Title: Identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's disease

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IDENTIFYING PATTERNS IN SIGNS AND SYMPTOMS PRECEDING

THE CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

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Ph.D.

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ABSTRACT

Previous research indicates that there is a major challenge caused by the late diagnosis of Alzheimer's disease (AD), with no suitable diagnostic tool available for use in primary care.

Aim:

This research is aimed at identifying patterns in the early signs and symptoms of AD to suggest the development of a predictive model for the early detection of AD.

Objectives: To; a) map, synthesise and appraise the quality of existing literature on the signs and symptoms preceding the diagnosis of AD via the systematic scoping review of the literature; b) identify patterns in signs and symptoms preceding the clinical diagnosis of AD in general practices via a retrospective medical record review study (RMRRS); c) explore the clinicians perspectives regarding the early signs and symptoms, issues surrounding the late diagnosis and collect recommendations for overcoming barriers to timely detection of AD via a semi-structured interview.

Methods:

This was a mixed method research comprising a systematic scoping review of literature from 1937-2016, undertaken using the descriptive analysis on the sequence and the timing of signs and symptoms preceding the diagnosis of AD. Methodological quality of studies was assessed with the QUADAS-2 tool as well as PRISMA guidelines and descriptive analysis followed. A RMRRS followed using the logistic regression analysis and a semi-structured interview of general practitioners (GPs) in Milton Keynes (MK) and Luton, using the framework analysis.

Results:

The findings from the review suggest that neurological and depressive behaviours are an early occurrence in early-onset AD with depressive and cognitive symptoms in the measure of semantic memory and conceptual formation in late-onset AD. It appears that there is a big variation in the patterns of signs and symptoms with cases of misdiagnosis. However,

there was limited evidence due to the limited number of studies of this kind. The nested case control design of 109 samples indicates that auditory disturbances could have diagnostic value, with a range of signs and symptoms that appears at different time. While the interviews highlight and confirm areas for consideration in the primary care and NHS. Additionally, the study reports practices in relation to the early diagnosis of AD. However, the result is not an overall representation of the views of GPs.

Conclusion:

Findings suggest that individuals with auditory disturbances have increased odds of AD. This was more striking in the white female population, with borderline significance due to limited data that is too small to detect such an uncommon symptom(s).
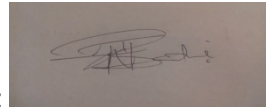
Declaration

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy (Ph.D.) at the University of Bedfordshire.

It has not been submitted before for any degree or examination in any other University.

Part of the thesis has been published as indicated on page VI, appendices XVIII & XIX.

Name of Candidate: Fidelia Bature   Signature:

Date: 24/08/2018.

In memory of my father Emmanuel Elisha Kuhiyop

1935-1985, & to you Baba P.Y Jatau.

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Publications

Peer-reviewed Publications

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Bature, F.N., Pang, D., Pappas, Y. & Guinn, B. (2018). Retrospective medical record review that identifies the patterns in the signs and symptoms preceding the clinical diagnosis of Alzheimer's disease; a nested case-control study. *Current Alzheimers Research* V. 15, Pg. 723-730. doi: 10.2174/1567205015666180404155358.

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Glossary

AD	Alzheimer's disease
ADRDA	Alzheimer's disease and Related Disorders Association
AMCI	Amnestic Mild Cognitive Impairment
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
Aβ	Amyloid Beta
BACE 1	β-Site APP Cleavage Enzyme-1
BDNF	Brain Derived Neurotropic Factor
BMI	Body Mass Index
CANPI	Care Giver Neuropsychiatric Inventory
CCG	Clinical Commissioning Group
CK	Cohen Kappa (Kappa Coefficient)
CPRD	Clinical Practice Research Database
CSF	Cerebrospinal Fluid
CT	Computed Tomography
EOAD	Early Onset Alzheimer's disease
EOFAD	Early Onset Familial Alzheimer's disease
FAD	Familial Alzheimer's disease
FDG PET	Fluoro-2-deoxy-D-glucose Positron Emission Tomography
FDG	Fluoro-2-deoxy-D-Glucose
GP	General Practitioner
HSCIS	Health and Social Care Information System
LC	Latent Class
LOAD	Late Onset Alzheimer's disease
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NFT	Neurofibrillary Tangle
NIA-AA	National Institute of Aging and Alzheimer's Association
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NSS	Neurological Soft Signs
OR	Odds Ratio

