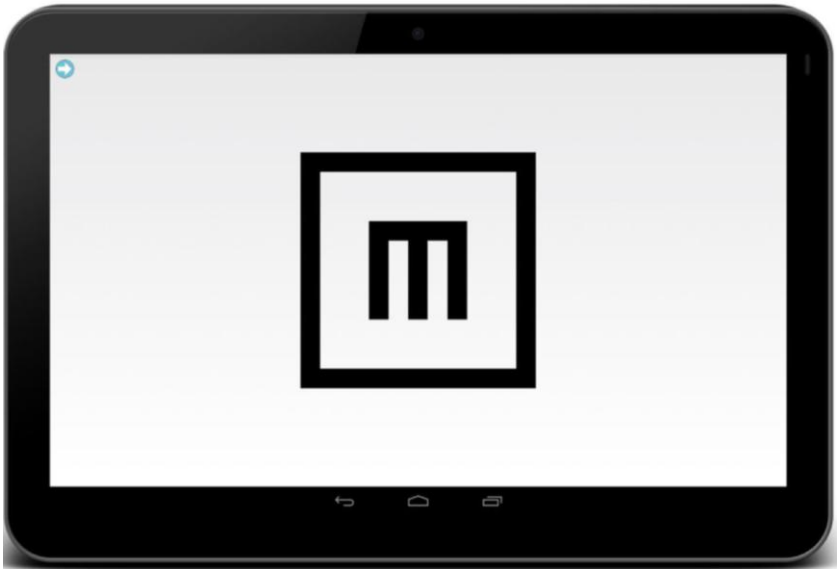

Figure 11: Peek Acuity App; E Shape used to measure visual acuity [169]

A logMAR result was generated for each eye and recorded. The WHO classification [170] of the severity of visual impairment was used to classify patient's visual acuity into categories ranging from normal to blindness using the logMAR score generated by the Peek Acuity app. LogMAR scores and the corresponding visual category can be seen in *Table 11* which was adapted from the Peek Acuity validation study which used the same visual categories [141].

Table 11: WHO visual categories by logMAR score [141]

LogMAR score	Visual Category
4.0 3.0 2.5 1.8	Blindness
1.3	Severe Visual Impairment

1.0 8.8 0.6	Moderate Visual Impairment
0.5	Mild Visual Impairment
0.3 0.2 0.0 -0.1	Normal

4.3.6.4. Auditory assessment

An auditory assessment was carried out at the initial brain health clinical assessment using the Siemens HearCheck™ Screener [140]. This is a handheld device that can screen for possible hearing impairment and indicate whether further evaluation through formal audiology testing is needed. The HearCheck™ Screener has been previously shown to be an accurate, easy-to-use tool for screening for potential hearing loss [171, 172]. Patients with test results indicative of potential hearing loss were then referred to the audiology department for a formal assessment of hearing.

The testing process was initially explained to the patient. The Siemens HearCheck™ device was then gently placed over the ear with the edges of the cup in contact with the patient's head. Glasses, earrings, hairbands etc which may interrupt the seal were removed. During the assessment 3 tones were played at 1000 Hz followed by 3 further tones at 3000 Hz. The patient raised their hand each time they heard a tone, with a score out of 6 recorded. The same process was then repeated for the other ear, with each patient receiving a score out of 6 for both left and right ears.

Scores were interpreted using guidelines in the Siemens HearCheck™ user manual, with 6 tones heard in by one ear indicating that the patient is unlikely to need further hearing assessment. If fewer than 6 tones are heard in more than one ear, this was considered a positive test. A decision grid, shown in Figure 12 below, was devised to interpret the results obtained from the Siemens HearCheck™ device. Any patient with a positive screening test was referred onwards for formal audiology testing.

		Right ear total score						
		0	**1**	**2**	**3**	**4**	**5**	**6**
Left ear total score	**0**	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	1	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	2	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	3	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	4	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	5	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Positive screen □	Negative screen □
	6	Negative screen □	Negative screen □	Negative screen □	Negative screen □	Negative screen □	Negative screen □	Negative screen □

Figure 12: Decision grid used in the Brain Health Clinic to interpret positive and negative screening tests using the Siemens HearCheck™ Device.

4.3.6.5. Blood tests

On the day of their initial brain health clinic assessment patients underwent non fasting blood tests which included a glycated haemoglobin (HbA1c) measured in mmol/mol, a random lipid profile including total cholesterol, Low density lipoprotein (LDL) and triglycerides, a full blood count and a renal and liver profile

4.3.7. Tota Demential Risk calculator – The Lifestyle for Brain Health (LIBRA) Index

The LIBRA index was developed following a systematic literature review and Delphi consensus around the epidemiological evidence for dementia risk factors [173]. It includes 12 modifiable risk and protective factors for dementia which can be targeted by lifestyle interventions and vascular risk factor management. Higher scores indicate higher dementia risk. The rationale behind choosing this risk score, along with modifying it to include the non-modifiable risk factors of age and educational attainment is explored further in Chapter 9. The LIBRA index score used can be seen in Appendix B: Section 12.2.7. This score was calculated at the time of the patient assessment in the brain health clinic and recorded in the database.

4.4. Statistical Analysis

Data from patient assessments in the brain health clinic were prospectively collected and collated in a Microsoft Excel database. Demographic data, diagnostic data, blood results and results from each risk factor assessment discussed were recorded. This database was then exported into IBM SPSSv27 for analysis. Risk factor prevalence was calculated using frequencies and percentages while comparison was made across the MCI, SMC and AD biomarker positive patients using either a t-test, Mann-Whittney U Test, Chi-Square test, one way ANOVA or a Kruskal-Wallis test where appropriate. The specific analysis performed for each risk factor grouping (vascular, sensory, lifestyle and total LIBRA score) is discussed in the methodology section of Chapters 7 to 9.

4.5. Conclusion

The study population, assessments performed during the brain health clinical assessment and the data collection process are detailed above. This will enable the exploration of modifiable risk factors for dementia in this clinical patient cohort.

Chapter 5. Results: Patient Demographics, risk factors, and socio-economic profiles of people with subjective and mild cognitive impairment attending a Brain Health Clinic

5.1. Introduction

The demographic profiles and cognitive diagnoses of the patients included in this study are outlined in this chapter and will characterize the patient cohort attending the Brain Health Clinic and allow for comparison between patients based on their cognitive profiles. Along with basic demographic details such as age and sex, other information captured included educational attainment and socio-economic status by way of the Pobal deprivation index score described in Section 4.3.

5.1.1. Cognitive Profiles

Patients are grouped based on their consensus clinical diagnosis and this diagnostic process is outlined in Section 4.3.4.1. Patients are diagnosed with either subjective memory complaints (SMC) or mild cognitive impairment (MCI), and those with MCI are further subdivided into amnestic or non-amnestic, single or multidomain MCI based on the outcome of their cognitive testing. As outlined in section 1.1.1, a diagnosis of SMC is given to a person with a self-reported decline in cognitive capacity without detectible deficits on a standardised cognitive test while those with MCI will exhibit reduced performance on cognitive testing without subjective or objective functional impairment.

Trajectories of patients with MCI and SMC attending a memory service has been longitudinally explored by Gallassi et al over a 4-year period. Of the MCI cohort, 18.4% had

progressed to dementia while 13.9% of the SMC cohort progressed to MCI, with only 2.3% progressing to dementia [174]. While this progression rate of SMC to dementia is low, the follow-up period is relatively short. In a systematic review with follow up periods ranging from 1 to 8 years, Parfenov et al concluded that individuals with SMC were 2.17 times more likely to develop dementia than controls with no cognitive concerns [175]. Given this higher progression rate to dementia and MCI in persons with SMC, Warren et al [176] argue that it is an important risk factor for the development of AD.

5.1.2. Socio-economic Status

There is some debate around the exact mechanisms which link socio-economic status to dementia risk. Individuals from higher social classes have better access to education, pursue more cognitively demanding occupations, have higher income levels and have better access to healthcare [150]. The systematic review from Bodryzlova et al found education and occupational status to be the most relevant indicators of social class and deemed them more significant with regard to stratifying dementia risk [150] while a previous study has linked area-based social disadvantage to increased incidence of AD pathology on autopsy reports [177].

Geographical area-based or neighbourhood socio-economic status scores have been used in previous studies looking at social class and dementia and cognitive functioning [177-184]. Area based socio-economic status was shown to contribute to cognitive functioning [182-184] of older adults, while living in a deprived neighbourhood was associated with increased dementia risk in one study, but only in the females [178]. Ouvrard et al found no

association between dementia and geographical deprivation [181] but comparison between studies is limited given the different indices used.

The Pobal deprivation index used in this study to stratify patients attending the brain health clinic is based on the combination of relative affluence and social deprivation namely: demographic profile, social class composition and labour marked situation. This incorporates educational attainment, but it does not include income data as this was felt to fluctuate over time and in accordance with family composition. Inclusion of this metric will enable a neighbourhood-based metric of socioeconomic status to be considered in the analysis of risk factor profiles.

5.1.3. Educational Attainment

While it is incorporated into the deprivation index at a population level, educational attainment data at an individual level was also recorded. It has been identified by Livingston et al as an early life dementia risk factor, with higher levels of education and the occupational complexity that this enables people to pursue contributing to an increased cognitive reserve [90].

5.1.4. Traumatic Brain Injury

A history of a traumatic brain injury (TBI) was also cited as a midlife risk factor by the Lancet Commission [90], with mild TBI defined as a concussion and severe TBI associated with skull fracture, oedema or brain bleed. Cohort studies have shown an increased risk of dementia in patients with TBI [185, 186], while the association appears to increase with increasing frequency and severity of head injury [186]. While evidence around the association

between a TBI and dementia is limited by variable definitions of TBI, its severity staging, and the observational designs of many studies investigating the association [187], it was felt it was an important risk factor to capture in this brain health clinical cohort.

5.2. Methods

The study population along with the data collection process has been outlined in Chapter 4. Demographic and diagnostic data from patients assessed in the brain health clinic were compiled prospectively. Data was collected in Microsoft Excel, cleaned and coded and then exported to IBM SPSSv27 for analysis. Where data was normally distributed, means and standard deviations were used, otherwise medians and interquartile ranges were reported. Patients were categorized by cognitive diagnosis (MCI – single domain, multidomain, amnestic or non-amnestic, SMC) and by AD biomarker positivity (see Section 4.3.4). Differences in age, sex, educational attainment and symptom duration across each group were compared using chi square tests, t-tests or Mann Whittney U tests where appropriate. A p value of <0.05 was considered statistically significant.

5.3. Results

5.3.1. Patient inclusion and demographic data

Patients attending the brain health clinic for their first visit on the brain health clinical pathway outlined in Figure 9 in Chapter 3 from March 2022 until April 2024 were prospectively included in the database and make up the patient cohort for this study. March 2022 was chosen as the inclusion date as the current risk factors identified and the instruments used to quantify them are in use since this date. In total 118 patients were included in the study, with 30 attending in 2022, 64 attending in 2023 and 24 attending in

2024. The demographic characteristics of the patients included in the study are outlined in Table 12 below.

Table 12: Demographic characteristics of patients attending the Brain Health Clinic for initial assessment (March 2022-April 2024)

Patient Characteristics (n=118)	
Sex	**Number (%)**
Female	72 (61%)
Male	46 (39%)
Age	**Median (IQR)**
Age in Years	71.9 (65.6-77.5)
BMI	**Mean (SD)**
BMI in Kg/m^2	29.4 (5.6)
Socio-Economic Status	**Number (%)**
Extremely Affluent	0 (0%)
Very Affluent	5 (4.2%)
Affluent	14 (11.9%)
Marginally Above Average	46 (39.0%)
Marginally Below Average	30 (25.4%)
Disadvantaged	14 (11.9%)
Very Disadvantaged	9 (7.6%)
Extremely disadvantaged	0 (0%)
Educational attainment	**Median (IQR)**
Years in full time education	12 (10-14)
Medical History	**Median (IQR)**
Number of comorbidities	5.0 (5-7)
Number of medications	6 (4-9)
	N (%)

Patient Characteristics (n=118)	
Polypharmacy ≥ 5 medications	79 (66.9%)
History of Head Trauma	9 (7.6%)
History of Epilepsy	9 (7.6%)
History of Depression/Anxiety	45 (38.1%)

5.3.2. Diagnostic Profiles

As described in Chapter 3 and Chapter 4 prior to attending the brain health clinic patients undergo a rigorous clinical-biological diagnostic workup and are discussed at a MDT case conference. Following this discussion patients receive a diagnosis disclosure at their memory clinic appointment. Patient diagnostic profiles from this consensus MDT approach are outlined in Table 13.

Table 13: Diagnostic Profiles of the Brain Health Clinic cohort

Diagnostic Data (n=118)	
Diagnosis	**Number (%)**
MCI	94 (79.7%)
SMC	24 (20.3%)
Mild Cognitive Impairment Subtype	**Number (% of MCI patients)**
Amnestic	77 (81.9%)
Non-Amnestic	17 (18.1%)
Single Domain Impairment	26 (27.7%)
Multidomain Impairment	68 (72.3%)
CSF Alzheimer's Disease Biomarkers	**Number (% of MCI Patients)**
LPs performed	49 (52.1%)
- A+T+	14
- A+T- with positive AB42/pTau ratio	7
- A+T-	9
- A-T+	9

Diagnostic Data (n=118)	
- A-T- AD pathology identified (A+T+ or A+ with positive ratio)	17 21 (22.3%)
Duration of symptoms prior to diagnosis Symptom duration in months Time from diagnosis to review in BHC in months	**Median (IQR)** 24 (12-36) 6 (2-15.25)

5.3.3. Patient characteristic categorized by cognitive diagnosis

The SMC and the MCI patient cohorts were compared in terms of their patient demographics and medical history and this information is displayed in Table 14 below.

Table 14: Patient Characteristics categorized by cognitive diagnosis

Patient Characteristic	MCI (n=94)	SMC (n=24)	P-value
Female, n (%)	56 (59.6%)	16 (66.7%)	X^2 0.401, p=0.527
Age	**Median (IQR)** 73.3 (68.5-77.8)	**Median (IQR)** 62.3 (57.9-68.7)	Mann-Whitney U 1886, p=0.000
Educational Attainment in years	**Median (IQR)** 12 (10-14)	**Median (IQR)** 13.5 (12-18)	Mann-Whitney U 822, p=0.039
Socioeconomic Status - Extremely Affluent - Very Affluent - Affluent - Marginally Above Average - Marginally Below Average - Disadvantaged	**n (%)** 0 (0%) 5 (5.3%) 9 (9.6%) 37 (39.4%) 24 (25.5%) 10 (10.6%)	**n (%)** 0 (0%) 0 (0%) 5 (20.8%) 9 (37.5%) 6 (25%) 4 (16.7%)	Mann-Whitney U 1038, p=0.531

Patient Characteristic	MCI (n=94)	SMC (n=24)	P-value
- Very Disadvantaged - Extremely disadvantaged	9 (9.6%) 0 (0%)	0 (0%) 0 (0%)	
Polypharmacy ≥ 5 Medications	**n (%)** 66 (70.20%)	**n (%)** 13 (54.2%)	X^2 2.206, p=0.137
Number of comorbidities	**Median (IQR)** 5.5 (4-7)	**Median (IQR)** 4 (3-6)	Mann-Whitney U 1484, p=0.016
History of Anxiety/Depression	**n (%)** 36 (38.3%)	**n (%)** 9 (37.5%)	X^2 0.05, p=0.943
History of Head injury	**n (%)** 5 (5.3%)	**n (%)** 4 (16.7%)	X^2 3.465, p=0.063
Duration of symptoms prior to diagnosis in months	**Median (IQR)** 24 (12-36)	**Median (IQR)** 24 (12-48)	Mann-Whitney U 1127, p=0.995

There was a significant difference in the age profile of the patient cohorts with patients receiving a diagnosis of SMC younger than patients diagnosed with MCI. This can be seen graphically in the box and whisker plot in Figure 13 below.

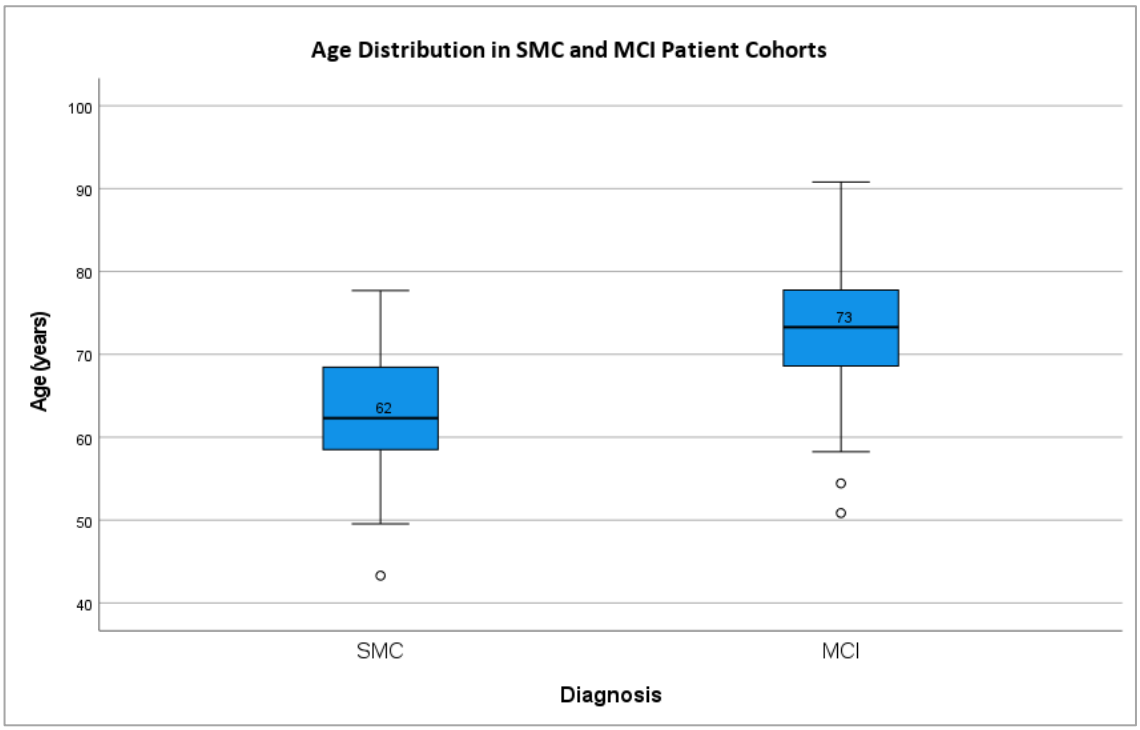

Figure 13: Spread of Age across the MCI and SMC patient cohorts

Regarding educational attainment, patients with SMC spent a median of 2 additional years in full-time education as outlined in Figure 14 below. This difference was not statistically significant; however, this may be due to the smaller sample size in the SMC group.

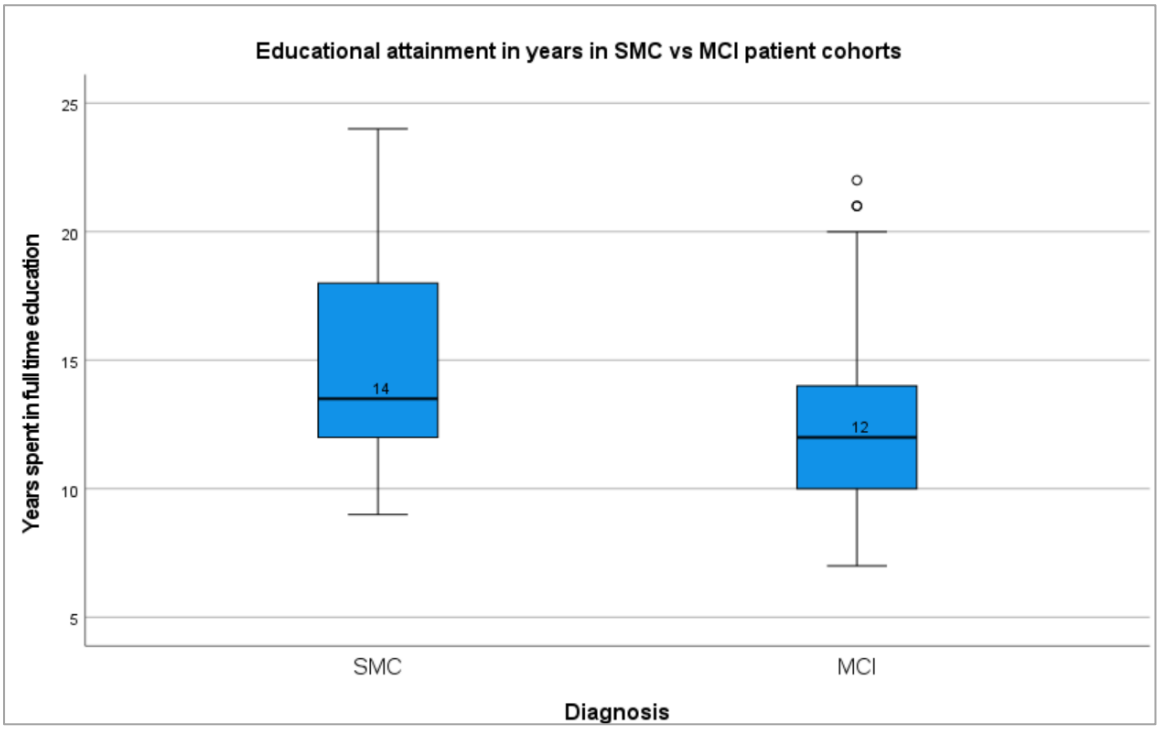

Figure 14: Educational Attainment in years in the MCI and SMC patient cohorts

There was no significant difference between the SMC and the MCI patient cohorts in terms of duration of symptom onset prior to diagnosis, gender, history of head trauma, epilepsy or anxiety or depression. Socio-economic status was explored across the MCI and the SMC patient cohort, and this is graphically shown in Figure 15.

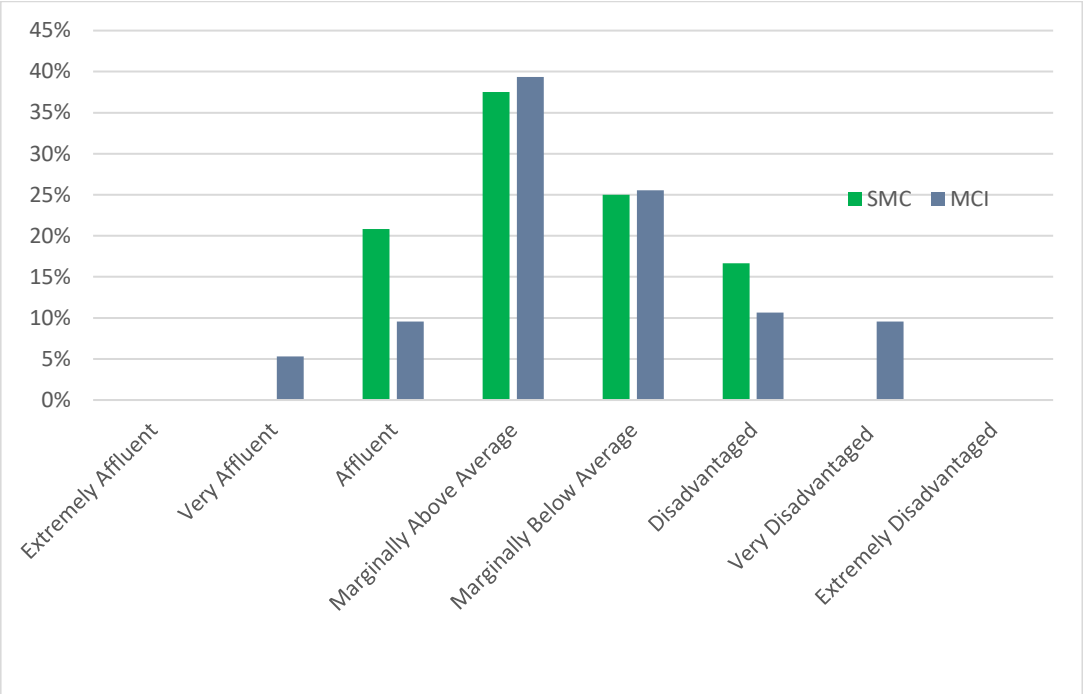

Figure 15: Socio-economic classification of patients diagnosed with SMC and MCI

5.4. Discussion

The majority of patients attending the Brain Health Clinic do so with a consensus diagnosis of MCI (79.7%), with only 20.3 % having a diagnosis of SMC. Most MCI patients were amnestic (81.9% % vs 18.1% non-amnestic), while 72.3% of patients had a multi-domain cognitive impairment. Over half (52.1%) of this clinical cohort underwent CSF testing for AD biomarkers with 22.3% of the patient population having positive AD biomarkers based on the diagnostic criteria outlined in Section 4.3.4. The disparity in the size of the MCI and SMC groups is a limitation of the study, but it reflects the real-world through put of patients attending a brain health clinic embedded within a memory service.

The median age of the patients included in this clinical patient cohort is 71.9 (IQR 65.6-77.5). The majority of patients attending the Brain Health Clinic were female (62%). The only other previous study to look at patients attending a clinic focusing on modifying

dementia risk factors was based out of the Alzheimer's Prevention Clinic (APC) [98, 99] whose framework was explored in the scoping review in Chapter 2. Patients attending the APC clinic were younger, with an average age of 63 years (range: 25-96). This service also had a higher rate of female patients at 57%. As the APC is not linked to an existing memory clinic and patients are usually self-referred on foot of subjective complaints this may explain the younger patient cohort.

The inclusion of the Pobal deprivation index scores for patients based on their address allows for the socio-economic status to be accounted for when looking at risk factor prevalence which will be included in the analysis in subsequent results chapters. There is a good spread of socio-economic status across this clinical patient cohort, with patients coming from a variety of social backgrounds based on the Pobal social deprivation index scores. 55.1% of patients were classified as either very affluent (4.2%), affluent (11.9%) or marginally above average (39%) while the remaining 44.9% of patients were from areas classified as marginally below average (25.4%), disadvantaged (11.9%) or very disadvantaged (7.6%). There was no significant difference in the spread of socio-economic status across patients in the MCI and SMC cohorts.

The median number of years spent in full time education by patients attending the clinic was 12 years. In Ireland primary school education consists of 8 years, with secondary education completed following a minimum of five years in full time education. This implies a requirement of 13 years in full time education at a minimum to complete secondary education in Ireland. Most patients in this study did not finish second level education. While it is not statistically significant, patients with SMC had a higher educational attainment than

those with a diagnosis of MCI (median of 13.5 years vs 12 years). It is important to consider that some SMC patients may in fact have an MCI with a high baseline IQ which makes detection of deficits on standard cognitive testing difficult.

There is a high rate of polypharmacy (66.9%) in this patient cohort and a high rate of multimorbidity with the median of 7 recorded medical comorbidities. These high rate of multimorbidity and polypharmacy may be because this is a clinical patient cohort recruited from patients attending a memory service with a diagnosis of MCI or SMC rather than a self-referral brain health clinical service. There was no significant difference in the rate of comorbidities or polypharmacy between MCI and SMC patient groups.

Only 7.6% of patients reported a history of previous head trauma. The frequency, severity or mechanism of the trauma involved were not recorded in the database which is a limitation. By contrast there is a relatively high rate of anxiety and depression in the patient cohort with 38.1% of patients having a documented history of anxiety/depression in their medical record. The duration of symptoms or whether a patient is receiving pharmacological or psychological treatment was not recorded which is a limitation of the study's data collection process.

5.5. Conclusion

This chapter outlines the demographic and diagnostic profiles of the clinical patient cohort in this study attending the Brain Health Clinical model outlined in Chapter 3. Risk factor profiles of this patient cohort will be explored in the subsequent results chapters.

Chapter 6. Results: An analysis of the prevalence of cardiovascular risk factors in patients with Mild Cognitive Impairment or Subjective Memory Complaints attending a Brain Health Clinic

6.1. Introduction

There are strong links between cardiovascular disease and dementia and the declining age specific incidence of dementia with over time in certain geographical areas has been linked in part to improved long term treatment of cardiovascular disease [188]. Approximately 60-80% of dementia cases are caused by Alzheimer's Disease while 5% of cases can be attributed to vascular dementia alone [189]. Vascular dementia is a term given to dementias which involve cognitive deficits as a result of impaired blood flow [190]. It is characterised by the temporal relationship between a cerebrovascular insult and symptom onset and requires the exclusion of other dementias like AD [191].

Recent evidence suggests that cardiovascular risk factors also play a role in AD and its progression, with one study of autopsy based neuropathological diagnosis in America showing a 79.9% incidence of vascular pathology in patients with an AD diagnosis when inspected at autopsy [192]. This can be attributed to multiple mechanisms including chronic neuroinflammation and altered blood-brain barrier integrity [193], abnormal cerebral perfusion and increased vascular resistance [194]. The relationship between heart health and brain health supports the importance of controlling cardiovascular risk factors when addressing dementia prevention.

6.1.1. Hypertension

Targeted anti-hypertensive treatment is the only known effective preventative pharmacological treatment for dementia with a number of meta-analyses suggesting a reduction in dementia incidence in patients receiving antihypertensive treatment. Ou et al in a meta-analysis of longitudinal cohort studies found a midlife systolic BP >130mmHg was associated with an increased risk of cognitive disorders and commented on excessive blood pressure variability, high systolic blood pressure and orthostatic hypotension as being associated with an increased dementia risk in later life [167]. A 2023 meta-analysis of longitudinal cohort studies looking at antihypertensive treatment in later life (mean age 72.5 years) showed anti-hypertensive use was associated with a decreased dementia risk in individuals with hypertension when compared with those with untreated hypertension but acknowledged that BP in later life is a sensitive biomarker and that more than one measurement is required to inform treatment [195].

A further meta-analysis that explored RCTs looking treatment with calcium channel blockers only in later life found a lower dementia risk over a median follow up period of 8.2 years [196]. However, in their meta-analysis Peters et al found no consistent difference in dementia reduction according to antihypertensive class used and also found the greatest association between antihypertensive use and dementia reduction was in the 60-70 year old age cohort, which no significant association found in patients over 70 years of age [197]. The Lancet Commission citeed hypertension as a mid-life risk factor and advocated for a systolic BP of 130mmHg or less in midlife from 40 years of age onwards [90]. While there is conflicting evidence on the impact of blood pressure control in late life, hypertension is an important risk factor for dementia and needs to be targeted in brain health clinics.

6.1.2. Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrythmia worldwide, with an increase in prevalence after 65 years of age [198]. Recent studies have shown that AF increases the risk of all cause dementia [199-202] and that this increase remains significant when adjusted for cerebrovascular clinical events [203].

Mechanisms linking AF to dementia risk independent of stroke include altered cerebral blood flow dynamics (cerebral hypoperfusion as a result of diastolic dysfunction and extreme variability in distal cerebral perfusion due to both arteriolar hypoperfusion and capillary hypertension) [204], cerebral microbleeds [205], silent cerebral ischemia [206] and vascular inflammation resulting in damage to the blood brain barrier [207]. These altered vascular hemodynamic favour amyloid protein accumulation and tau phosphorylation in patients with AD [199]. Studies suggest that early rhythm control, particularly with ablation improve cognitive function and reduce dementia risk [208] while AF patients prescribed direct acting oral anticoagulants (DOACs) were found to have a lower incidence of dementia than AF patients compared with non-DOAC users [209].

6.1.3. Diabetes

Type 2 diabetes mellitus (T2DM) was highlighted by the Lancet Commission in 2017 as a later life risk factor for dementia. Studies suggest the mechanism behind cognitive decline in older people with diabetes relates to episodes of severe hypoglycaemia, poor glycaemic control [210], inflammation, atherosclerosis, oxidative stress and dysregulation of lipid metabolism [211]. In their 2015 meta-analysis Chatterjee et al found that diabetes was

associated with a 60% increased risk of all cause dementia [212] which was consistent with findings of pervious meta-analyses [213-215].

However, it is acknowledged that distinguishing between treated and un-treated diabetes in observational studies is challenging [90] and the effect of treatment of diabetes on cognitive decline remains unclear. A narrative review of metformin and dementia risk in individuals with T2DM suggested a positive association between metformin use and reduced dementia risk in individuals with T2DM [211]. However, the authors point out that the lack of standardized methodologies and outcome reporting limit accurate comparisons between studies. A Cochrane review found no evidence to support the contention that a specific treatment strategy for T2DM could delay onset of cognitive decline, with moderate quality evidence that there is no impact of intensive glycaemic control over standard care [216]. While there is no consensus on the optimal treatment plan to mitigate dementia risk in those with T2DM, it is a clear risk factor for development of future dementia and therefore should be screened for to guide risk discussions with patients attending memory services.

6.1.4. Hyperlipidaemia

Evidence suggests that high total cholesterol in midlife increases risk of later-life AD [217]. It has been incorporated as a biological metric into cardiovascular risk factor scores in midlife that have shown reduced hippocampal atrophy on neuroimaging and lower dementia risk [218]. Hyperlipidaemia was added to the Lancet Commission for Dementia Prevention's list of modifiable risk factors in 2024 [45] .The association has been linked to the conversion of cholesterol into 27-hydroxycholestrol which has been shown to cross the

blood-brain barrier and promote the deposition of amyloid and tau proteins [219] while LDL-mediated neuronal cell death has also been implicated [220].

A 2023 meta-analysis which included 1.2 million participants found midlife (under 65 years) hyperlipidaemia (defined as any of total cholesterol, LDL, HDL, or triglycerides higher than the normal range on a blood test) to be associated with an increased incidence of MCI and all cause dementia, with each 1mmol/L increase in LDL associated with an 8% increase in incidence of all cause dementia [220]. Despite this a previous Cochrane review of 2 RCTs reported that statin use in older persons (over 70 years of age) at risk of cognitive decline or dementia had no protective effect [221]. However, the association of statin use in midlife with dementia reduction has yet to be fully evaluated.

6.1.5. Smoking

The association between smoking and cognitive impairment may be due the increased risk of vascular disease and endothelial damage and cigarette smoke as a source of oxidative stress damage resulting in neurotoxicity [222]. The high prevalence of smoking worldwide results in its high population attributable risk and both a public health and individual patient approach will be required to address this modifiable risk factor.

6.2. Methodology

The data collection process is outlined in Chapter 4 for the patient cohort described in Chapter 5.

6.2.1. Defining Hypertension

Blood pressure was measured as described in Section 4.3.6.2 and a known history of hypertension was recorded as described in Section 4.3.1. A blood pressure reading of ≥130mmHg systolic or ≥85mmHg diastolic was considered abnormal as per European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines [223]. Patients with this one-off reading were referred for 24hr ambulatory blood pressure monitoring. Patients attending the brain health clinic were stratified into the following four distinct groups based on their one off blood pressure reading and their medical history.

1. Existing diagnosis of hypertension with adequately controlled blood pressure
2. Existing diagnosis of hypertension with inadequately controlled blood pressure
3. No previous diagnosis of hypertension with abnormal blood pressure
4. No previous diagnosis of hypertension with normal blood pressure

6.2.2. Defining Hyperlipidaemia

Non-fasting blood samples were taken on the day of each patient's initial assessment in the brain health clinic. As reported by the ESC hyperlipidaemia guideline, non-fasting samples have at least the same prognostic value as fasting samples in general risk screening [224]. Hyperlipidaemia was defined as an LDL >3.0 mmol/L. Again, patients were stratified into four groups based on their hyperlipidaemia status and previous diagnosis as outlined below.

1. Existing diagnosis of hyperlipidaemia with a controlled LDL <3.0 mmol/L
2. Existing diagnosis of hyperlipidaemia with an uncontrolled LDL >3.0 mmol/L
3. No previous diagnosis and LDL >3.0 mmol/L
4. No previous diagnosis and normal LDL.

6.2.3. Diabetes

Patients' history of diabetes was documented in the brain health clinic database. This was obtained from their medical history as recorded at their brain health clinic appointment. Patients had their HbA1c level measured as part of their clinical blood testing. Fasting glucose was not measured. The ESC guidelines for treatment of diabetes in cardiovascular disease [225] quotes the WHO criteria for diagnosis of diabetes and pre-diabetes [226]; a diagnosis of pre-diabetes is defined by a HbA1c of 42–47.9 mmol/mol and diabetes defined by a HbA1c ≥48 mmol/mol. A target of HbA1c < 53 mmol/mol was cited in the ESC guidelines for patients with a diagnosis of type 2 diabetes. Patients were again broken down into the following groups based on their medical history and their HBA1c values:

1. No history of diabetes, HbA1c <42 mmol/mol (normal)
2. No history of diabetes, HbA1c 42-47.9 mmol/mol (pre-diabetes)
3. No history of diabetes, HbA1c ≥48 mmol/mol (potential new diagnosis of diabetes)
4. History of diabetes, HbA1c <53 mmol/mol (within target range)
5. History of diabetes, HbA1c >53mmol/mol (sub-optimal HbA1c)

6.2.4. BMI

Every patient attending clinic had their BMI recorded as outlined in Section 4.3.6.1. Patients were classified based on their BMI as outlined in Table 15 below.

Table 15: BMI categories [227].

BMI (Kg/m^2)	**Classification**
<18.5	Underweight
18.5 – 24.9	Normal weight

BMI (Kg/m^2)	Classification
25 – 29.9	Overweight
30 – 34.9	Obesity class I
35 – 39.9	Obesity Class II
≥ 40	Obesity Class III

6.2.5. Smoking status, history of Atrial Fibrillation and Ischemic Heart Disease

Patients were documented as ex-smokers, never smokers or current smokers in the brain health clinic database. Pack year history was not recorded. A previous history of Atrial Fibrillation was recorded, however history of previous ablation, use of rate or rhythm control and whether the atrial fibrillation was permanent or paroxysmal was not included in the database. If patients had a documented diagnosis of ischemic heart disease (IHD) or a history of previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, they were recorded in the database as having a history of IHD.

6.2.6. Statistical Analysis

Data relating to hypertension, hyperlipidaemia, diabetes, BMI, smoking status, history of Atrial Fibrillation and IHD were captured in the Excel database and exported into SPSS version 27. Here frequencies and percentages were calculated to outline the proportion of patients with known cardiovascular risk factors at the time of initial review in the brain health clinic. Individual modifiable risk factors were then examined in greater detail. Blood pressure readings of patients with and without an existing diagnosis of hypertension were analysed to determine the percentage of patients with controlled (BP < 130/85) and

uncontrolled (BP ≥130/85) blood pressure readings. Patients were similarly categorized for hyperlipidaemia and diabetes. Results were tabulated and graphed in Microsoft Excel.

Modifiable vascular risk factor prevalence was compared across cognitive groups (MCI and SMC) and also by AD biomarker status. Either chi-square tests or one-way ANOVA tests were used where appropriate to compare differences in risk factor profile across these groups. A p-value of <0.05 was considered significant.

6.3. Results

The demographic and diagnostic profiles of the 118-patient cohort attending the Brain Health Clinic are documented in Chapter 5. The proportion of these patients who had a known cardiovascular risk factor at the time of attending the brain health clinic is documented in Table 16 below. Of the 118 patients who attended the service, 113 (95.8%) underwent blood tests to measure their random lipid profile and HbA1c.

Table 16: Proportion of patients attending the Brain Health Clinic with a known cardiovascular risk factor

Pre-existing diagnosis of:	**N=118 (%)**
Hypertension	70 (59.3%)
Hyperlipidaemia	81 (68.6%)
T2DM	19 (16.1%)
Atrial Fibrillation	10 (8.5%)
Ischemic Heart Disease	22 (18.6%)
Current Smoker	17 (14.4%)
BMI > 25 kg/m^2	96 (81.4%)

6.3.1. Hypertension

Of the 70 patients attending the brain health clinic with a known diagnosis of hypertension, only 15 of these patients had a blood pressure reading below the 130/85 mmHg cut-off. Of the remaining 48 patients without a diagnosis of hypertension, 20 had a blood pressure reading within the target range, while the remaining 28 patients had a potential new diagnosis of hypertension and met the criteria for referral for 24hr ABPM. This is graphically displayed in Figure 16. When looking at the entire patient cohort, 70.3% of patients attending the brain health clinic had a one-off reading above the blood pressure target of a systolic blood pressure ≤ 130mmHg or a diastolic BP ≤ 85 mmHg.