PET SCAN	Photo Emission Tomography Scan
PSEN1	Pre Senilin 1
PSEN2	Pre Senilin 2
P-Tau	Phosphorited Tau
RCD	Rapid Cognitive Decline
RPAD	Rapidly Progressive Alzheimer's disease
T-Tau	Total tau

CHAPTER ONE: Introduction

1.1 Background

Alzheimer's disease (AD), named after Alois Alzheimer, is a neurodegenerative disease in which the nerves cells gradually degenerate, due to the deposition of β-amyloid plaques (Seiko & Dennis, 2001; Fonte et al., 2001; Shoji et al., 2001; Zhan et al., 2015) and twisted intracellular strands of protein tau in the brain cells (Igbal et al., 1986; White & Lon, 2009; Flammang et al., 2012; Liu et al., 2013). This results in memory loss, cognitive and functional decline (Jack et al., 2014; Barnes & Yaffe, 2014).

A century has passed since the discovery and description of the clinical and neuropathological characteristics of AD, including the genetic and environmental risk factors as well as potential treatment. In particular, the last two decades have witnessed research on the early signs and symptoms, which led to the formation of the diagnostic criteria by the National Institute of Neurological and Communicative Disorders - AD and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). The diagnostic criteria have allowed early identification of this disease, but there is a gap between the number of early diagnosed and undiagnosed cases due to diagnostic uncertainties, including a lack of a recognised pattern of the signs and symptoms preceding the diagnosis of the disease.

There is a discourse in the meaning of early diagnosis, which is interwoven both in understanding the disease and ways to deal with it. Early diagnosis is considered as a set of interpretive packages that make sense of diagnostics (Mueller et al., 2005; Whitehouse & George, 2008; Cuijpers et al., 2014). In the context of healthcare technology (HCT), this involves value for money, changing health care, innovation trajectories, changing the definition of AD, steps on the road to medication and early management (Dubois et al., 2007; Cuijpers et al., 2014). Early diagnosis here refers to the diagnosis at the lowest threshold of the disease or at the stage of mild cognitive impairment (MCI) with a cluster of early signs and symptoms, as well as the diagnosis of the pathology of AD before dementia.

The late diagnosis of AD has become a public health issue (Health and Social Care Information Centre (HSCIC), 2014) despite the research conducted and the financial

expenditure on the disease. Indeed, the number of individuals receiving a late AD diagnosis remains high among the ever-increasing ageing population in the United Kingdom (UK) that accounts for about 11 million of older adults aged 65 years and 14.7 million aged 60 years and over. This is more than the number of 18 years old in the UK (National Statistics, 2014). The situation is similar in countries campaigning for early diagnosis.

It has been estimated that one in four individuals (25%) with the disease in the UK have been diagnosed (HSCIC, 2014), and late diagnosis of AD is documented to result in severe health consequences to individuals affected and their caregivers. In a study to describe the factors associated with a late diagnosis of AD, 62% of patients remained undiagnosed for a year after their symptoms were first presented to the physician for diagnosis (Knopman, Donohve & Gutterman, 2000). The current trend in the UK is that it takes two to four years before an AD diagnosis is established (National Health Service, 2014). However, a timely diagnosis in the UK varies depending on locality. In some areas, less than 40% of individuals with the signs and symptoms of the disease have received a diagnosis (Alzheimer's Society, 2014). This is attributed to a shortage in specialised diagnostic services, lack of training and lack of disease-modifying options, which makes the healthcare professional reluctant to give a diagnosis (Dubois et al., 2015) among other reasons.

Furthermore, the All Party Parliamentary Group on dementia (2013) indicates that the Black, Asian and Minority Ethnic Groups (BAME) are less likely to receive a diagnosis or support than their white counterparts; the prevalence rate for these groups has not been updated since 2014. Waiting for a long time to be diagnosed can increase the degenerative processes, resulting in anxiety and depression. Globally, the picture is the same, as 78% of the 36 million individuals with the disease are yet to receive a diagnosis (World Alzheimer's Report, 2015). Similar findings have been noted in other developed countries (Carpentier et al., 2010), such as in France where only 50% of AD patients were diagnosed in 2011 and the average time from first warning signs to AD diagnosis takes two years (Rapp et al., 2014). The situation is even worse in developing countries, with an estimated 90% of individuals with the disease in India as yet undiagnosed (World Alzheimer's Report, 2015). According to Dementia Statistics, UK (2017), the number of

individuals diagnosed with all-cause dementia is 539,062; however, the number of those with AD dementia, which is the late stage of AD, is unknown.