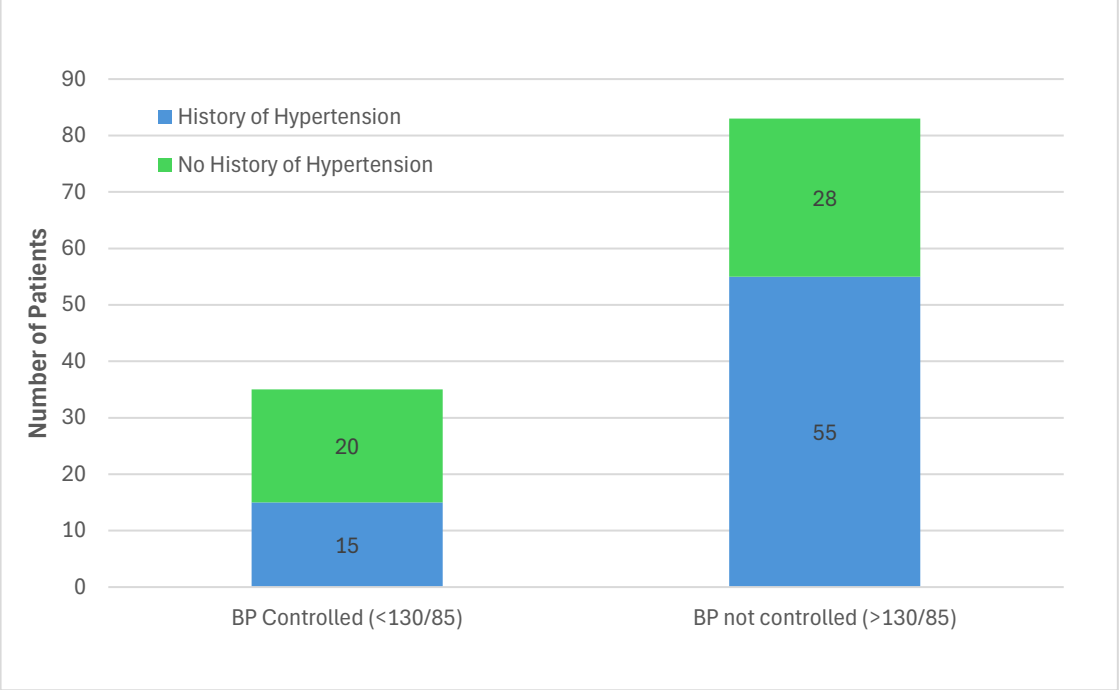

Figure 16: Patients attending clinic with BP measurements indicative of hypertension, stratified by pre-existing diagnosis of hypertension

In total 83 patients met criteria for referral for a 24ABPM, with only nine patients having this test performed at the time of data analysis. Two of these patients had their antihypertensive medications adjusted.

6.3.2. Hyperlipidaemia

Hyperlipidaemia was the most prevalent pre-existing vascular risk factor diagnosed prior to attendance at the brain health clinic with 68.6% of patients having an established diagnosis at the time of their initial assessment. Of the 113 patients who had a lipid profile measured as part of their clinical work up, 77 (68.1%) had a known diagnosis of hyperlipidaemia, while 36 (31.9%) had no prior diagnosis. Of these 113 patients who underwent LDL testing, 25 (22%) had an LDL of > 3, meeting the diagnostic threshold for hyperlipidaemia. Fifteen patients had a previous diagnosis of hyperlipidaemia with suboptimal lipid control, while 10 patients were newly diagnosed. The cohort was split into four groups of patients namely known diagnosis of hyperlipidaemia with either a controlled LDL <3.0 mmol/L or an uncontrolled LDL >3.0 mmol/L, and patients with no previous diagnosis and a raised LDL >3.0 mmol/L or a normal LDL < 3.0 mmol/L. This is graphically illustrated in Figure 17 below.

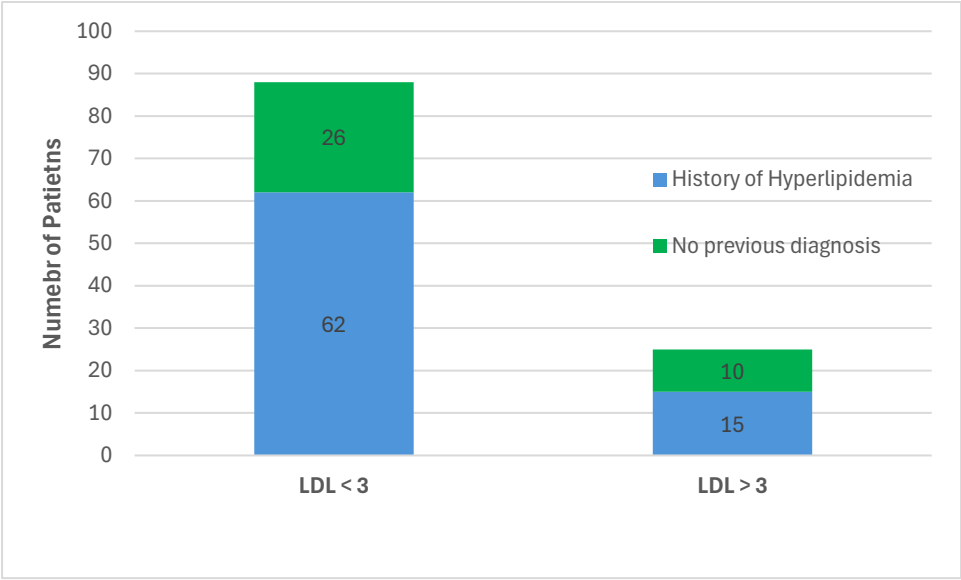

Figure 17: Lipid control in patients with and without a history of hyperlipidaemia

6.3.3. Diabetes

Only 16.1% (n=19) of patients attending the brain health clinic had a pre-existing diagnosis of T2DM. Of these 19 patients, 15 (78.9%) also had a co-existing diagnosis of hyperlipidaemia. Of the patient cohort of 118 patients, 113 had a blood test to measure their HbA1c. All patients (n=19) with a known diagnosis of T2DM having their Hba1c checked. The remaining 94 patients had no previous diagnosis of T2DM. Patients were classified based on their HbA1c results and previous as shown in Table 17 below.

Table 17: Patient groups based on their diabetes status

Diagnosis based on HbA1c	**N (%)**
Known T2DM – HbA1c within target range (<53 mmol/mol)	15 (13.3%)
Known T2DM – HbA1c sub-optimally controlled (>53 mmol/mol)	4 (13.3%)
New diagnosis of pre-diabetes (HbA1c 42-47.9 mmol/mol)	20 (16.9%)
New diagnosis of diabetes (HbA1c ≥48 mmol/mol)	2 (1.8%)
No previous diagnosis, normal HbA1c (<42 mmol/mol)	72 (63.7%)

6.3.4. Smoking status

Patients attending the brain health service were classified as either ex-smokers, never smokers or current smokers as outlined in Table 18.

Table 18: Brain Health Clinic patients grouped by smoking status

Smoking Status	**N (%)**
Ex-Smoker	54 (45.8%)
Never smoker	47 (39.8%)
Current Smoker	17 (14.4%)

The majority of current smokers were female (n=13, 76.5%) while 51.9% of ex-smokers were also female but there was no significant difference in gender across the smoking status patient groups (X^2 1.096, p=0.129). Current smokers were younger (mean age 68.0 years, SD 6.2) than ex-smokers (mean age 72.1, SD 7.8) and never smokers (mean age 70.4, SD 9.4) but this difference was not significant on one-way ANOVA analysis (p=0.191).

6.3.5. BMI

The mean BMI of patients attending the brain health clinic was 29.5 Kg/m^2 (SD 5.6). Patients were classified as underweight, normal weight, overweight based on their BMI and this is shown in Figure 18. Of the 118 patients attending the clinical service, 81.4% (n=96) were either overweight or obese class I-III based on their BMI.

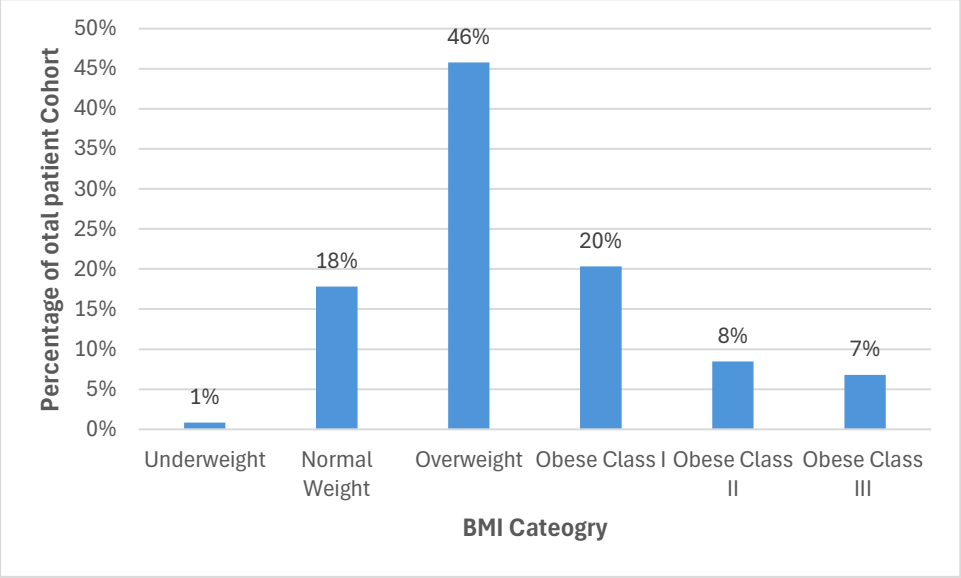

Figure 18: Percentage of Patients per BMI category

6.3.6. Cumulative Cardiovascular risk factors

Cardiovascular risk factor burden is examined in Table 19 below. This shows how many individuals attending the clinical service have a specific number of cardiovascular risk

factors (defined as new or known hypertension, new or known hyperlipidaemia, new or known T2DM, A.Fib, current smoker or BMI in the overweight or obese range).

Table 19: Number of Cardiovascular Risk Factors in Brain Health Clinic Participants

Number of cardiovascular risk factors per person	Frequency n (%)
0	1 (0.8%)
1	13 (11.0%)
2	21 (17.8%)
3	58 (49.2%)
4 or more	25 (21.2%)

Table 20 outlines the number of patients attending the service with specific different combinations of cardiovascular risk factors.

Table 20: Combinations of cardiovascular risk factors identified in patients attending the brain health clinic

Modifiable Cardiovascular Risk Factor combinations	Frequency n (%)
BP >130/85 and BMI >25	67 (56.8%)
Uncontrolled hyperlipidaemia (LDL >3) and BMI >25	21 (17.8%)
Uncontrolled hyperlipidaemia (LDL >3) and BP >130/85	19 (16.1%)
Uncontrolled hyperlipidaemia (LDL >3) and BP >130/85 and BMI >25	16 (13.6%)
Uncontrolled hyperlipidaemia (LDL >3) and current smoker	11 (9.3%)
BP >130/85 and new diagnosis of prediabetes	11 (9.3%)
BP >130/85 and current smoker	10 (8.5%)
BP >130/85 and diabetes diagnosis with HbA1c >53	4 (3.4%)
Uncontrolled hyperlipidaemia (LDL >3) and Pre-Diabetes	3 (2.5%)
Uncontrolled hyperlipidaemia (LDL >3) and BP >130/85 and BMI >25 and currently smoking	2 (1.7%)

6.3.7. Comparison of modifiable cardiovascular risk factors across diagnostic groups

Risk factor profiles of the SMC and the MCI patient groups are compared in the Table 21. Differences in risk factor profiles between patients with positive AD CSF biomarkers are outlined in Table 22 below.

Table 21: Comparison of modifiable cardiovascular risk factors across diagnostic groups

Modifiable Cardiovascular Risk Factor	MCI (n=94) n (%)	SMC(n=24) n (%)	P-value
Current Smoker	12 (12.8%)	5 (20.8%)	0.317
Uncontrolled Hypertension (BP>130/85)	72 (76.6%)	11 (45.8%)	0.003
Pre-diabetes	16 (18%)	4 (16.7%)	0.882
Diabetes – controlled HbA1c	7 (29.2%)	8 (9%)	0.010
Diabetes – poorly controlled HbA1c	1 (4.2%)	3 (3.4%)	0.852
Uncontrolled hyperlipidaemia (LDL >3)	20 (21.3%)	5 (20.8%)	0.864
Overweight or Obese BMI	75 (79.8%)	21 (87.5%)	0.389

Table 22: Comparison of modifiable cardiovascular risk factors by CSF AD biomarker positivity

Modifiable Cardiovascular Risk Factor	Negative CSF AD biomarker (n=28) n (%)	Positive CSF AD biomarkers (n=21) n (%)	P-value
Current Smoker	7 (25.0%)	2 (9.5%)	0.171
Uncontrolled Hypertension (BP>130/85)	21 (75.0%)	14 (66.7%)	0.527
Pre-diabetes	7 (28.0%)	2 (9.5%)	0.120
Diabetes – controlled HbA1c	0 (0.0%)	1 (4.8%)	0.275
Diabetes – poorly controlled HbA1c	1 (4.0%)	1 (4.8%)	0.901
Uncontrolled hyperlipidaemia (LDL >3)	9 (34.6%)	4 (21.1%)	0.327
Overweight or Obese BMI	27 (96.4%)	16 (76.2%)	0.034

6.4. Discussion

This chapter outlines the cardiovascular risk factor profiles of patients attending a brain health clinic. Hyperlipidaemia was identified as the most common cardiovascular risk factor diagnosed in patients prior to attending the clinic, with 68.8% (n=81) patients diagnosed. Hypertension was the second most common pre-existing risk factor (59.3%, n=70) followed by smoking (14.4%, n=17). The mean BMI of patients attending the clinic was at the upper end of the overweight range (29.5 kg/m^2, SD 5.6) with the majority of patients (81.4%) attending the service classified as either overweight or obese.

When comparing risk factors across MCI and SMC patients, patients in the MCI cohort were significantly more likely to have a blood pressure reading above the target of 130/85mmHg ($\chi 2$ =8.598, p=0.003) and significantly more likely to have a pre-existing diagnosis of T2DM with a controlled HbA1c of <53 mmol/mol ($\chi 2$ =6.685, p=0.010). There was no significant difference in smoking status, BMI or hyperlipidaemia across these two diagnostic categories. Risk factor profiles were also compared in patients with MCI who underwent CSF testing for AD biomarkers. Whie there was no significant difference in the prevalence of any cardiovascular risk factor based on AD biomarker positivity, the study is likely underpowered as a result of low and unequal numbers across the groups. The higher rate of prediabetes in the AD biomarker positive MCI cohort (28%) compared to the non-AD MCI (9.5%) cohort, while not statistically significant is noteworthy.

6.4.1. The Potential for Intervention

An additional 10 patients met the criteria for a new diagnosis of hyperlipidaemia based on their LDL blood test result and 15 of the 81 patients with an existing diagnosis were shown

to have poorly controlled hyperlipidaemia. This highlights the potential to improve this risk factor in over 21% (n=25) of the patient cohort attending the brain health clinic by intervening with lifestyle advice or pharmacological therapy. Six of these patients were commenced on or had their existing medication regime changed as a direct result of attending the clinic, with the remainder of patients receiving tailored lifestyle advice. The fact that 65% (11/17) of current smokers also had an LDL ≥3 also emphasized the importance of targeted delivery of lifestyle advise along with pharmacological therapy to this patient cohort, something that was facilitated by the brain health clinic model.

Examining hypertension as a cardiovascular risk factor also highlights the potential for improving known and newly diagnosed cardiovascular risk factors. Of the 70 patients with a known diagnosis of hypertension, 78.6% (n=55) had a one-off blood pressure measurement higher than the target cut-off of ≤130/85 mmHg. A further 28 patients without a diagnosis of hypertension also had blood pressure reading above the 130/85mmHg cut off. Thus, 83 patients (70.3%) met criteria for referral for 24hr ambulatory BP monitoring to investigate this further. However, due to a lack of resources only nine patients had this test performed at the time of data analysis. Two of these patients had their antihypertensive medications adjusted. This data has been used as part of a successful business to purchase blood pressure monitors for use in the brain health service and the rate of referral for 24hr ABPM will be improved as a result.

Most patients attending the service were referred to the RSMC by their general practitioner (GP). The high prevalence of cardiovascular risk factors in this patient cohort highlights that these risk factors had not been identified in primary care despite patients attending their

GP to seek referral to the memory service. Barriers to providing brain health interventions in primary care were discussed in Section 1.1.7.2, with the non-reimbursable nature of preventative health care cited by primary care physicians in the UK as a potential obstacle. This is likely mirrored in general practice in Ireland. A chronic disease management prevention programme exists that enables patients with a diagnosis of cardiovascular disease or diabetes in possession of a medical card or GP visit card to have one yearly review to address their medications and obtain health promotion advice. However screening appointments for those without a diagnosed cardiovascular disease often rely on opportunistic case finding by GPs or practice nurses. This invites consideration around whether there should be a national primary care screening programme for cardiovascular risk factors and prioritisation of preventative health care.

6.4.2. Limitations

There are some limitations that must be considered when interpreting the results around cardiovascular risk factor profiles in this patient cohort. Firstly, not all patients had blood tests taken as part of their assessment therefore for these 5 patients without a recorded LDL and HbA1c, it was not possible to include them in the analysis of diabetic status or lipid control. Secondly while the database captured smoking status it did not capture the number of cigarettes currently smoked or the pack year history of ex-smokers which limits the broader interpretation of smoking status as a risk factor.

While history of atrial fibrillation was captured as a non-modifiable cardiovascular risk factor, it was not specified whether this was permanent or paroxysmal and use of either

rate or rhythm control medication or DOAC use was not recorded. Compliance with an appropriate DOAC therapy and established rhythm control may reduce the risk of subsequent cognitive impairment associated with atrial fibrillation (as outlined in section 6.1.2).

The number of medications and as a result polypharmacy were captured for each patient, the class of medications were not which is another limitation. For patients with a pre-existing diagnosis of hypertension, hyperlipidaemia or T2DM, use of relevant pharmacological therapy, number of agents and compliance with them was not recorded. As a result, it was not possible to stratify patients with a known history of hyperlipidaemia into those managed with medications and those managed using lifestyle advice alone.

Lack of access to 24hr ABPMs was a limitation of the brain health service, and by extension, of this study. Of the 83 patients who met criteria for referral for 24hr ABPM to investigate their elevated one-off blood pressure monitor readings, only 9 monitors had been completed at the time of writing, with two of these patients having their medications adjusted due to confirmation of hypertension >130/85mmHg on their ABPM reading. The lack of timely access to ABPMs will limit the longitudinal results of this study going forward. However it was used to successfully create a business case to purchase additional ABPMs for the service which help the brain health clinic meet the key performance indicator (KPI) of all patients requiring ABPM based on their one-off BP reading having access to this in a timely manner.

6.5. Conclusion

This results chapter highlights the prevalence of cardiovascular risk factors in patients attending a memory service with MCI or SMC. While over 80% of patients with hyperlipidaemia diagnosed prior to their clinical review were found to have an LDL within the target range, 16% of these patients were still smoking highlighting the opportunity for personalized preventative lifestyle advice to augment ongoing management of their lipid disorder. Hypertension with a blood pressure reading of >130/85mmHg was the most prevalent risk factor across both the MCI and the SMC patient cohorts. The high prevalence of modifiable cardiovascular risk factors identified in patients attending the Brain health clinic highlight the potential impact of personalized preventative medicine in this patient cohort, and the need for thorough investigation of cardiovascular risk factors in patients attending a memory service. This can be facilitated by the brain health clinical model outlined in this study.

Chapter 7. Results: Sensory impairment and its prevalence among patients attending a Brain Health Clinic

7.1. Introduction

There is a growing body of evidence to support the association between sensory impairment and dementia risk [228-230]. Hearing impairment was identified by the first Lancet Commission on dementia prevention in 2017 as a modifiable risk factor for dementia, with the largest population attributable fraction of 8%, the largest of any of the initial nine modifiable risk factors identified [231]. In July 2024 the Lancet Commission on Dementia Prevention updated their previous list of modifiable risk factors to include untreated visual loss as a late-life modifiable risk factor for dementia with a 2% population attributable fraction [45].

7.1.1. Untreated Visual Loss

On a global scale, over 2.2 billion people have a visual impairment, while the WHO estimate that only 36% of people with visual impairment due to a refractive error and only 17% of people with impaired vision secondary to cataracts have received appropriate intervention [232]. Advancing age is a risk factor for cataracts, age related macular degeneration (ARMD) and glaucoma and consequently the prevalence of avoidable vision loss and blindness increases with increasing age. Research over the last number of years indicates that there is an association between untreated visual loss and risk of dementia, with this risk potentially mitigated by appropriate corrective treatment [45].

Two recent meta-analyses have looked at the association between vision loss and dementia in prospective studies [233, 234]. In their meta-analysis of 12 prospective cohort studies, Shang et al showed a relative risk associated with incident dementia was 1.35 (95% CI, 1.28-1.41) [234]. Kuzma et al also found visual loss was associated with an increased risk of all cause dementia in their meta-analysis. This was further subdivided into different causes of visual loss with cataracts and diabetic retinopathy shown to be associated with an increased dementia risk [233]. A prospective UK biobank study also found an increased dementia incidence in patients with cataracts, but there was no significant reduction in those who had cataract surgery [235]. A US longitudinal study of adults over 65 years with cataracts did find a significantly reduced dementia risk in patients who had their cataracts removed when controlling for age, educational attainment and APOE status among other comorbidities [236].