Studies indicate that this could be due to under-reporting by patients and their families, as the symptoms are confused with normal ageing and emerge so gradually that they are not recognisable (Ording & Sorensen, 2013; Jones et al., 2015). Additionally, there is a high cost of diagnosis and treatment (Alzheimer's report, 2014), which arguably delays individuals and family members seeking help, and a subsequent concealment of symptoms that results in late diagnosis (Ording & Sorensen, 2013; NHS Choices, 2014; Alzheimer's Report, 2014; Marquer et al., 2014). Other factors associated with the delay in diagnosis include the limited understanding of the differences between memory processes in ageing and AD by both caregivers and physicians (Knopman et al., 2000; Shim et al., 2013). The inaccurate specification/unclear pattern of the signs and symptoms also contribute to the late diagnosis. The pathological results of 119 of 533 patients diagnosed with AD and retrospectively reviewed in a database study did not meet the diagnostic criteria for definite AD (Shim et al., 2013). An earlier post-mortem examination of individuals diagnosed with prion disease indicated that they actually suffered from AD (Schmidt et al., 2010). This may be attributed to technical reasons, however, a distinction in signs and symptoms of AD might have made the difference.

Major advances in the identification of structural molecular neuroimaging and cerebrospinal fluid (CSF) biomarkers with cognitive assessment (Didic et al., 2011) have made the diagnosis of AD pathology possible (Holtzman et al., 2011; Dubois et al., 2014). However, these laboratory tests are restricted to tertiary care centres (academic centres and clinical trials) and are not available in primary care in the community (Albert et al., 2012). Moreover, the examination of the proposed biomarkers (such as neuroimaging and PET scan) can be expensive and invasive, with an addictive value that could delay the diagnosis in clinical settings (Schoonenboom et al., 2012; Zahodne et al., 2013). Identifying patterns of the clinical manifestations of the disease, in measuring disease progression, can be a marker that can easily be assessable in primary care settings, potentially reducing the number of individuals waiting to be diagnosed and complement the assessment of biomarkers in the tertiary sector.

Additionally, the Mini-Mental State Examination (MMSE), a test carried out by clinicians in the general practice consisting of eleven series of questions and examinations to assess the changes in memory or other mental abilities, increases the time it takes for routine screening. It consists of many questions that need to be answered within a short time (Mendiondo et al., 2003). The test does not detect subtle memory loss in highly educated individuals (Costa et al., 2013), as this can be viewed as average intelligence. Moreover, the test is not appropriate for patients with learning or communication disabilities (NICE guideline, 2006) due to communication uncertainties in these individuals.

In a Canadian survey of 398 caregivers, 78% were family members who manifested the symptoms of AD and comorbid conditions (Black et al., 2010). The financial expenditure for AD in the UK is approximately £26 billion annually, equating to a £30,000 annual cost of treating an individual, more than treating cancer (£5,500), diabetes (£2,500) and heart disease (£4,560) per patient put together (Alzheimer's Research UK, 2014). This expenditure includes the medical (institutionalisation) and non-medical costs. A UK cross-sectional observational study (18 UK sites) of 249 possible/probable AD indicated that the median and mean direct non-medical costs of care for individuals with AD were £168 and £2,924 per annum respectively (Jones et al., 2015).

As affirmed by Barnett et al. (2014), the net benefit of early intervention, which is the intervention to delay the degenerative process and institutionalisation, economic and social benefit, is reduced by approximately 17% for every year intervention was delayed. Early detection and starting intervention early may be associated with less cognitive decline, longer survival and financial savings of about £7,000 per patient annually (Mittelman et al., 2006; Chamberlain et al., 2011; Getsios et al., 2013; Barnett et al., 2014). An economic evaluation of early assessment of AD in the UK reported that early assessment reduces health care costs by £3,600 per patient and societal costs by £7,750 per patient annually (Getsios et al., 2013). Late diagnosis is a burden to patients, family members, as well as health and social care (Black et al., 2009; Barnett et al., 2014; Jones et al., 2015).

AD is a reverse causality for conditions such as cholesterolemia, hypertension and depression (Rao et al., 2014). It has been discovered that multiple comorbid pathologies or concomitant health conditions associated with advanced age contribute to the clinical

manifestation of AD, exacerbating the rate of cognitive decline (Feldman et al., 2014). These comorbidities include musculoskeletal, genitourinary, ear, nose and throat (ENT), vascular/heart conditions, gastrointestinal tract diseases, endocrine/metabolic, psychiatric conditions/depression and related dementias (Katz et al., 1997; Doraiswamy et al., 2002). They can act as a confounder, threatening the internal validity, or as an effect modifier, threatening the internal and external validity of empirical studies (Greenfield et al., 1993). This calls for a clear distinction between AD and the comorbidities for appropriate intervention.

1.2. The prevalence of the disease and cost of treatment in the UK

Globally, AD prevalence has been estimated to be about 36 million in 2014 in a world population of 7.3 billion individuals (United Nations, 2015), with a projected increase of about 115 million in 2050, due to the improvement in health and economic conditions (Alzheimer's Research, UK 2014) (**Figure 1.1**). According to the Alzheimer's report (2015), there are almost 900 million people aged 60 years and above living globally with AD due to the rising life expectancy; which is contributing to the rapid increase predicted in the number of patients diagnosed with AD and other chronic diseases such as cancer and diabetes.
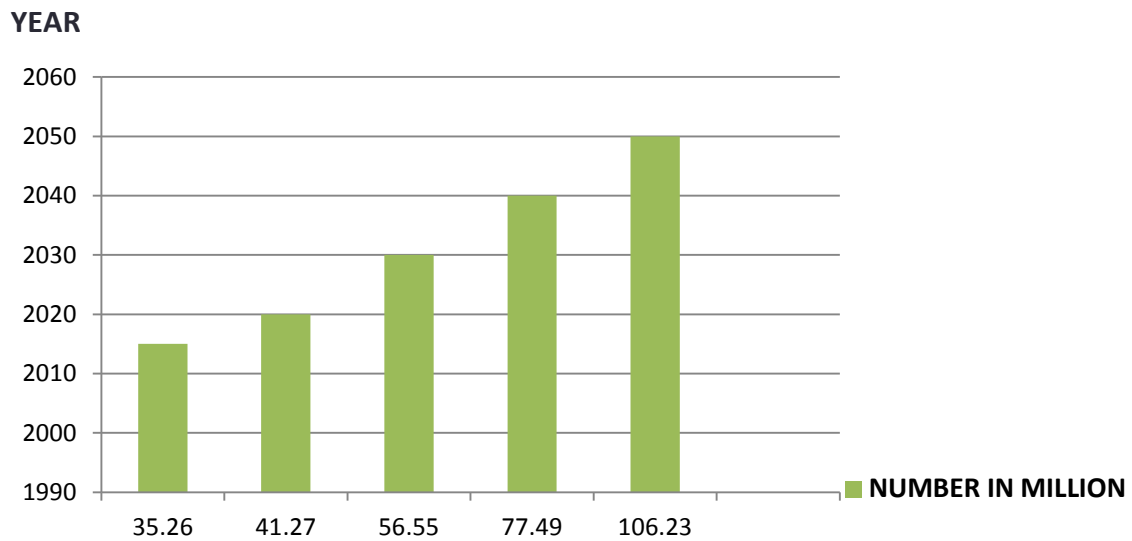
Figure 1.1. The projected increase in the prevalence of AD. The graph represents the projected prevalence of AD in the world population in 35 years' time.