7.1.2. Hearing Loss and the use of Hearing Aids

It is estimated that 20% of the global population has some degree of hearing loss, with the majority (62%) over 50 years of age [237]. This hearing loss is often left untreated. There are multiple mechanisms hypothesized to link hearing loss and incident dementia. The fact that a longer exposure to hearing loss results in a greater dementia risk suggests a causal link between hearing loss and dementia incidence [45]. Two possible mechanisms explored by Griffiths et al [238] are outlined in Figure 19. The first mechanism suggests a “common cause”, with AD or vascular pathology building up in both in the medial temporal lobe and also the auditory pathways in the ascending auditory nuclei, the auditory cortex and the cochlea itself resulting in both hearing loss and cognitive impairment. The second mechanism suggests that untreated hearing loss and subsequent auditory deprivation and

diminished language input results in reduced stimulation of the cognitive domains of the brain and subsequent alteration of brain structure and function. This impaired sensory input can also lead to reduced social interaction, social isolation and loneliness which are themselves risk factors for dementia which will be explored in Chapter 8.

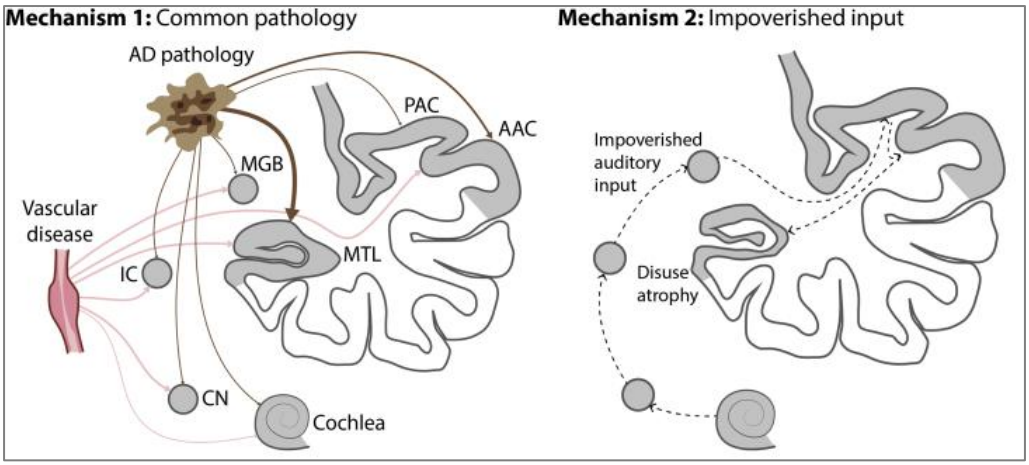

Figure 19: Proposed mechanisms linking hearing loss and dementia [229]. IC (inferior colliculus), MGB (Medial geniculate body), MTL (medial temporal lobe), PAC (primary auditory cortex), AAC (auditory association cortex).

A third proposed mechanism linking hearing loss and dementia proposes that those with reduced hearing use greater cognitive resources (working memory, language processing and attention) when listening and as a result decreases cognitive resources available for other activities, meaning people with hearing loss are required to dual-task which leaves limited resources for other cognitive tasks [238].

There have been multiple meta-analyses which report a significant association between hearing loss and subsequent dementia [239-243]. There is also evidence to suggest that there is a dose-dependent relationship between hearing loss and dementia risk, with one study showing that risk increases by 16% with every 10 dB reduction in hearing [239]. There

is consistent evidence indicating that the use of hearing aids is a protective factor against developing dementia [244, 245]. One retrospective longitudinal study of over 1,000 people with hearing loss and MCI not only showed a significantly lower risk of developing dementia in those who wore hearing aids, but also a 2 year delay in developing dementia in the people who used hearing aids compared to those who did not [246]. Screening for hearing loss and correcting this with hearing aids presents an opportunity for cost effective intervention.

7.1.3. Dual sensory impairment – vision and hearing loss

When considering sensory impairment, it is important to consider not just the effect of isolated hearing or visual impairment but to explore the role of dual sensory impairment and dementia risk. Several longitudinal studies have suggested dual sensory impairment infers a greater risk of developing dementia than either visual impairment or auditory impairment alone [247-250]. While these studies are observational in nature, differ in their methodology and some rely on self-reported visual and hearing impairments, they imply strong observational evidence for the important role dual sensory impairment may play in the development of dementia. This highlights the importance of screening for both hearing and visual impairment in patients attending a memory service.

7.2. Methodology

Vision and hearing were assessed in the brain health clinic using the Peek Acuity smartphone app and the Siemens HearCheck^{TM} Screener respectively. The details of these devices and the steps taken to preform vison and hearing screening tests using them are outlined in the methodology chapter Section 4.3.6.3 and Section 4.3.6.4. Results were

recorded prospectively in the brain health clinic database. Patients' vision was classified as normal, mild visual impairment, moderate visual impairment, severe visual impairment or blindness based on the Peek Acuity results as outlined in *Table 11* on page 104. The LogMAR score for the more impaired eye was used to classify visual impairment status. Results of the HearCheck™ screening test were recorded for each ear. The scoring grid in Figure 12 on page 106 was used to determine if the results for each ear indicated a positive screening test.

Data was recorded in the Excel database and imported to SPSSv27 for analysis. Frequencies and percentages were calculated to highlight the prevalence of ICD-11 categories of visual impairment and to show patients with a positive HearCheck™ screen indicating possible hearing impairment. Patients referred onwards for formal audiology testing were recorded in the database. Risk Factor prevalence between SMC and MCI patients, and also AD and non-AD biomarker positive patients were compared using chi square tests, t-tests or Mann Whittney U tests where appropriate. A p-value <0.05 was considered significant.

7.3. Results

7.3.1. Assessments performed

Not every patient underwent hearing and vision assessments in the brain health clinic. As a result, there was some missing data when evaluating sensory risk factors. Table 23 shows the numbers (and percentages) of patients who underwent sensory assessments as part of their clinical evaluation.

Table 23: Sensory data captured during Brain Health Clinic Assessments

Assessments performed in clinic (n=118)	**n (%)**
Hearing Assessed in clinic	92 (78.0%)
Vision assessed in clinic	90 (76.3%)
Both vision and hearing assessed	74 (62.7%)
Glasses wearers	78 (66.1%)
Wear glasses and vision checked in BHC	60 (76.9%)
Hearing aid use	20 (16.9%)
Wear hearing aids and hearing checked in BHC	2 (10.0%)

The demographic profile of patients who had hearing, visual and both hearing and auditory assessments performed are outlined in Table 24.

Table 24: Demographic and diagnostic profiles of patients who had sensory assessments carried out in the brain health clinic

Demographic and diagnostic profiles	**Hearing Checked (n=92)**	**Vision Checked (n=90)**	**Vision & Hearing Checked (n= 74)**
Age in years (median, IQR)	70.1 (64.3 – 76.3)	71.9 (65.5-77.1)	70.0 (62.8 – 76.8)
Female (n, %)	59 (64.1%)	59 (65.6%)	50 (67.6%)
Socio-economic Status (n, %):			
- Very Affluent	5 (5.4%)	5 (5.6%)	5 (6.8%)
- Affluent	11 (12.0%)	8 (8.9%)	7 (9.5%)
- Marginally above average	37 (40.2%)	35 (38.9%)	29 (39.2%)
- Marginally Below average	22 (23.9%)	25 (27.8%)	20 (27.0%)
- Disadvantaged	11 (12.0%)	10 (11.1%)	8 (10.8%)
- Very Disadvantaged	6 (6.5%)	7 (7.8%)	5 (6.8%)
Diagnosis (n, %)			

Demographic and diagnostic profiles	Hearing Checked (n=92)	Vision Checked (n=90)	Vision & Hearing Checked (n= 74)
- MCI	69 (75%)	71 (78.9%)	56 (75.7%)
- Amnestic (n)	53	57	43
- Multidomain impairment	47	50	38
- SMC	23 (25%)	19 (21.1%)	18 (34.8%)
- CSF for AD biomarkers done	35 (38.0%)	35 (38.9%)	26 (35.1%)
- Positive AD biomarkers	17	15	11
- Negative AD biomarkers	18	20	15

7.3.2. Vision Screening

Patients' vision was classified based on the LogMAR score in their most impaired eye. The majority of patients (n=76, 84%) fell into the normal vision category while no patients met the criteria for severe visual impairment or blindness (see Figure 20).

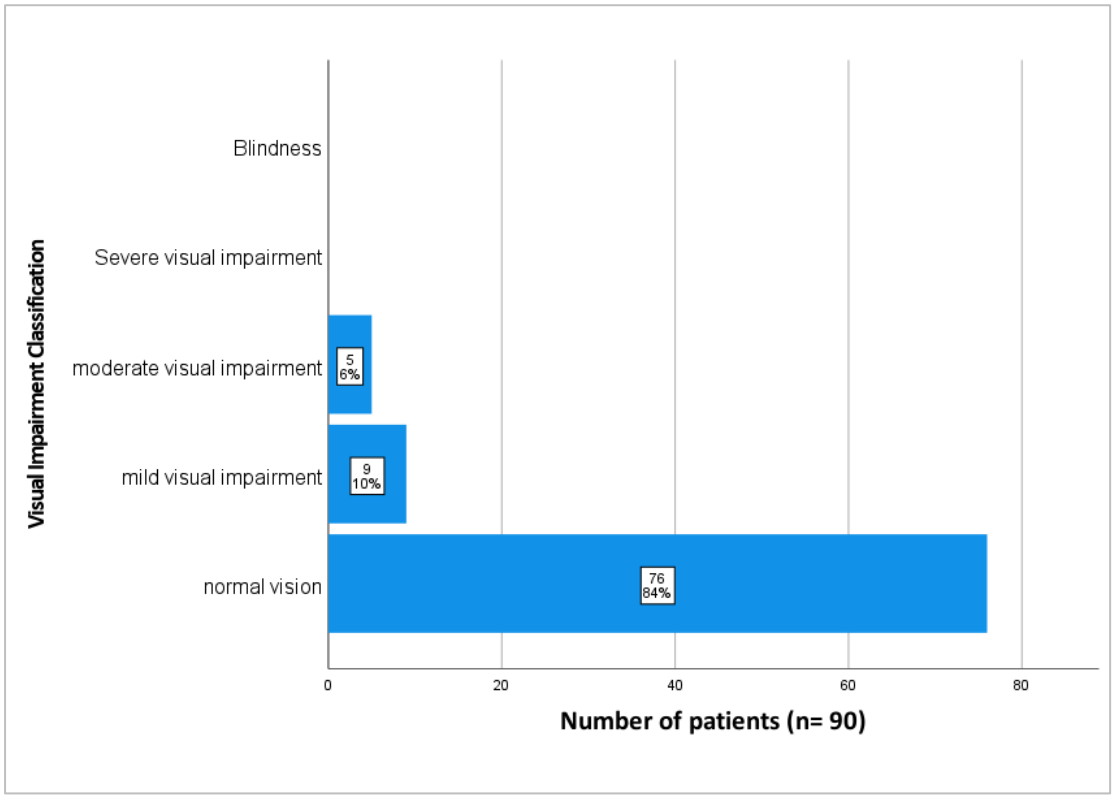

Figure 20: Prevalence of visual impairment based on PeekAcuity LogMAR score

It is important to note visual assessments were performed using the patients' own glasses where appropriate. Table 25 below breaks down the visual impairment categories by whether or not patients had a known visual impairment (i.e. if they are glasses wearers or not). This highlights that of the n= 14 patients with either a mild or moderate visual impairment on screening, 6 (45.7%) were wearing glasses.

Table 25: Visual classification broken down by pre-existing known visual impairment or not

Visual classification	**Glasses wearers (n=60)**	**No glasses (n=30)**
Normal vision (n)	54	22
Mild visual impairment (n)	5	4
Moderate visual impairment (n)	1	4

7.3.3. Hearing Screen

As described in the methodology section above, the Siemens HearCheck^{TM} Screener was used to group patients into a positive or negative screening test. Patients with a positive screening test met criteria for formal audiology referral. Of the 92 patients who underwent hearing screening, 30 (32.6%) had a positive test. Referral for formal audiology testing was sent for 27 of these patients. The results of the hearing screening are show in Figure 21.

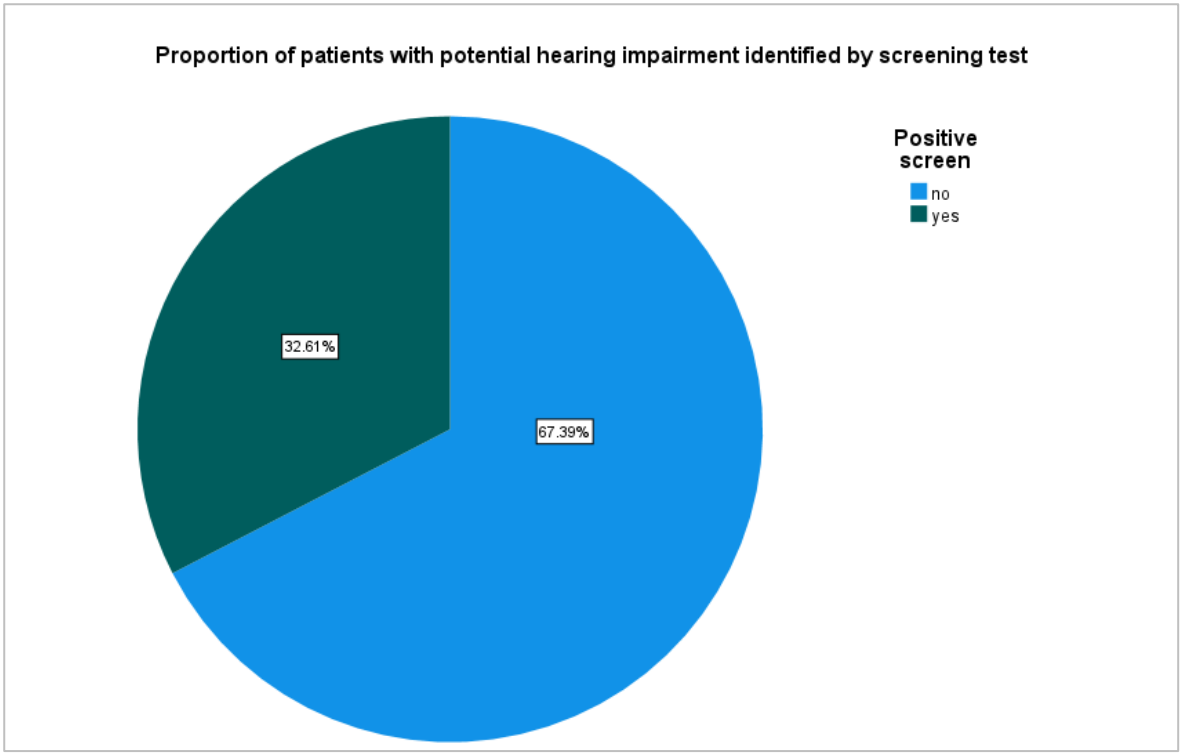

Figure 21: Patients identified as having a possible hearing impairment

Patients who had a positive hearing screen are compared with those who did not in terms of their demographic and diagnostic profiles. This comparison can be seen in Table 26.

Table 26: Demographic and diagnostic profiles of patients based on their hearing screen results

Demographic and diagnostic details	**Positive hearing screen (n=30)**	**Negative hearing screen (n=62)**	**Significance test, P-value**
Age (median, IQR)	72.9 (67.7 – 78.8)	68.7 (61.9 – 74.9)	Mann-Whitney U 557.0, p=0.002
Female gender (n, %)	24 (80.0%)	35 (56.5%)	X^2 4.874, p=0.027
Diagnosis			
- MCI	24 (80%)	45 (72.6%)	X^2 0.594, p=0.441
o Amnestic	18	35	
o Multidomain Impairment	15	32	
- SMC	6 (20%)	17 (27.4%)	
Patients who underwent CSF testing	9 (30%)	26 (41.9%)	
Confirmed AD pathology	5	12	X^2 0.237, p=0.627

The distribution of socioeconomic class in the positive and negative hearing screen groups is outlined in Figure 22. When socio-economic status was compared across both groups there was no significant difference between those with a positive screen (indicating a potential hearing impairment) and those with a negative screen (indicating normal hearing) (X^2 3.627, p=0.604).

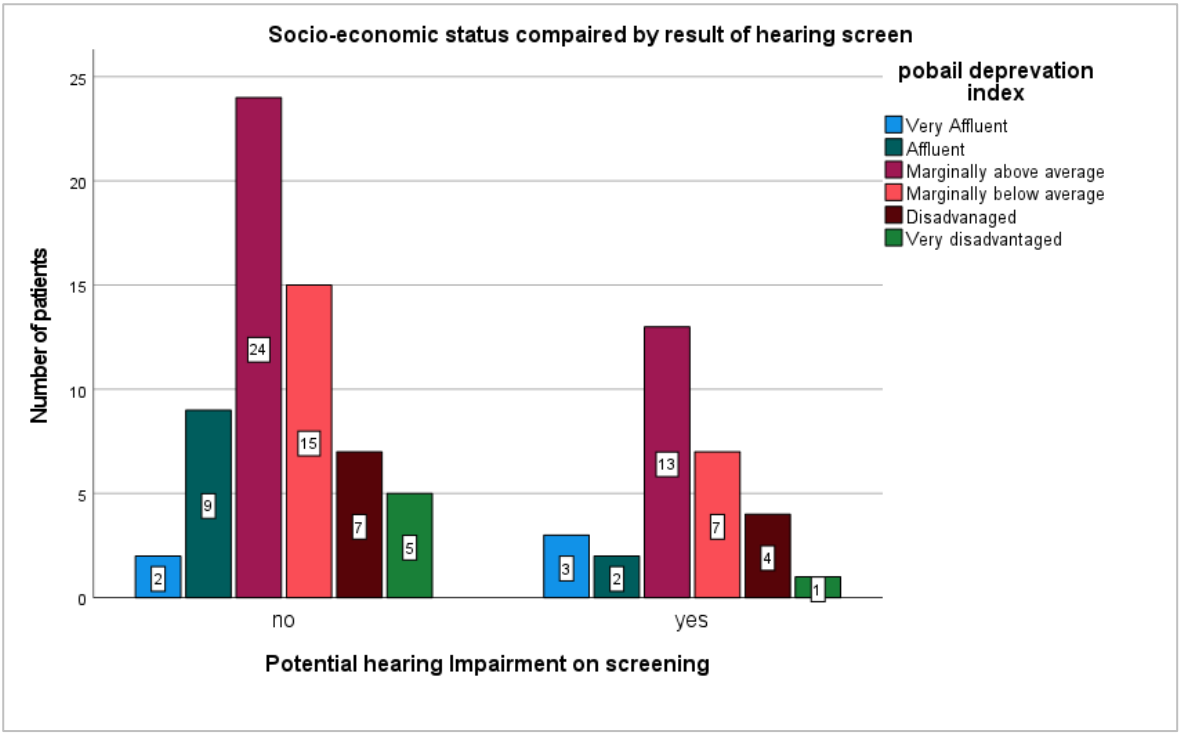

Figure 22: Distribution of Pobail deprivation index classes across patients with and without positive hearing screen

7.3.4. Dual sensory impairment

Of the 118 patients in this brain health clinic cohort, 74 patients underwent both hearing and vision screening checks. Of these 74 patients, 6 (8.1%) could be classified as having dual sensory impairment; meaning they had a positive hearing screen and either mild visual impairment (n=3) or moderate visual impairment (n=3) on their PeekAcuity visual screen.

7.3.5. MCI vs SMC

The prevalence of sensory impairments (in those who underwent testing) was compared across both the SMC and the MCI patient groups. In total 19 patients with SMC and 71 patients with MCI underwent vision assessment using the PeekAcuity App while 23 patients with SMC and 69 patients with MCI had their hearing screened. Both vision and hearing assessments were carried out on 18 SMC patients and 56 MCI patients. These numbers of

patients in each cohort who underwent sensory testing are used to calculate the percentages in the Table 27 below.

Table 27: Sensory impairments across MCI and SMC patient cohorts

Sensory Impairment	MCI n (%)	SMC N (%)	Significance test, P-value
Mild or moderate visual impairment	14 (19.7%)	0 (0.0%)	X^2 4.437, p=0.109
Positive HearCheck™ Screen	24 (34.8%)	6 (26.0%)	$X^2$0.594, p=0.441
Dual sensory impairment	6 (10.7%)	0 (0.0%)	$X^2$2.099, p=0.147

7.4. Discussion

7.4.1. Risk Factor Prevalence

This chapter highlights the prevalence of sensory impairment in patients attending a brain health clinic. Potential hearing impairment highlighted by the screening tool used during the clinical assessment was more prevalent than any degree of visual impairment (32.6% vs 16%). The prevalence of dual sensory impairment was 8.1% of all patients tested (n=74). There was no significant difference in the prevalence of sensory risk factors between the MCI and the SMC patient cohorts. Among patients who underwent CSF testing for AD pathology, there was no significant difference in hearing in those with AD pathology vs those who had negative AD biomarkers.

The higher prevalence of hearing impairment compared to visual impairment may reflect the fact that people delay seeking assessment for subjective hearing loss, and those that

do tend to delay the adoption of hearing aids once their use has been advised [251] . This may be due to several factors including cost barriers, comfort and social embarrassment. Almost one third of patients in this cohort met the criteria for referral for formal audiological assessment to investigate a potential hearing loss. This highlights a significant unmet need in this patient cohort and emphasises the importance of a brain health clinic to screen for and address modifiable risk factors in patients with cognitive impairment.

There was a much larger proportion of glasses wearers compared to hearing-aid users in this study (66.1% vs 26.9%). People already using corrective lenses are more likely to engage in regular vision assessments than those who do not [252] which may explain the lower prevalence of new/undertreated visual impairment in this cohort. Of the 14 patients who were identified as having mild or moderate visual impairment, 6 were known glasses wearers. This again highlights the importance of encouraging regular vision and hearing checks in patients with and without a known visual impairment.

7.4.2. Limitations

The main limitation of the analysis into sensory risk factor prevalence in this brain health clinic patient cohort is the presence of missing data. While attending the brain health service, 23.7% (n=28) of patients did not have their vision assessed using the PeekAcuity app and 22% (n=26) did not have their hearing screened. The cohort of patients who underwent screening is similar in age profile (median age of the overall patient cohort 71.9 years vs 70.0 years in those who underwent both vision and hearing screen) while there were marginally more females in the patient cohort who underwent sensory assessments in clinic (61% female in the total patient cohort vs 67.6% female in patient cohort who

underwent both vision and hearing screen). The breakdown of MCI vs SMC patients in the total patient cohort is also largely similar to the patients who underwent sensory screening (79.7% MCI in the total cohort vs 75.7% MCI in the subset of patients who had both hearing and vision assessed).

Specific reasons for not pursuing screening were not documented at the time of assessment and will be a focus of quality improvement for this service going forward. Only 2 of the 20 patients who wore hearing aids at baseline had their hearing screened which was a missed opportunity to ensure the corrective measures in place for hearing loss were working appropriately. This is particularly important as adequate correction of hearing loss using hearing aids has been shown to be protective in terms of dementia onset in patients with hearing loss [246]. While 20 patients were documented as hearing aid-users, compliance with hearing aid use was not further investigated. It is known that hearing aid compliance is an issue among patients with a diagnosed hearing impairment with one meta analyses reporting a significant proportion of patients (38%) to be non-compliant with hearing aid use [253]. It is important that as the brain health service evolves hearing aid compliance is explored, potential reasons for non-compliance addressed and patients educated on the protective benefits of hearing aid use.

7.5. Conclusion

This chapter highlighted the importance of screening for sensory risk factors in patients with memory complaints. Potential hearing loss was more prevalent than visual impairment. As the brain health service evolves it will be important to longitudinally follow

patients identified as having potential hearing loss by the HearCheck^{TM} screening tool and investigate how many underwent formal audiology testing, how many were prescribed hearing aids and how many comply with this treatment.

Chapter 8. Results: How prevalent are lifestyle factors including exercise, poor sleep, social isolation and alcohol intake among patients with MCI and SMC?

8.1. Introduction

This chapter focuses on lifestyle risk factors which have been linked to the development of cognitive impairment. Physical activity levels, sleep quality, dietary and alcohol intake along with depression, loneliness and social isolation are all discussed here. The prevalence of these risk factors in the population of patients attending a brain health clinic is investigated.

8.1.1. Levels of Physical Activity

Strong evidence suggests exercise reduces dementia risk. As far back as 2006, a large US longitudinal study followed 1,740 people over 65 years of age without a cognitive impairment for 6 years and found that the incidence of dementia was 50% higher among those who exercised less than 3 times per week compared to those who exercised 3 or more times [254]. Further large observational studies suggest that physically active individuals appear less likely to develop vascular dementia, Alzheimer's disease dementia and cognitive decline compared to inactive individuals [255-257]. It appears that the grater the level of physical activity a person is involved in, the greater the protective effect [258].

The mechanism by which physical activity reduces dementia risk is multi-modal with both direct and indirect effects at play. Regular exercise contributes to several pathways that affect brain health during ageing. Rovio et al demonstrated a reduction in brain atrophy in persons who participated in physical activity in midlife [259]. Exercise has been shown to

increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, subsequently activating molecular and cellular cascades that promote brain plasticity through vascularisation, neurogenesis and improved neuronal resistance to injury [260]. Regular physical activity also has a positive effect on cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes, obesity) which themselves increase dementia risk as discussed in Chapter 6. Furthermore, physical activity particularly in a group setting can improve social interaction and reduce loneliness which have been linked to dementia and will be discussed further in Section 8.1.5.

The 2019 WHO guidelines for risk reduction of cognitive decline and dementia advise that physical activity should be recommended to adults with normal cognition to reduce the risk of dementia [261]. These guidelines suggest that adults aged 65 years and above should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or engage in at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate and vigorous-intensity activity. Incorporating the measurement of physical activity levels in a brain health clinic can help patients to self-identify current levels of activity and set out personalised goals to increase their exercise levels in line with the WHO guidelines.

8.1.2. Sleep

Sleep is described by the Lancet Commission as a potentially modifiable risk factor, and while it was not included in their 2024 report, there is some evidence to suggest a link between poor sleep quality and cognitive decline [262]. There is a bi-directional relationship between poor sleep and dementia. Sleep disturbances such as rapid eye

movement sleep behaviour disorder (RBD), periodic limb movement syndrome (PLMS), restless leg syndrome (RLS), insomnia, excessive daytime sleepiness and sleep related breathing disorders are common symptoms of various neurodegenerative disorders [263]. This is due to neurodegenerative processes directly effecting areas of the brain responsible for regulating the sleep-wake cycle. On the other side of this bi-directional relationship disordered sleep may exacerbate neurodegeneration as a result of increased oxidative stress, reduced memory consolidation and impaired clearance of toxic proteins via the glymphatic system [264].

There is also emerging evidence that sleep apnoea may increase dementia risk. Obstructive sleep apnoea (OSA) is a commonly occurring disorder affecting breathing during sleep that is characterized by repeated upper airway obstruction and resultant hypoxia, hypercapnia and heightened sympathetic nervous system activation [265]. OSA results in fragmented, disturbed sleep which often decreases the time spent in REM sleep. Potential mechanisms linking OSA to cognitive decline included sleep fragmentation, sleep deprivation and excessive daytime somnolence resulting in decreased attention and slowing of cognitive processing along with a disruption to the restorative sleep process itself [266]. A systematic review of 11 studies found that those with sleep apnoea had an increased risk of developing any type of neurocognitive disorder, with one study reporting a two-fold increased risk for dementia with Lewy bodies (LBD). There was no significant association between sleep apnoea and vascular dementia, while no studies looked at frontotemporal dementia risk [267]. This highlights the need to screen for undiagnosed and untreated OSA in memory services.

8.1.3. Alcohol intake

Excessive alcohol intake (>21 units per week) is listed as a mid-life modifiable dementia risk factor by the Lancet Commission on Dementia Prevention [45]. The WHO guidelines for dementia risk reduction advocate for interventions that reduce hazardous and harmful drinking in adults with normal cognition or MCI to reduce the risk of cognitive decline or dementia [261]. A systematic review of 28 studies found that heavy alcohol use was associated with an increased risk of all cause dementias and a reduction in brain volume [268].

A U-shaped or J-shaped dose response relationship between alcohol intake and cognitive performance has been reported in observational studies. This implies that not drinking is associated with increased dementia risk when compared with light drinking [269, 270]. However, as a result of methodological limitations in many of observational studies and the inclusion of ex-heavy drinkers in the non-drinker groups, the Lancet Commission found that there is insufficient clear evidence to support the theory that not drinking alcohol is associated with increased dementia risk [45].

The WHO advocates for behavioural and psychological interventions to achieve reduction in alcohol consumption in those with harmful drinking habits. Screening for excessive consumption followed by a brief intervention in a primary care setting has been shown to be a cost-effective method of reducing alcohol-associated morbidity [271]. Exploring patients' alcohol consumption in a brain health clinic and initiating a conversation around risk and potential methods to reduce consumption could have similar positive effects on dementia risk and overall general health.

8.1.4. Diet

Mediterranean-like diets include the Dietary Approaches to Stop Hypertension (DASH) diet [272] and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet [273]. The 2019 WHO guidelines on risk reduction of cognitive decline and dementia made a conditional recommendation based on moderate quality evidence for a Mediterranean-like diet for adults with MCI and normal cognition to reduce the risk of cognitive decline and/or dementia [261]. The Lancet Commission on Dementia Prevention highlight the challenges involved in researching the impact of specific diets on dementia prevalence, with observed effects potentially related to lifestyle factors linked to a person's diet [45].

Studies examining the association between Mediterranean dietary patterns and cognitive decline or dementia have shown mixed results. A Swedish prospective cohort study of 28,025 midlife participants reported that a modified Mediterranean diet was not associated with a decreased risk of developing all cause dementia [274]. However previous meta-analyses have reported a protective effect of the Mediterranean diet against cognitive decline [275, 276] while a US cohort study of 581 older adults (mean age 84.2) found that adherence to a Mediterranean diet was inversely correlated with beta-amyloid and p-tau burden at post mortem [273].

Intervention RCTs looking at the impact of dietary interventions on cognitive decline have also had varying results. An RCT looking at the MIND diet versus a control diet in cognitively unimpaired participants showed the primary and secondary outcomes (changes to cognition and MRI changes from baseline) did not differ between the trial groups at a 3-year follow-up period [277]. While trials looking at dietary interventions to reduce cognitive

impairments have not shown significant results, compliance with a diet rich in leafy green vegetables and fruit and low in processed foods is likely to have a positive effect on health conditions which impact vascular risk factors such as diabetes, hyperlipidaemia, hypertension and obesity.

8.1.5. Loneliness, Social Isolation and Depression

8.1.5.1. Loneliness and Social Isolation

Loneliness and social isolation are separate but interconnected concepts. Loneliness is can be defined as a subjective, complex set of feelings encompassing reactions to the absence of intimate and social needs which can be transient or chronic [278]. Loneliness is often thought of as a disparity between the social interactions one desires and those actually experienced. Social isolation refers to the objective absence of contacts between a person and a social network [279]. Both are associated with a broad range of adverse health outcomes including depression and cardiovascular health [280].

There is consistent evidence to suggest that less frequent social contact is associated with a higher risk of dementia [281-283]. Loneliness was also linked with an increased dementia risk in three separate studies [284-286], with one study finding the association was still present following adjustment for confounders such as poor social contacts [284]. It is however important to recognise that loneliness, social isolation and a lack of social contacts may be a symptom of early cognitive decline rather than a cause of it. To minimize the risk of reverse causation studies should incorporate a long interval between the measurement of social engagement and the assessment of dementia and should exclude participants with a known cognitive impairment [287]. It is thought that social contact affects dementia risk

by enhancing cognitive reserve through mental stimulation. Better social health has been linked to increased frontal, temporal and hippocampal grey matter volumes [288].

There is some suggestion that regular contact with others promotes better health behaviours which can reduce cardiovascular risk. An Ecuadorian longitudinal study found an increased progression of while matter hyperintensities in older adults with poor social relationships [289]. However, this must be interpreted within a cultural context, with social interactions in many settings accompanied by smoking and excessive alcohol consumption which would negate cardiovascular health benefits.

8.1.5.2. Depression

Depression is listed as a mid-life modifiable risk factor by the Lancet Commission on Dementia Prevention [90]. Similarly to loneliness and social isolation, dementia can be a symptom of the prodromal stage of early dementia and as a result reverse causation must again be considered when looking at it as a risk factor. It is likely that there is a bi-directional relationship between dementia and depression. The exact mechanism linking subsequent dementia risk and depression is unknown, but it has been linked to loneliness, social isolation and as a result reduced cognitive stimulation. Other pathophysiological theories include excess cortisol leading to hippocampal atrophy, inflammatory changes, increased amyloid plaque deposition and deficits of nerve growth factors [290].

A meta-analysis included in the Lancet Commission 2024 report included seven studies with a 10-14 year follow-up period and concluded that people with a depression were at an increased risk of developing dementia over those without depression [45]. It was noted

that in later life some of this association may be caused by a prodromal dementia syndrome. This led to its being classified as a mid-life risk factor.

8.2. Methodology

8.2.1. Risk Factor Assessment

Lifestyle risk factors were screened for during the initial patient visit at the brain health clinic. Measurement tools used to quantify these risk factors have been described in Chapter 4.

8.2.1.1. Physical Activity Levels

Physical activity levels were explored using the IPAQ described in Section 4.3.5.1. Patients were grouped based on their IPAQ score in MET minutes/week into low, moderate or high levels of physical activity as outlined in Table 10 on page 100.

8.2.1.2. Sleep

Sleep quality was measured using the PSQI (see Section 4.3.5.3) and patients were also screened for OSA using the Epworth Sleepiness Scale (see Section 4.3.5.4). A global PSQI score > 5 was considered indicative of poor sleep quality [163] and the prevalence of poor self-reported sleep quality in this patient cohort was calculated based on this PSQI cut off. An Epworth score of ≥ 10 was used to characterize EDS [144]. The prevalence of EDS was calculated using percentages and frequencies. The number of patients referred for formal sleep studies was also reported.

8.2.1.3. Alcohol intake and Diet

Alcohol intake was recorded by patients' self-reported intake which was converted to units per week. Patients were grouped into those with excessive alcohol intake (>21 units per week) and low/moderate alcohol intake (1-14 units per week for males and 1-7 units per week for females).

Diet was assessed using the Mediterranean Diet Score Tool (Section 4.3.5.2). The mean Mediterranean diet score for the patient cohort was recorded.

8.2.1.4. Loneliness, Social Isolation and Depression

Loneliness was measured using the UCLA three-item loneliness scale (Section 4.3.5.6). A cut off score of 5 was used, with patients who scored 3-5 were classified as "not lonely" while patients with a score of 6-9 were classified as "lonely" [166]. Social isolation was measured using the Lubben Social Network Scale-6 (Section 4.3.5.7). A cut off score of 12 or lower was used to delineate a patient being "at risk" for social isolation [146]. Frequencies and percentages of each category were calculated, and demographic profiles compared.

Anxiety and depression were screened for using the HADS (Section 4.3.5.5) and patients' history of depression (yes or no) was recorded in the patient database. A cut off score of 8 or above on HADS-A and HADS-D was used to define depression or anxiety. Frequencies and percentages of patients meeting this cut off were calculated and compared to the proportion of the patient cohort with an existing diagnosis of depression/anxiety.

8.2.2. Data processing and statistical analysis

Data was recorded in the Excel database and imported to SPSSv27 for analysis. Frequencies and percentages were calculated to highlight the prevalence of lifestyle risk factors among this population. Comparisons were made between patients in each lifestyle risk factor group (e.g. low, moderate and high physical activity levels) using chi square tests, t-tests, Mann Whittney U-tests, One-Way ANOVA or Kruskal-Wallis test where appropriate. Differences in risk factor profiles between the MCI and SMC patient groups were compared using chi square tests, Mann Whittney U-tests, One-Way ANOVA or Kruskal-Wallis test where appropriate.

8.3. Results

8.3.1. Physical Activity Levels

The majority of patients (n=57, 48.3%) fell into the low activity level category based on their IPAQ score of <600 MET minutes/week. The spread of patients across the three activity levels (low, moderate, high) can be seen in Figure 23.

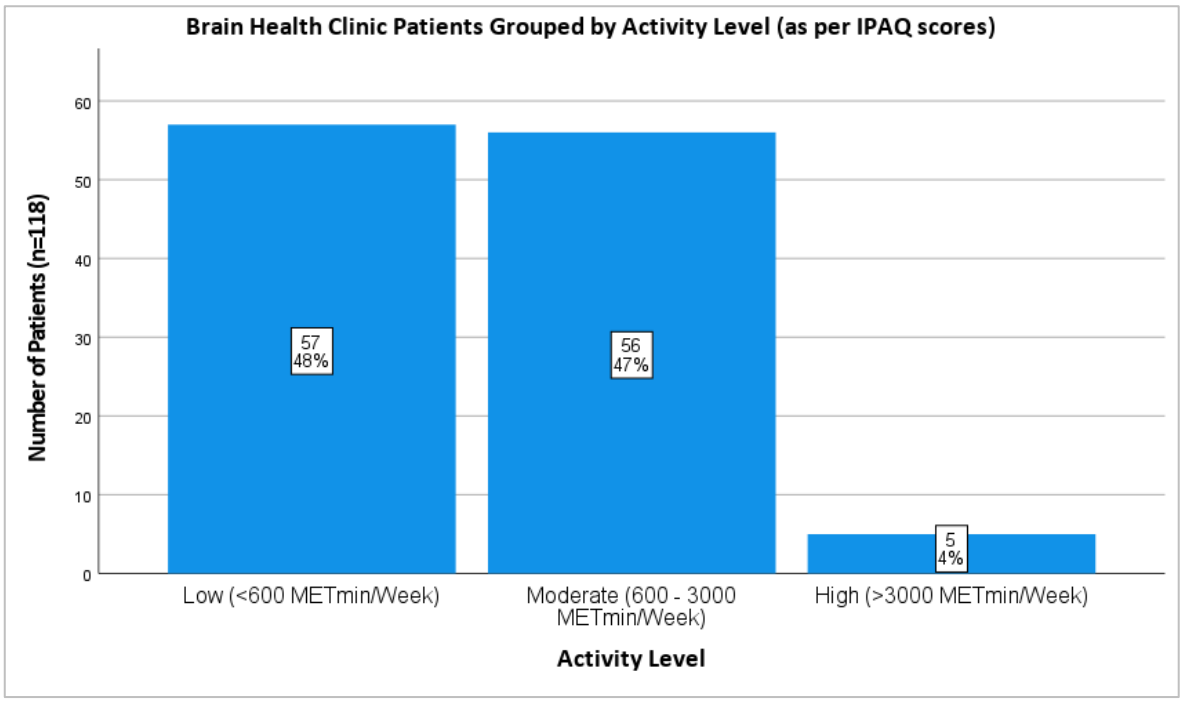

Figure 23: Activity levels as defined by IPAQ score

Patient demographic profiles are examined across each IPAQ defined activity level in Table 28 below.

Table 28: Demographic details of patients by activity level category

	Low (n=57)	**Moderate (n=56)**	**High (n=5)**	**P-Value**
Age (mean, SD)	71.1 years (8.6)	70.5 years (8.4)	71.9 (1.8)	P=0.900
Sex- female (n, %)	36 (63.2%)	35 (48.6%)	1 (1.4%)	P=0.159
Number of comorbidities (mean, SD)	5.63 (2.2)	4.95(2.1)	5.6 (3.13)	P=0.201
Number of medications (mean, SD)	7.51 (4.0)	5.38 (3.1)	5.6 (2.4)	P=0.009
Diagnosis (n,%) - MCI - SMC Underwent CSF testing	 46 (80.7%) 11 (19.3%) 22	 43 (46.8%) 13 (23.2%) 25	 5 (100%) 0 2	p=0.449

- AD + biomarkers	8	13	0	p=0.255
BMI (kg/m^2); mean (SD)	30.1 (6.3)	29.1 (5.0)	25.6 (1.59)	p=0.175

Following their initial brain health clinical assessment, 29 patients (n=24.6%) consented to a referral to a local, medically supervised group exercise program while 104 patients (88.1%) were given targeted, tailored exercise advice.

8.3.2. Sleep Quality and OSA risk

Sleep Quality was self-rated using the PSQI which ranged from 0-21 with a score of >5 indicative of poor sleep quality. The mean PSQI in the brain health clinic patient cohort was 6.94 (SD 4.5) and 70 people (59.3%) met the criteria for poor self-reported sleep quality. Patients with self-reported poor sleep quality were more likely to be female (n=41 (58.6%) vs n=31 (43.1%)) but this difference was not statistically significant (X^2 0.433, p=0.567). There was also no significant difference in age between the poor sleep quality group (mean =70.2 years; SD 8.8) and the normal sleep quality group (mean=71.8; SD 7.6); t(116)=1.067, p = 0.276.

The mean Epworth Sleepiness Scale score was 4.03 (SD 3.4). 7 patients (5.9%) had an Epworth score ≥ 10 (57.1% male, mean age 72.9 (SD 9.4)) which implied excessive daytime somnolence and potential OSA risk. The BMI of patients with an Epworth score ≥ 10 was significantly higher (mean 33.8 kg/m^2, SD 9.4) than those with an Epworth score <10 (mean 29.1 kg/m^2, SD 5.3); t(116) = -2.196, p = 0.030). In the group of patients with an Epworth score ≥ 10 indicative of excessive daytime somnolence, 85.7% of patients also reported poor sleep quality based on their PSQI score. In total 8 patients from the brain health clinic

cohort (6.8%) were referred to the respiratory department for formal sleep studies to screen for OSA.

8.3.3. Diet and Alcohol

The mean self-reported alcohol intake in units per week was 4.1 (SD 9.7). Only 4 (3.4%) patients met criteria for excessive alcohol intake, while 28 (23.7%) patients (mean age 71.6 years (SD 7.51), 46% female) met criteria for mild/moderate intake which is considered protective in the LIBRA index discussed in Chapter 9. Over sixty percent (n=73) of patients were documented as having an alcohol consumption rate of 0 units. In total 11 patients (9.3%) received targeted advice around alcohol reduction.

The mean mediterranean Diet score was 7.37 (SD 1.9) which is roughly at the midpoint of the Mediterranean diet score used which is on a scale of 0-14. Nine patients (7.6%) were referred to a dietician for assessment following their brain health clinic visit. The mean BMI of patients referred to the dietician for assessment was 30.3 kg/m^2 which was higher than those not referred (29.4 kg/m^2).

8.3.4. Loneliness, Social Isolation and Depression

Over 20% of patients (n=28) were deemed at risk of social isolation by the Lubben Social Network Scale 6. Their profiles are compared to patients who were not at risk of social isolation in Table 29 below. While 23.7% of patients were deemed at risk of social isolation, only 13.5% (n=16) were considered lonely by their UCLA Loneliness score.

Table 29: Comparison of patients with and without risk of social isolation

	At risk of Social Isolation (n=28)	**Not at risk of Social Isolation (n= 90)**	**P-value**
Age (mean, SD)	68.9 years (7.9)	71.4 years (8.4)	p=0.139
Sex, female (n, %)	17 (60.7%)	55 (61.1%)	p=0.970
Poor Sleep (PSQI >5) (n,%)	19 (67.9%)	54 (56.7%)	p=0.292
Positive HearCheck™ screen (n,%)	7 (31.8%)	23 (32.9%)	p=0.928
Lonely by UCLA Loneliness score (n,%)	10 (62.5%)	6 (37.5%)	P=0.000

When looking at depression and anxiety history, 38.1% (n=45) of patients had a documented diagnosis of depression or anxiety at the time of their initial visit to the brain health clinic. Patients with a diagnosis of depression/anxiety were of a similar age (mean 70.8 years, SD 7.9) to those who did not (mean 70.8 years, SD 8.7) and there were a high proportion of females in the diagnosis of depression group (n=32, 71.1%) than in the group without a depression diagnosis (n=40, 54.8%) but this difference was not statistically significant (X^2 3.116, p=0.78). Patients with an existing diagnosis of depression or anxiety were on a higher number of medications (mean 7.0 (SD 4.1) vs 6.0 (SD 3.4)) than those without a depression/anxiety diagnosis but this difference was not significant (p=0.180). They were also more likely to have an excessive alcohol intake (>21 units/week) (n=4, 8.9%) than those without a diagnosis (n=0) and this was a significant difference (P X^2, p=0.01) however the sample size is small.

Depression and anxiety were also screened for during the initial brain health clinic assessment. Twenty-two patients (18.6%) had a positive screen for either anxiety or

depression or both. Eighteen patients (15.3%) had a positive anxiety screen (HADS-A >7) while nine patients (7.6%) had a positive depression screen (HADS-D >7). Five patients (4.2%) had positive anxiety and depression screens and 4 of these patients had a known diagnosis of anxiety/depression.

Of the patients who screened positive for potential anxiety, 61.1% (n=11) had a pre-existing diagnosis of anxiety, while in the cohort who screened positive for depression, 77.8% (n=7) had a pre-existing diagnosis of depression. Eight patients (6.8%) were highlighted as having a potential new diagnosis of anxiety or depression by the HADS screening tool, while 14 patients (11.9%) were highlighted as having ongoing uncontrolled symptoms despite an existing diagnosis. All patients with a HADS-A or HADS-D score >7 were directed to local primary care counselling services.

8.3.5. Comparison of lifestyle risk factors across diagnostic profiles

The prevalence of lifestyle risk factors in the MCI (n=94) and the SMC (n=24) patient cohorts are displayed in Table 30 below. Risk factor prevalence by AD biomarker positivity is show in Table 31.

Table 30: Lifestyle risk factors compared by diagnosis

	Total Clinic Cohort (n=118)	**MCI (n=94)**	**SMC (n=24)**	**P-value (MCI vs SMC)**
Low Physical Activity Level based on IPAQ; n (%)	57 (48.3%)	46 (48.9%)	11 (45.8%)	p=0.449
Poor-Sleep Quality; n (%)	70 (59.3%)	56 (59.6%)	14 (58.3%)	p=0.912
Excessive Daytime Somnolence; n (%)	7 (5.9%)	5 (5.3%)	2 (8.3%)	p=0.577

	Total Clinic Cohort (n=118)	MCI (n=94)	SMC (n=24)	P-value (MCI vs SMC)
Excessive Alcohol intake (>21 units/week); n (%)	4 (3.4%)	3 (3.2%)	1 (4.2%)	p=0.814
History of Depression/Anxiety; n (%)	45 (38.1%)	36 (38.3%)	9 (37.5%)	p=0.043
HADS-A screen positive (>7); n (%)	18 (15.3%)	13 (13.8%)	5 (20.8%)	p=0.394
HADS-D screen positive (>7); n (%)	9 (7.6%)	6 (6.4%)	3 (12.5%)	p=0.314
Lonely by UCLA Loneliness score; n (%)	16 (13.6%)	9 (9.6%)	7 (29.2%)	p=0.013
At risk of social isolation; n (%)	28 (23.7%)	22 (23.4%)	6 (25%)	p=0.870

Table 31: Lifestyle risk factors compared by AD biomarker status

	CSF AD biomarkers positive (n=21)	CSF AD biomarkers negative (n=28)	P-value
Low Physical Activity Level based on IPAQ; n (%)	8 (38.1%)	14 (50%)	p=0.255
Poor-Sleep Quality; n (%)	8 (38.1%)	21 (75%)	p=0.009
Excessive Daytime Somnolence; n (%)	0 (0%)	2 (7.1%)	p=0.211
Excessive Alcohol intake (>21 units/week); n (%)	0 (%)	3 (10.7%)	p=0.122
History of Depression/Anxiety; n (%)	5 (23.8%)	16 (57.1%)	p=0.020
HADS-A screen positive (>7); n (%)	1 (4.8%)	4 (14.3%)	P=0.276
HADS-D screen positive (>7); n (%)	0 (0%)	3 (14.3%)	p=0.122
Lonely by UCLA Loneliness score; n (%)	1 (4.8%)	5 (17.8%)	p=0.166
At risk of social isolation; n (%)	7 (33.3%)	7 (25%)	p=0.523

8.4. Discussion

This chapter shows the prevalence of lifestyle risk factors in a cohort of patients with MCI and SMC attending a brain health clinical service. Poor sleep quality was the most prevalent risk factor in this cohort, with 59.3% of patients meeting criteria for self-reported poor sleep on the PSQI. This was consistent across MCI and SMC patient cohorts. Although only a small proportion of patients (5.9%) met the criteria for excessive daytime somnolence based on their Epworth Sleepiness Score, the value of identifying these individuals is particularly significant. The brain health clinic model facilitated onward referral for formal sleep studies for these patients which has the potential to identify and treat previously undiagnosed OSA. This would reduce their risk of developing a neurodegenerative disorder, potentially improve subjective cognitive symptoms and improve cardiovascular risk factors.

While there was no significant difference in levels of physical activity across the MCI and SMC groups almost half of patients attending the clinic (48.3%) had a self-reported low physical activity level. There were a higher proportion of females in the lower activity group, but this was not statistically significant. There was however a statistically higher rate of polypharmacy in the low activity group indicating a higher multimorbidity rate here. Referral to a medically supervised exercise class was facilitated for 29 patients (n=24.6%). By using a measurable physical activity rating scale, the impact of this intervention can be tracked longitudinally. To facilitate an analysis of the impact of this intervention on falls risk, gait speed could be measured and tracked longitudinally in this patient cohort and this could be easily incorporated into a clinical setting.

When looking at the data around alcohol use, the reliability of the patient's self-report and the recording mechanism must be questioned. In the brain health clinic, 61.9% of patients were recorded as having an alcohol intake of 0 units per week. This is not consistent with the most recent 2023 Healthy Ireland survey that reported 30% of adults over 15 years of age had not consumed alcohol in the previous year [291]. When recording data there was no differentiation made between patients who were totally abstinent from alcohol and those who reported themselves as "seldom" drinkers. Alcohol consumption in both cases was recorded at 0 units/week.

There is scope to improve both the recording process and make patients own self-reporting of their weekly and monthly alcohol consumption more accurate by incorporating elements of the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) questionnaire structure [292]. This self-reported questionnaire explores alcohol intake by asking participants how often they have a drink containing alcohol (with options of never, monthly or less, 2-4 times per month, 2-3 times per week or 4 or more times per week) before enquiring about the number of drinks consumed on a typical day when drinking. Pictorial information on a standard unit looks like in wine, beers and spirits is also included. Adopting this format for use in the brain health clinic could improve the accuracy of alcohol consumption recording going forward.

Over one third (38.1%) of patients attending the brain health service has a pre-existing diagnosis of depression or anxiety. As mentioned in Section 8.1.5.2 depression can be either a risk factor for developing dementia or also a prodromal symptom of the disease itself. No information on the duration or severity of symptoms, whether patients had

received either pharmacological or psychological intervention for their symptoms or if they required hospitalization was recorded and this is a limitation of the study. Without data around the duration of symptoms (e.g. if they began in mid-life vs late life) it is not possible to explore further whether depression in this cohort could represent a prodromal symptom or indeed a modifiable risk factor. When looking at current symptoms of depression or anxiety, 16.9% of patients had a positive screen. Almost one third (31.1%) of patients with a diagnosis of depression or anxiety had a HADS-A or HADS-S score above the cut off (>7) which indicated ongoing, under-treated symptoms. This highlights the need for ongoing screening of mood in patients with an existing depression diagnosis and the potential for intervention with psychological or pharmacological therapy.

Almost a quarter of patients were identified as being at risk of social isolation, and these patients were significantly more likely to also exhibit symptoms of loneliness. A previous Irish survey on awareness of modifiable risk factors of dementia highlighted that poor social engagement was a poorly recognised risk factor, particularly among people with lower educational attainment [293]. Given the high prevalence of this risk factor in the brain health clinic cohort it is important not only to address it on an individual level in a clinical setting by highlighting ways to combat social isolation such as signposting towards group activities, but also for public awareness around this important risk factor to improve.

The prevalence of lifestyle risk factors is spread evenly across both diagnostic groups, with the exception of loneliness which was significantly higher in the SMC group. The spread of risk factors across both MCI and SMC patients highlights the importance of screening all patients with a cognitive impairment in a memory service for presence of these risk factors

and initiating an appropriate personalised prevention plan. Furthermore, the development of a clinical service to objectively measure and offer personalised intervention plans for modifiable lifestyle risk factors for dementia also offers the opportunity for longitudinal follow up over time of these patients. Future research should aim to explore these risk factors longitudinally and identify the barriers to adhering to targeted interventions for improving lifestyle risk factor in this patient cohort.

8.5. Conclusion

This chapter highlights the high prevalence of modifiable lifestyle risk factors in patients attending a brain health clinic with SMC or MCI. Disrupted sleep and low levels of physical activity were the most prevalent lifestyle risk factors, highlighting them as an important areas of focus. Identifying lifestyle risk factors at an individual level highlights the potential for targeted intervention. Following this patient cohort longitudinally in a brain health clinic over a 54-month period provides the opportunity to assess patient understanding of the importance of modifying these risk factors and any barriers to compliance with suggested interventions.

Chapter 9. Results: Calculating An Individuals Dementia Risk

9.1. Introduction

Risk prediction or stratification tools are commonly used in many areas of medicine to support clinical decision making. These tools allow clinicians to investigate the probability of diseases using preclinical risk factors [294].The heterogenous nature of many medical conditions means that risk stratification tools that include a wide range of patient and disease-related variables can be useful in highlighting those at higher risk of developing a certain condition. They can be used to educate patients on their own individual risk and to guide treatment decisions. One of the most widely used risk prediction tools is the Framingham Risk Score (FRS) which incorporates cardiovascular risk factors and uses a logistical regression model to predict probability of a major cardiovascular outcome such as stroke or myocardial infarction. This can then be used to guide the initiation of statin treatment [295]. Risk stratification tools have evolved to incorporate individual patient biomarkers and genetic data to improve their accuracy [296].

9.1.1. Dementia Risk prediction models

Several dementia risk prediction models have been developed to stratify dementia risk on an individual level with the aim of directing high-risk individuals towards targeted interventions to reduce their overall risk score. These dementia risk prediction models vary in their composition and the extent to which they have been externally validated. Tools which have not been externally validated have limited potential for general use outside of the population in which they were developed. A systematic review conducted in 2019 revealed that of the 61 dementia risk scores studied, only eight had undergone external

validation, while many of those that were validated performed poorly when used to assess external patient samples [297]. This is likely due to the variable nature of dementia risk factors across lifespan and across differing geographical locations [298].

Four models which have been previously highlighted as the most promising in a systematic review [299] and included in a previous head-to-head validation comparison [300] are discussed here. These are the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) score, the Brief Dementia Screening Indicator (BDSI), the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) and the Dementia Risk Score (DRS). The 'LIfestyle for BRAin health' (LIBRA) index [301] was also included in the analysis.

9.1.1.1. The CAIDE Dementia Risk Score [302]

This dementia risk score is based on population data from the Finnish population-based CAIDE study which was an observational study investigating the role of risk factors on subsequent dementia diagnosis [302]. The CAIDE score uses mid-life vascular risk factor data to predict future dementia risk over a 20-year follow up period and as a result it is designed to only be applied to middle aged (39-64 years) individuals. These individual components of the CAIDE scoring tool are shown in Table 32. It generates a score which corresponds to a percentage probability of developing dementia in the next 20 years. It has poor performance when applied to patients in late life (>65 years) [303].

9.1.1.2. The Brief Dementia Screening Indicator (BDSI) [304]

The BDSI was developed using data from four cohort studies including the Framingham Heart Study. It is designed it be used in primary care to identify high risk patients who should be referred for detailed cognitive assessment. It is aimed at 65–79-year-olds and includes seven items which calculate a 6-year dementia risk. A score of ≥ 22 identifies patients who should be screened for cognitive impairment. The individual elements and scoring systems are identified below in Table 32.

9.1.1.3. The Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) [292]

The ANU-ADRI is a self-report Alzheimer's Disease risk index developed to predict individual level risk for the development of AD in late-life. Unlike the CAIDE and the BDSI it has not been developed from existing cohort studies and therefore is not limited by the risk indices included in them. Instead it was developed from the literature around dementia risk and protective factors, with each factor given a weighting based on effect sizes obtained from population studies. It was limited to items that could be assessed via self-report to facilitate ease of use in primary care settings. There are 45 questions in total in the self-administered questionnaire exploring protective and risk factors, and the information is used to generate a total risk score. The model was then validated in three population-based cohort studies [303]. The components of the ANU-ADRI model are detailed in Table 32.

9.1.1.4. The Dementia Risk Score (DRS) [305]

This risk model was developed using data from a large, representative primary care database in the UK and validated to predict a 5-year dementia risk [305] with two separate

risk calculations for those aged 60-79 years. The risk and protective factors included were restricted to routinely collected data from this primary care database given that known risk factors such as physical activity levels not routinely recorded in primary care could not be included in the model. The risk factors included in the model can be seen in Table 32.

Table 32: Risk and protective factors included in each risk prediction model (adapted from [300, 306].

Risk/Protective Factor	**CAIDE**	**BDSI**	**DRS**	**ANU-ADRI**	**LIBRA**
Age	X	X	X	X	
Sex	X		X	X	
Social Deprivation			X		
Educational Attainment	X	X		X	
Hypertension	X		X	X	X
History of Diabetes			X	X	X
History of Stroke/TIA		X	X		
History of A. Fib			X		
History of TBI				X	
Depression screen		X		X	X
Engagement in cognitive stimulation				X	X
High cholesterol	X			X	
BMI	X	X	X	X	X
Smoking			X	X	X
Alcohol consumption			X	X	X
Strength of social Network:				X	
Physical activity level	X			X	X
Pesticide Exposure				X	
Need help to manage money/medications?		X			
Fish Intake				X	
Heart Disease					X
Adherence to a mediterranean diet					X

9.1.1.5. The 'LIfestyle for BRAin health' (LIBRA) Index [301]

The LIBRA index, as discussed in Section 4.3.7, was developed following a systematic review and Delphi consensus. This resulted in a weighted sum scoring system that included 14 modifiable risk and protective factors for dementia with higher scores indicating a higher dementia risk. It was developed to highlight an individual's potential for dementia prevention. The LIBRA index was initially validated in the Dutch Maastricht Aging Study [301] and it has subsequently externally validated in a number of cohort studies, predicting cognitive decline and dementia risk over a range of ages from mid-life to older ages [307-309].

The LIBRA index was also used in a post hoc analysis of the FINGER multidomain intervention trial, with the 2 year intervention shown to be effective in decreasing LIBRA scores over time independent of APOE4 status, patient demographics and socioeconomic status [310]. A 12-point LIBRA score was used in a recent French study which investigated if a person's genetic susceptibility to dementia (e.g. because of APOE4 status) could be lowered by addressing modifiable risk factors. An increasing LIBRA score was associated with higher dementia risk across all levels of genetic susceptibility which suggests that a preventative approach targeting modifiable risk factors would be of benefit to all, regardless of genetic vulnerability to dementia, but should be prioritised in those with high genetic predisposition [311].

9.1.2. Selection of Risk Prediction Model for use in the Brain Health Clinic

As highlighted above, the CAIDE, the BDSI and the DRS were developed from cohort studies and limited by the risk factor data reported in these studies. The BDSI aimed to highlight

patients who would benefit from cognitive screening. This may be useful in some primary care scenarios but given that patients attending the BHC have undergone cognitive testing it was not considered appropriate for use in the Brain Health Clinic cohort. Since the ANU-ADRI used a 45 item self-reported questionnaire. However, it was felt that this would be too long for use in the 1-hour brain health clinic appointment and it would not use the data captured during the assessment such as BP measurements and total cholesterol levels. The LIBRA index was selected for use in the brain health clinic and was modified to include the non-modifiable risk factors of age, sex and educational attainment.

9.1.2.1. Modified LIBRA Index

In the original studies published on the LIBRA index, the original 12-point LIBRA index of solely modifiable risk factors was extended to include the non-modifiable risk factors of age, sex and educational attainment [301, 307]. Including, sex and educational attainment increased the predictive value for dementia, probably because of age being the most important risk factor. As a result, Schiepers et al regarded the LIBRA index (when the 14 modifiable risk factors alone were included) as a model for *dementia prevention*, while the adjusted LIBRA model to include age, educational attainment and sex was considered a *risk prediction* model [301]. It was believed that the use of a risk prediction model would be particularly beneficial in the brain health clinic setting, where most patients present with mild cognitive impairment and education around their risk of progression is central to the consultation process.

The modified LIBRA index was used in a post hoc analysis of the pre-DIVA trial to assess the effect of a multi-domain intervention on cognition during follow up across groups stratified

by the risk calculated by the modified LIBRA index [312] and was chosen for use in the brain health clinic setting. This may be incorporated into longitudinal follow up of the brain health clinic cohort in the future. The Modified LIBRA index used as part of the Brain Health Clinic Assessment is outlined in Appendix 12.2.7.

9.2. Methodology

As part of their initial assessment in the brain health clinic, patients had their LIBRA index calculated (see Chapter 4 Section 4.3.7). The LIBRA index used routinely in the brain health clinic is documented in Appendix B: 12.2.7 and includes a mix of modifiable and non-modifiable risk factors. Using this tool a score in the range of -1.0 to +24.6 is generated for each patient with higher scores indicating higher dementia risk. This score was recorded in the brain health clinic database. Adjustments were made If patients attending the clinic had an age outside of the range accounted for in the modified LIBRA score used here (note the age range limited to the 70-78 year old patient cohort from the pre-DIVA study [312]). If patients were under 70, they were given a score of 0, and if they were over 78, they were given the risk score for the 75-78 year old range based on their sex (+6.8 for males and + 9.2 for females).

The LIBRA index score was used to stratify patients into low, intermediate and high-risk groups based on tertiles, which has been done in previous studies [307, 312]. The median risk score for the cohort was also calculated and interquartile ranges reported. Demographic and diagnostic details were then compared across the low, intermediate and high-risk groups using chi-square, t-tests or Mann-Whitney U tests where appropriate. Other modifiable risk factors recorded during the brain health clinical assessment which

were not included in the LIBRA score were also compared across the rick groupings using chi-square or Kruskal-Wallis Tests where appropriate. A p-value of < 0.05 was considered significant. An ordinal regression model was used to predict risk factor grouping (low, intermediate or high), controlled for age and educational attainment based on patients' diagnosis, and other modifiable risk factors which were significantly different across the risk groups.

9.3. Results

The median LIBRA index score for patients attending the brain health clinical cohort was 8.4 (IQR 4.7 – 11.5). Patients were classified based on tertiles into low (n=39, LIBRA index score range: -1.0 – 5.7) intermediate (n=39, 5.8 – 10.4) and high (n=40, 10.7 – 16.6) risk groups. The mean age, time spent in full time education and gender of each group are shown in Table 33 below, and these variables were used in calculating the modified LIBRA score.

Table 33: Age, sex and educational attainment across risk groups

	Low Risk (n=39)	**Intermediate Risk (n=39)**	**High Risk (n=40)**
Age in years (mean, SD)	62.7 (6.5)	72.1 (6.2)	77.6 (4.0)
Female (n, %)	21 (53.8%)	21 (53.8%)	30 (75.0%)
Years spent in full-time education (mean, SD)	13.6 (3.63)	13.3 (3.3)	12.0 (3.0)

The proportion of patients in each risk category with an SMC or MCI diagnosis is show in Figure 24 below. The spread of patients within each Pobail Deprivation Index defined socio-economic grouping can be seen across the low, intermediate and high-risk groups in Figure 25. The spread of medical co-morbidities and number of medications per patient in each risk category is show in Figure 26 and Figure 27.

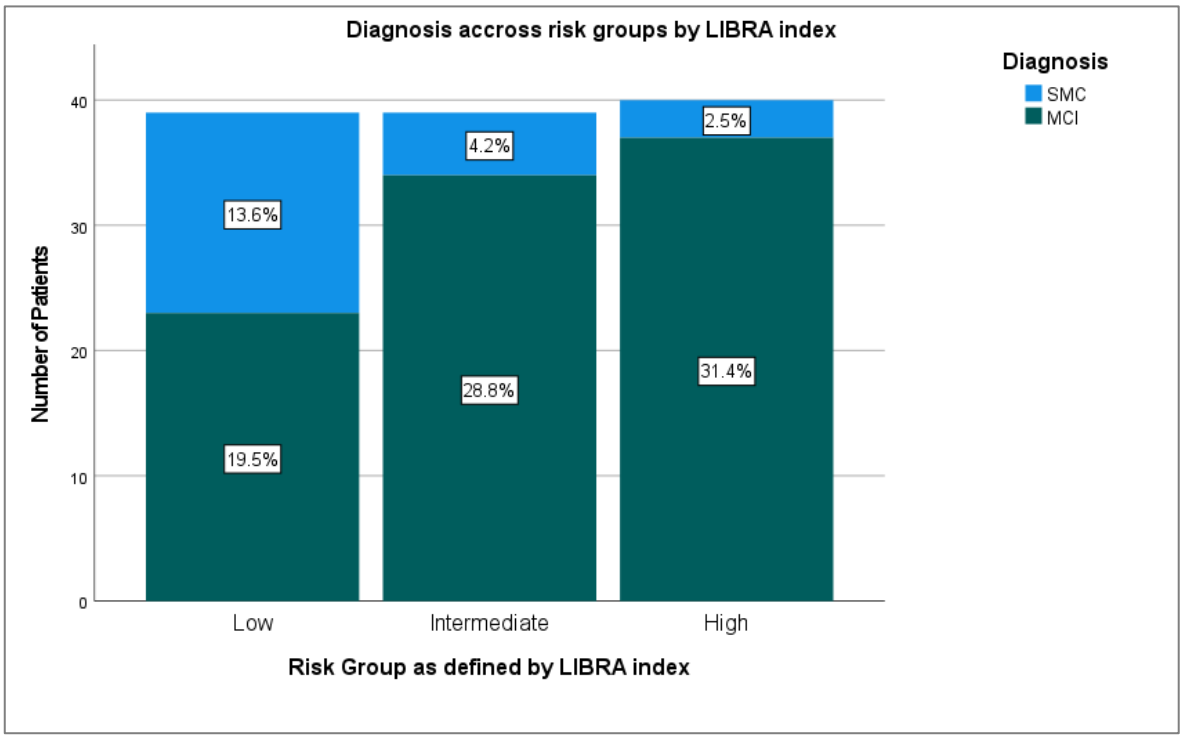

Figure 24: Spread of Diagnosis across low, intermediate and high-risk patient groups

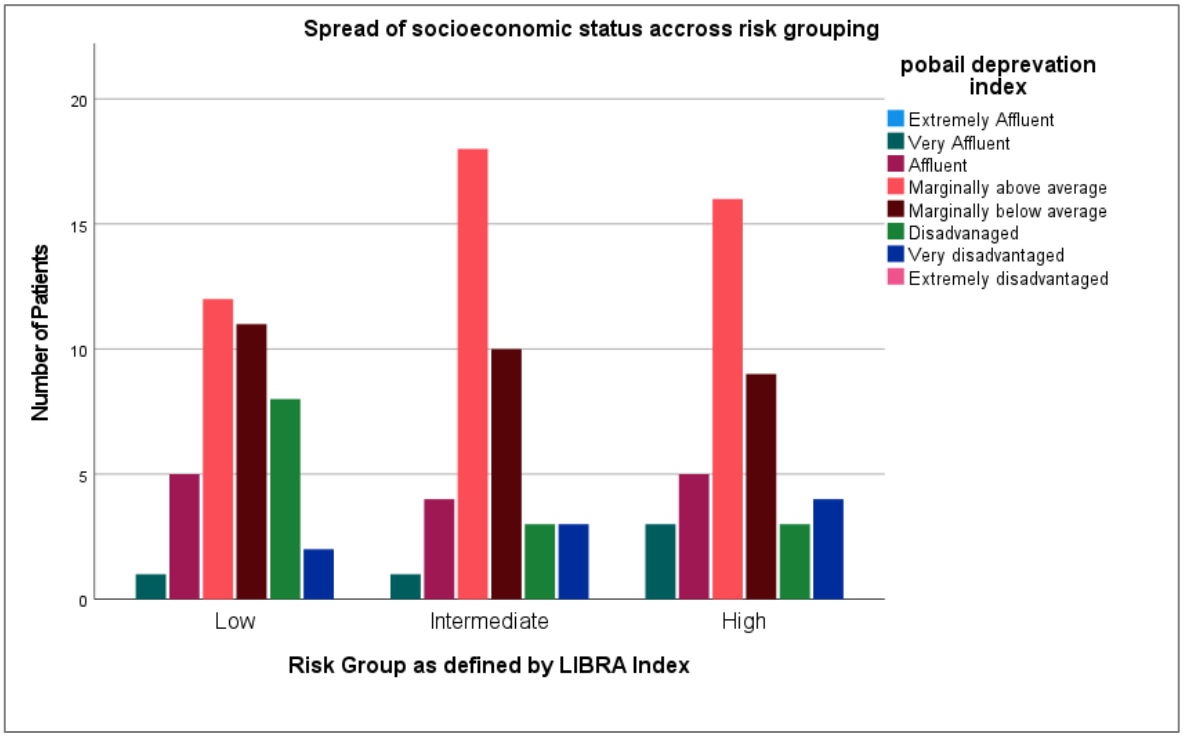

Figure 25: Spread of socio-economic status across each risk grouping

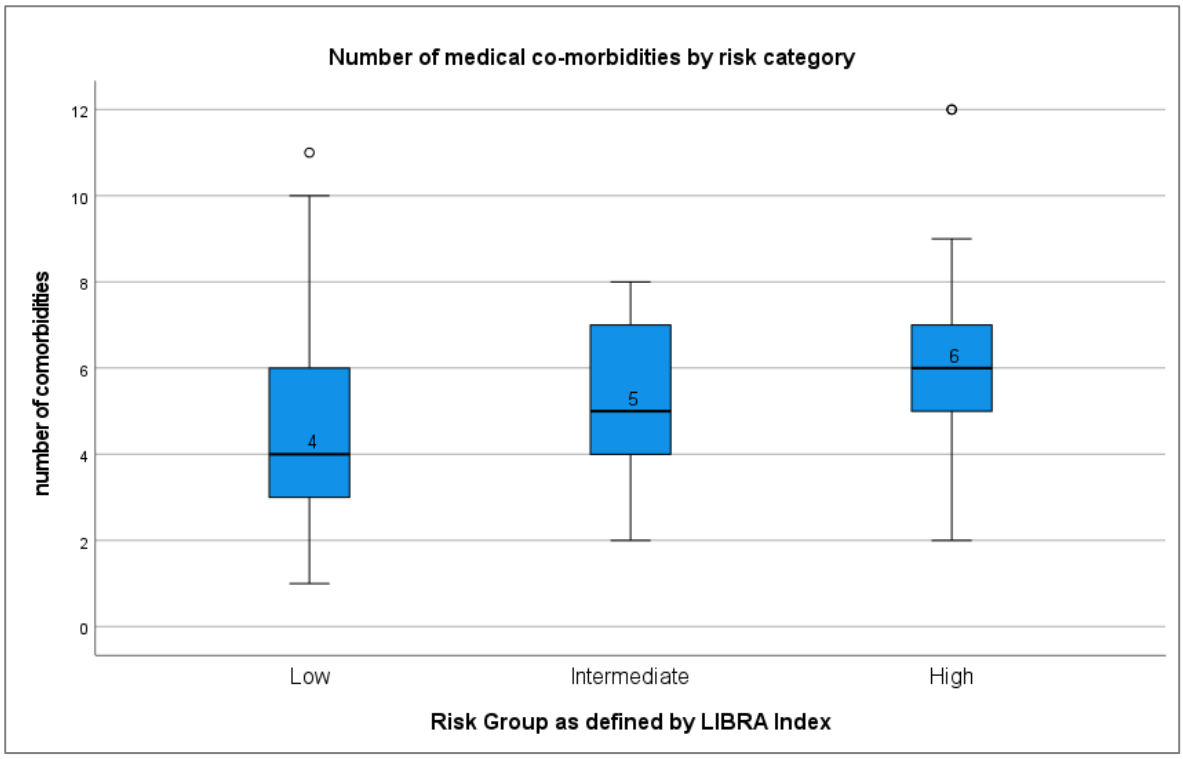

Figure 26: Number of co-morbidities by risk grouping

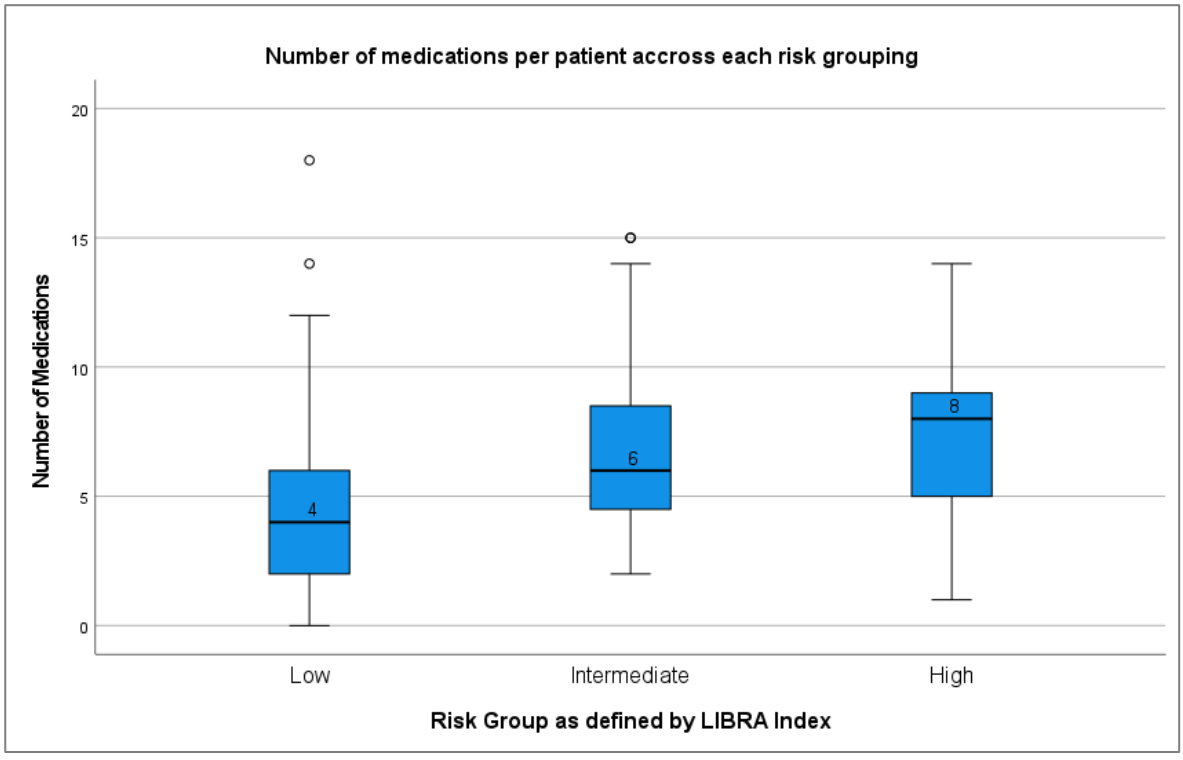

Figure 27: Number of medications per patient in each risk grouping

Diagnostic details, along with demographic details not included in the calculation of the LIBRA index are compared across the three risk groups in Table 34 below. Modifiable risk factors which were not used to calculate the LIBRA Index score are compared across each risk category in Table 35.

Table 34: Demographic and Diagnostic details compared across risk groups

	Low Risk (n=39)	**Intermediate Risk (n=39)**	**High Risk (n=40)**	**P-value**
Median *Pobail* Deprivation Index Score	Marginally Below Average	Marginally above Average	Marginally Above Average	0.507
Duration of Symptoms prior to diagnosis in months (median, IQR)	24 (12 - 48)	24 (12-36)	18 (12 – 34.5)	0.116
Number of co-morbidities (median, IQR)	4 (3-6)	5 (4-7)	6 (5-7)	0.006
Number of Medications per patient (median, IQR)	4 (2-6)	6 (4-9)	8 (5-9)	0.001
Diagnosis:				
- SMC (n,%)	16 (41%)	5 (12.8%)	3 (7.5%)	0.0003
- MCI (n,%)	23 (59%)	34 (87.2%)	37 (92.5%)	
- Amnestic (n)	14	28	35	
- Multidomain impairment (n)	14	24	30	
- CSF testing done (n)	15	18	16	
- Positive AD biomarkers (n)	7	9	5	0.511

When an ordinal regression model was employed to assess the predictive impact of diagnosis on risk factor grouping when controlling for age and level of education, diagnosis was shown to not significantly affect whether patients were classified as low, intermediate or high risk (Wald=0.399, diff = 1, p= 0.528).

Table 35: Modifiable risk factors explored across risk groups

	Low Risk (n=39)	Intermediate Risk (n=39)	High Risk (n=40)	P-value
Poor Sleep (PSQI > 5) (n, %)	23 (59%)	27 (69.2%)	20 (50.0%)	0.220
Lonely by UCLA score (n, %)	7 (17.9%)	3 (7.7%)	6 (15.0%)	0.395
At risk of Social Isolation (n, %)	9 (23.1%)	10 (25.6%)	9 (22.5%)	0.941
Positive hearing screen (at risk of hearing impairment (n, %)	7 (20%)	10 (33.3%)	14 (48.1%)	0.020
Mild or moderate visual impairment by LogMAR score (n, %)	5 (12.8%)	4 (10.3%)	5 (12.5%)	0.975
Low activity level by IPAQ (n, %)	17 (61.5%)	18 (46.1%)	22 (55.0%)	0.540

An ordinal regression model was used to assess the predictive impact of a positive hearing screen on risk factor grouping when controlled for age. A positive hearing screen indicating a potential hearing impairment (Wald=0.049, df=1 p=0.825) did not significantly predict dementia risk.

9.4. Discussion

9.4.1. A comparison of risk factor groups

By stratifying patients into low, intermediate and high-risk groups based on their LIBRA index score it is possible to compare the characteristics of patients in these groups both in terms of their demographic and diagnostic profiles as well as their other modifiable risk factor profiles. When looking at diagnostic profiles, there were significantly more patients with SMC in the lower risk category compared to the intermediate and higher risk categories. This is driven by the fact that patients with SMC in this cohort were significantly younger (median age 62.3 years vs 73.3 years, p=0.000) and also spent significantly more

time in education (median 13.5 years vs 12.0 years, p=0.039) than those with an MCI diagnosis (See Section 5.3.3 on page 115). When ordinal regression was employed, diagnosis was shown not to be a significant predictor of risk factor group when controlling for age and education.

Patients in the high-risk category had a shorter symptom duration prior to attending the memory service, however this difference was not significant. There was no difference between the number of patients in each risk grouping when AD biomarker positivity was compared. Patients in the high-risk group were significantly more likely to be taking more medications (8 vs 4, p=0.001) and have a higher number of medical comorbidities than patients in the low-risk group (6 vs 4, p=0.006) indicating that patients who were more multimorbid had a higher dementia risk.

When looking at other modifiable risk factors which were not included in the LIBRA index and comparing them across the low, intermediate and high-risk groups only a positive hearing screen were significantly different across the groups. Patients in the high-risk category were more likely to have a potential hearing impairment highlighted on their hearing screen than patients in the low-risk group. However once again when this was adjusted for age using an ordinal regression model, poor hearing did not predict whether patients would be in the low, intermediate or high-risk dementia groups.

9.4.2. The benefit of performing the LIBRA Index in a clinical cohort

The LIBRA index, when embedded into a clinical proforma can be used as an educational tool. It can also be used longitudinally to monitor the effects of lifestyle modification on

changing dementia risk over time. In the brain health clinic, the LIBRA index can be used to show patients how specific risk factors contribute to their overall dementia risk. As a result, this can be used to highlight the positive impact that reducing such risk factors, by positive lifestyle changes, could have on this risk. This is used as health promotional tool, highlighting the positive impact that patients can make on their own individual risk.

There is scope for the LIBRA index to be used longitudinally to track compliance with lifestyle advice given as part of the brain health assessment. In the TIMC brain health clinic model, this score is repeated 4 times over the course of the brain health clinic cycle at 18-month intervals. Going forward it will be useful to track this score in patients who develop a dementia syndrome over the course of their time in the brain health service, and to compare its impact on progression.

9.4.3. Limitations

There are limitations to the interpretation of the results of the LIBRA index recorded for patients attending the brain health clinical service. The modified LIBRA index used which was adapted from the post hoc analysis of the pre-DIVA trial [312] has a narrow age attributable risk range which is limited by the age range of the patients in this study (namely 70-78 years old). There were 52 patients in this brain health clinical cohort under the age of 70, who were all given a risk score of 0 for age, while the 13 patients in the cohort over 78 years of age were given the risk score attributable to someone 75-78 years of age. Going forward accuracy of this modified LIBRA index could be improved by using the age ranges and their associated risk weightings which are included in the modified LIBRA index used by Vos et al when looking at risk in the oldest old [307]. This index includes risk weightings

for patients under 65 years, 65-70 years and for patients beyond 78 years up to and including those greater than 90 years of age.

Another factor that limits analysis of individual's LIBRA scores and may affect the use of this score longitudinally is the lack of inclusion in the database of the individual components that contribute to a person's overall LIBRA score. As a result, it will not be possible to compare which elements of the score have resulted in a change over time. Neither will it be possible if looking at a baseline LIBRA score in patients who may progress to a dementia syndrome over the 54 month follow up period of the brain health cycle to compare the elements of the risk score that were more prevalent in that subset of patients. Without the breakdown of the individual elements of the total LIBRA score it is not possible to compare the mean LIBRA score of patients attending our brain health service with previously published data. Both studies that utilized a similar LIBRA index scoring system in their work only reported the mean and range of LIBRA scores without including age and educational attainment so therefore could not be compared to the LIBRA scores reported in this cohort.

9.5. Conclusion

This chapter highlights the benefit of measuring overall dementia risk on an individual level in patients without dementia attending a memory service. It has the potential to be used longitudinally to track patient's engagement with their personalised prevention plan developed following their risk factor assessment in the brain health clinic. While it is non-modifiable, age is the highest weighted risk factor, and the LIBRA index used in this clinical patient cohort was modified to include this. Broadening the elements included in the brain

health clinic database in the future to incorporate the individual components of this score will make it more accurate as a means of monitoring patient adherence to the tailored advice given to them in the brain health clinic.

Chapter 10. Conclusion

10.1. TIMC Brain Health Clinic Framework: A Comparison with Theoretical Models and Existing Services

This work is the first to describe a brain health clinic model which has been embedded into an existing memory service to educate patients with cognitive concerns about their dementia risk. In addition, their modifiable risk factors were quantified thus enabling patients to improve these through use of a personalised prevention plan. It demonstrates a model of how patients with MCI and SMC can be assessed and longitudinally followed up with a view to optimising brain health.

It differs from the clinical services described in the scoping review in Chapter 2. It does not accept self-referrals from the public or patients without cognitive symptoms but with a positive family history who are accommodated in the APC clinical model and the Brain Health Scotland model. Our clinical model focuses on individually tailored interventions based on a patient's personal risk factor profile and unlike Brain Health Scotland does not aim to deliver public health programmes. It provides a framework for delivering brain health interventions in a specialist memory clinic setting.

The TIMC brain health clinical pathway aligns with the European Task Force on Brain Health [86] by leveraging on the structure and function of an existing memory service which enables patients to access diagnostics, AD biomarker testing and specialist clinicians. It also facilitates early review in the memory service if there are signs that a patient's diagnosis has progressed over their time attending the brain health clinic. This bi-directional

relationship between brain health services and memory services is essential and was strongly recommended by the existing brain health clinical frameworks outlined by Leroi et and Frisoni et al [81, 86].

The range of risk factor assessments performed in this brain health clinical model largely aligns with the European Taskforce on Brain Health Services (see Table 2, page 47) and expands on this to include a formal vision assessment, as well as quantifying loneliness, sleep quality and screening for OSA. Both theoretical frameworks from Frisoni et al [86] and Leroi et al [81] advocate for APOEe4 testing to help stratify patients based on dementia risk, but this test is not currently available in Ireland. Patients in the framework outlined by Leroi et al, and in the APC and Brain Health Scotland clinical models are grouped based on their risk status, with the level of investigations a patient gets along with the frequency of longitudinal follow-up dependant on what specific risk category they fall into. Leroi et al advocate for patients in low and moderate risk groups to be monitored in primary care.

Currently all patients are followed at the same intervals across the TIMC brain health service, and initial medication changes based on vascular risk factor measurement are initiated in the brain health clinic without a need for patients to attend their general practitioner as is the case in the APC dementia prevention model. In the future, altering the frequency of follow-up visits may be considered based on a patient's risk grouping. The LIBRA index could be used to separate out patients into low, intermediate and high-risk groups.

10.2. Risk Factor prevalence and the opportunity for intervention

The results of this study highlight the high prevalence of a range of modifiable risk factors for dementia in a patient cohort with MCI and SMC attending a memory service. The most common risk factors identified in patients attending the brain health clinic along with their percentage prevalence are summarised in Table 36 below.

Table 36: Most identified modifiable risk factors identified in brain health clinic patients

Modifiable Risk Factor	Prevalence (%)
BP >130/85 mmHg	70.3%
Self-reported poor sleep	59.3%
Low physical activity level	48.3%
Hypertension history – uncontrolled BP	46.6%
BMI in the obese range	35.0%
Possible hearing impairment	32.6%
At risk of Social Isolation	23.7%
LDL>3	21.2%
Known T2DM or HbA1c >48 mmol/mol	18.8%
Positive depression/anxiety screen	18.6%
Mild or moderate visual impairment	15.6%
Current smoker	14.4%
Loneliness	13.5%
History of Head Trauma	7.6%
Epworth score suggestive of potential OSA	5.9%
Excessive alcohol consumption	3.4%

Hypertension is the most prevalent risk factor identified by the assessments performed in the brain health clinic. It is important to note that the lack of available 24hr ABPM results to confirm the presence of hypertension in patients who had a one-off blood pressure measurement above the target cut-off of 130/85 mmHg limits the interpretation of the hypertension data. However, almost half of the patient cohort had a pre-existing diagnosis of hypertension and had blood pressure readings above this target cut off which suggests an opportunity to optimize the management of this risk further. Almost one third of

patients were identified as having a possible hearing impairment. This is in keeping with the high population attributable risk fraction attributed to this risk factor by the Lancet Commission on Dementia Prevention [45].

When looking at risk factor prevalence across the SMC and MCI patient cohorts, risk factor prevalence is largely similar across both patient groups. The exceptions were loneliness being significantly more prevalent in the SMC cohort, while those in this cohort also had a significantly higher level of educational attainment than patients diagnosed with MCI. There was a significantly higher prevalence of patients with a history of diabetes, hypertension and depression/anxiety in the MCI cohort, although this may be as a result of the high prevalence of these co-morbidities in the total patient cohort and the unequal size of the MCI and SMC groups. The consistent range of risk factors across both patient cohorts and across those with and without AD pathology emphasises the importance of risk factor screening regardless of cognitive diagnosis or amyloid status.

The broad range of modifiable risk factors in this patient cohort emphasises the opportunity that exists for intervention on an individual level. Interventions were facilitated by the brain health clinic model of care. Screening for potential hearing impairment in the brain health clinic facilitated referral of 22.8% of patients to an audiology service for assessment and treatment with hearing aids if required. Almost one quarter of patients attending the clinical service were referred to a group based, medically supervised exercise program with a view to improving their overall physical activity levels. 6.8% of patients were referred for formal sleep studies to investigate for OSA while 7.6% of patients were referred to a dietician for optimization of their diet. Almost 20% of patients were

given advice about attending counselling or seeking psychological support for symptoms of depression and anxiety. Almost one quarter of patients (24.6%) were referred to a community exercise group as a result of their assessment in the brain health clinic.

10.3. Considerations for Future Directions

10.3.1. Improvements resulting from this research

This work outlines a novel clinical service for assessing modifiable risk factors for dementia in patients attending a memory service. It is important to build on the work done to develop this service to date to ensure that it continues to evolve and effectively meets the needs of its patients. From a service evaluation perspective, the metrics reported in this patient cohort for time from diagnosis to assessment in the brain health clinic (median time 6 months (IQR 2- 15)) falls significantly short of the KPI of review in the brain health clinic ideally within 6 weeks of diagnosis. Similarly, this cohort study highlighted that the rate of patients who meet the criteria for 24hr ABPM who had this test performed in a timely manner was low (11%). Both metrics have been used to improve the service by increasing the number of appointment slots per week to deal with the demand for the service and also by creating a business case for the purchase of ABPMs for use by the brain health clinic alone. It will be important to re-evaluate these metrics after incorporating these improvements into the service.

10.3.2. Longitudinal Follow up

The brain health clinical model presents an opportunity to longitudinally monitor progression of cognitive symptoms over time in a cohort of patients with MCI and SMC. By evaluating the compliance with the personalised prevention plan put in place and tracking

the modifiable risk factor burden over time in this patient cohort it will be possible in future to investigate the effect of this on progression of cognitive symptoms. The next phase of this work should look at outcomes following the patient's 3rd visit to the brain health service. At this appointment, their biophysical measurements such as blood pressure and BMI are repeated along with their cognitive assessment with a view to investigating changes in these measures over time. By continuing to follow this patient cohort over time it will enable us to assess the effectiveness of a multidomain personalised intervention in a clinical patient cohort attending a memory service.

10.3.3. Patient Perceptions of the Brain Health Clinic Framework

It is important in terms of service development and quality improvement to seek the opinions of the service users of any clinical service, particularly when looking at a new clinical model of care. It will be important to survey patients in the brain health clinic to assess their perceptions of the service, and to explore their understanding of modifiable risk factors for dementia and if this has improved after attending the service. It will also be important form a service development point of view to get patient feedback about the frequency of follow-up appointments, the utility of pursuing AD biomarkers and of the effectiveness of the LIBRA index as an education tool to demonstrate risk and the potential impact of removing certain risk factors through behavioural change.

10.4. Conclusion

This study outlines a clinical model for implementation of brain health interventions in a memory clinic setting. It highlights the value of observational research in exploring risk factors for dementia in this patient population. While wide scale public health messaging

and policy is required to raise awareness and address dementia risk factors on a broader scale, this study highlights the opportunity that exists for risk factor optimisation through individual patient assessments in a targeted clinical model for brain health.

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Chapter 12. Appendices

12.1. Appendix A: Scoping review Database search strategy and results

12.1.1. Database: OVID Medline

Ovid MEDLINE(R) ALL <1946 to August 22, 2023>

#	Query	Results from 23rd August 2023
1	dementia.mp.	160,546
2	Dementia, Vascular/ or AIDS Dementia Complex/ or Dementia/ or "Mental Status and Dementia Tests"/ or Frontotemporal Dementia/ or Dementia, Multi-Infarct/	78,023
3	1 or 2	160,546
4	Alzheimer Disease/	119,350
5	alzheimer$.mp.	203,302
6	alzheimer's disease.mp.	156,556
7	4 or 5 or 6	203,302
8	cognitive impairment.mp.	83,279
9	3 or 7 or 8	345,249
10	clinic.mp.	301,212
11	clinics.mp.	138,009
12	service.mp.	453,803
13	Outpatients/	21,601
14	outpatient.mp.	176,503
15	10 or 11 or 12 or 13 or 14	940,652
16	prevention.mp.	1,927,437
17	(risk adj1 reduction).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	36,090
18	(brain adj1 health).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept	3,198

	word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	
19	16 or 17 or 18	1,946,095
20	9 and 15 and 19	1,045
21	limit 20 to yr="2013 -Current"	725

12.1.2. OVID Embase

Embase <1974 to 2023 Week 33>

#	Query	Results from 23rd August 2023
1	dementia/	146,184
2	dementia.mp.	251,837
3	Alzheimer disease/	246,826
4	Alzheimer's disease.mp.	213,328
5	alzheimer$.mp.	303,817
6	1 or 2 or 3 or 4 or 5	455,552
7	(cognitive adj1 impairment).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	134,657
8	6 or 7	522,518
9	clinic.mp.	528,490
10	clinics.mp.	182,050
11	service.mp.	971,281
12	outpatient/	161,204
13	outpatient.mp.	388,883
14	outpatient/	161,204
15	outpatients.mp.	84,915
16	9 or 10 or 11 or 12 or 13 or 14 or 15	1,846,312
17	prevention/	297,201
18	prevention.mp.	2,159,245
19	(risk adj1 reduction).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	144,311

20	(brain adj1 health).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	4,252
21	17 or 18 or 19 or 20	2,251,034
22	8 and 16 and 21	2,439
23	limit 22 to yr="2013 -Current"	1,647

12.1.3. Database: PsychInfo

APA PsycInfo <1987 to August Week 2 2023>

#	Query	Results from 23 Aug 2023
1	dementia/	41,674
2	dementia.mp.	83,695
3	Alzheimer disease/	54,612
4	Alzheimer's disease.mp.	69,495
5	alzheimer$.mp.	75,728
6	1 or 2 or 3 or 4 or 5	122,285
7	(cognitive adj1 impairment).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	62,741
8	6 or 7	156,594
9	clinic.mp.	49,418
10	clinics.mp.	29,457
11	service.mp.	172,580
12	outpatient/	0
13	outpatient.mp.	39,875
14	outpatient/	0
15	outpatients.mp.	26,911
16	9 or 10 or 11 or 12 or 13 or 14 or 15	275,613
17	prevention/	35,072
18	prevention.mp.	157,709
19	(risk adj1 reduction).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	8,011

20	(brain adj1 health).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	1,283
21	17 or 18 or 19 or 20	163,483
22	8 and 16 and 21	373
23	limit 22 to yr="2013 -Current"	230

12.1.4. Database: Cinhal

Limiters: published date: 01/01/2013 – 23/08/2023
Expanders: Apply Equivalent Subjects
Search modes: Boolean/Phrases

#	Query	Results from 23 Aug 2023
1	“Alzheimer$”	29,504
2	(MH “Alzheimer’s Disease”) OR “Alzheimer’s disease” OR (MH “Lewy Body Disease”)	27,103
3	(MH “Dementia”) OR “dementia” OR (MH “Frontotemporal Dementia”) OR (MH “Dementia, Vascular”) OR (MH “delirium, Dementia, Amnestic, Cognitive Disorders”) OR (MH “dementia, Multi-Infarct”) OR (MH “AIDS Dementia Complex”) OR (MH “Lewy Body Disease”) OR (MH “Dementia, Senile”) OR (MH “dementia, Presenile”) OR (MH “Dementia Patients”) OR (MH “CADASIL”)	46,146
4	(MH “Mild Cognitive Impairment”) OR ““mild cognitive impairment””	7,813
5	1 OR 2 OR 3 OR 4	66,850
6	”clinic”	86,387
7	“clinics”	56,111
8	(MH “Outpatient Service”) OR (MH “Outpatients”) OR “outpatient”	106,427
9	“service”	286,265
10	6 OR 7 OR 8 OR 9	450,626
11	“risk reduction”	10,116
12	“prevention”	393,383
13	“brain health”	1,326
14	11 OR 12 OR 13	401,586

15	outpatients.mp.	26,911
16	9 or 10 or 11 or 12 or 13 or 14 or 15	275,613
17	5 AND 10 AND 16	386

12.2. Appendix B: Assessment Tools

12.2.1. Epworth Sleepiness Scale [144].

Instructions: How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:

- No chance of dozing =0
- Slight chance of dozing =1
- Moderate chance of dozing =2
- High chance of dozing =3

Situation	**Chance of Dozing**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (eg meeting or a cinema)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting & talking to someone	
Sitting quietly after lunch	

Total Score: _____

Interpretation:

0-7: It is unlikely that you are abnormally sleepy

8-9: You have an average amount of daytime sleepiness

10-15: You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention

16 – 24: You are excessively sleepy and should consider seeking medical attention

12.2.2. HADS – Anxiety and Depression [145]

Instructions: Tick the box beside the reply that is closest to how you have been feeling in the past week.

D	A		D	A	
		I feel tense or "wound up"			**I Feel as if I am slowed down**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very Often
	1	From time to time (occasionally)	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy			**I get a sort of frightened feeling like butterflies in the stomach**
0		Definitely not as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very Much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of time	0		As much as I ever did
	2	A lot of time	1		Rather less than I used to
	1	From time to time	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite Often

1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely		0	Often
	1	Usually		1	Sometimes
	2	Not often		2	Not often
	3	Not at all		3	Very seldom

Anxiety Score: _____ Depression score: _____

12.2.3. Lubben Social Inclusion (LSNS-6) [146].

Instructions: The LSNS-6 is a validated instrument designed to gauge social isolation in older adults by measuring the number and frequency of social contacts with friends and family members and the perceived social support received from these sources.

FAMILY: Considering the people to whom you are related by birth, marriage, adoption, etc.

1. How many relatives do you see or hear from at least once a month?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

2. How many relatives do you feel at ease with that you can talk about private matters?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

3. How many relatives do you feel close to such that you could call on them for help?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

FRIENDSHIPS: Considering all of your friends including those who live in your neighbourhood

4. How many of your friends do you see or hear from at least once a month?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

5. How many friends do you feel at ease with that you can talk about private matters?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

6. How many friends do you feel close to such that you could call on them for help?

None ☐ one ☐ two ☐ three or four ☐ five til eight ☐ nine or more ☐

Total Score: _____

12.2.4. UCLA Three Item loneliness Scale [147]

Instructions: The survey can be administered in various ways – either through asking the questions during an interview or assessment or provided to a patient to read and respond to the questions independently

Answer Scale:

- Hardly Ever = 1 point
- Some of the time = 2 Points
- Often = 3 points

Question	**Points**
How often do you feel you lack companionship?	
How often do you feel left out?	
How often do you feel isolated from others?	
Total Points	

Scoring: The scores for each individual question can be added together to give you a possible range of scores from 3 to 9. Higher scores indicate greater degrees of loneliness. Researchers in the past have grouped people who score 3 – 5 as “not lonely” and people with the score 6 – 9 as “lonely

12.2.5. IPAQ – SF [313]

Instructions: Please think about the activities you did at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport in the **last 7 days.**

(Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal)

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling? **_____ days per week**

No vigorous physical activities Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

_____ hours per day

_____ minutes per day

Don't know/Not sure □

(Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal)

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking. _____ days per week No moderate physical activities Skip to question 5

4. How much time did you usually spend doing moderate physical activities on one of those days?

_____ hours per day

_____ minutes per day

Don’t know/Not sure □

Instructions: Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time? _____ days per week

No walking Skip to question 7

6. How much time did you usually spend walking on one of those days?

_____ hours per day

_____ minutes per day

Don’t know/Not sure □

The last question is about the time you spent sitting on weekdays during the last 7 days.

7. During the last 7 days, how much time did you spend sitting on a week day?

_____ hours per day

_____ minutes per day

Don’t know/Not sure □

12.2.6. Mediterranean Diet Score [142]

Evidence shows overall dietary pattern (reflected in total score) as well as individual components reflect risk; a higher score is in response to dietary advice and support.

Question	**YES**	**NO**
Is olive oil the main culinary fat used?		
Are ≥ 4 tablespoons of olive oil used each day?		
Are ≥ 2 servings (of 200g each) of vegetables eaten each day?		
Are ≥ 3 servings of fruit (of 80g each) eaten each day?		
Is < 1 serving (100-150g) of red meat/ hamburgers/ other meat products eaten each day?		
Is < 1 serving (12g) of butter, margarine or cream eaten each day?		
Is < 1 serving (330ml) of sweet or sugar sweetened carbonated beverages consumed each day?		
Are ≥ 3 glasses (of 125ml) of wine consumed each week?		
Are ≥ 3 servings (of 150g) of legumes consumed each week?		
Are ≥ 3 servings of fish (100-150g) or seafood (200g) eaten each week?		
Is < 3 servings of commercial sweets/pastries eaten each week?		
Is ≥ 1 serving (of 30g) of nuts consumed each week?		
Is chicken, turkey or rabbit routinely eaten instead of veal, pork, hamburger or sausage?		
Are pasta, vegetable or rice dishes flavoured with garlic, tomato, leek or onion eaten ≥ twice a week?		
TOTAL SCORE (1 point for each 'Yes' answer)		

12.2.7. LIBRA Index (Extended for Age, sex and educational level) [312]

Modifiable Risk Factors	**Definition**	**Score**	**Patient Score**
Depression	Score > 7 on HADS-D	+2.1	
HTN	SBP ≥ 140mmHg, DBP ≥90 mmHg and or use of an anti-hypertensive medication	+1.6	
Obesity	BMI ≥ 30 Kg/m^2	+1.6	
Smoking	Current Smoker	+1.5	
Hypercholesterolemia	Total Cholesterol ≥ 6.2 mmol/L or use of lipid lowering medication	+1.4	
Diabetes	Diabetes mellitus present	+1.3	
Renal Dysfunction	Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2	+1.1	
Physical Inactivity	Not fulfilling WHO criteria for physical activity (≥ 150 min/week moderate intensity or ≥ 75 min/week vigorous intensity or an equivalent combination which is an IPAQ score <600 MET/min/week)	+1.1	
Coronary Heart Disease	Cardiovascular disease (defined as myocardial infarction, angina or peripheral arterial disease) – self report and cross checked with medical record	+1.0	
Low/Moderate Alcohol use	Alcohol use of 1-14 units/week for males and 1-7 units/week for females	-1.0	
Non-Modifiable Risk Factors	**Definition**	**Score**	
Age and sex	Male: 70-74 years Male: 75-78 Females: 70-74 Females: 75-78	+5.2 +6.8 +6.2 +9.2	
Education	High: ≥ 13 years Medium: 7-13 years Low: ≤ 7 years	0 +1.4 +2.7	

Total Score: _____