In the UK, an AD prevalence of 520,000 has been reported (National Statistics, 2014), which equates to 8.1% of the 64.1 million population and rising due to ageing and improved diagnostic techniques. There is an annual incidence of 62,000; the prevalence in the early onset AD (EOAD) accounts for approximately 40,000, 5% of the annual prevalence (NHS Choices, 2014). As expected, the frequency increases with age: approximately 1 in 20 (5%) adults aged 65 years and under, 1 in 14 (7%) adults over 65 years, 1 in 4 (39%) adults 75 years and older, and 1 in 6 (17%) over 80 years and above are affected by AD (HSCIS, 2014) (**Figure 1.2**). The prevalence is high among the 75-year-old plus due to the fact that late onset AD (predominant AD) begins at 65 years and above, which takes between 10–30 years before the onset of signs and symptoms, hence the highest prevalence in the group.
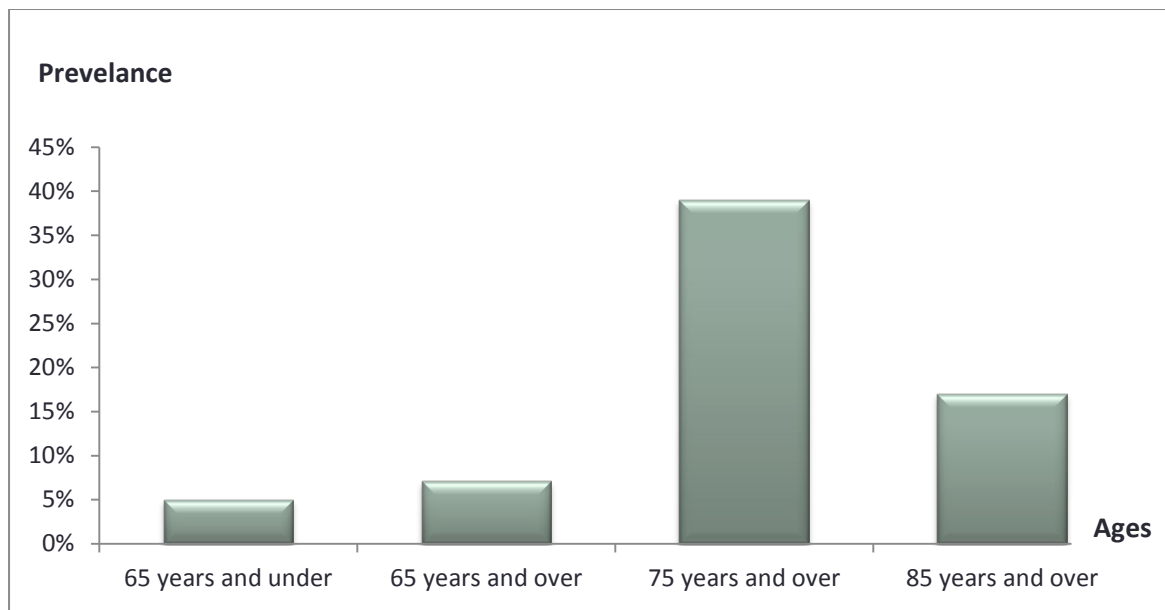
Figure 1.2: Prevalence of AD in the UK population. The X-axis represents the prevalence according to age and the Y-axis represents the ageing population; the prevalence among the UK population increases with age, with those aged 75 years and over accounting for 39% of the diagnoses.

In Buckinghamshire, among the population of 521,922 individuals, a dementia prevalence of 7,000 (Buckinghamshire City Council, 2015) was recorded in 2015 and a prevalence of 2,300 in Milton Keynes, of which 60–80% (1,380–1,840) was AD. The highest prevalence was recorded in individuals 85–89 years of age (Alzheimer's Society, 2015; JSNA, 2015), with the prevalence declining after the age of 90 years due to increased mortality among this group. As the prevalence of the disease continues to rise in the ageing population, there is an increasing need to identify cases of AD early, so that patients can receive appropriate therapy and care, while carers and family members can be helped and be supported.

1.3. The study rationale

The purpose of this research was to identify patterns in the sequence and timing of presentations preceding the clinical manifestation of AD for the development of a predictive model for early detection. Advances in AD research have led to the identification of appropriate biomarkers, including amyloid protein and phosphorylated tau that aid the diagnosis of the disease (McKhann et al., 2014; Dubois et al., 2007; 2014).

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Nevertheless, the late diagnosis of individuals with AD is a major challenge. In the UK, it has been estimated that three-quarter of individuals with AD have not received a formal diagnosis (Alzheimer's Statistics, 2014), the majority of whom belong to the ageing population also suffering from the degenerative process of ageing. Worldwide, studies have shown that adults of 60 years and above are projected to double from 2010–2025, the projection by 2050 is more than five times the number in 2010 in the upper medium income countries (**Table 1.1**).

Table 1.1: Projected number of adults aged 60 years and above globally.

YEAR	Higher	Upper medium	Lower middle	Lower	Worldwide
2010	232.3 (30.4%)	116.4 (15.2%	356.2 (46.6%)	59.8 (7.8%)	764.7 (100%)
2015	309.4 (34.6%)	319.8 (35.7%)	233.1 (26.0%)	32.9 (3.7%)	895.2 (100%)
2030	403.9 (29.4%)	531.5 (38.7%)	386.0 (28.1%)	53.5 (3.9%)	1347.8 (100%)
2050	482.5 (23.9%)	760.8 (37.7%)	665.3 (32.9%)	111.4 (5.8%)	2020.0 (100%)

The diagnostic rate of AD varies across the country, from 39% in low-performance areas on the diagnostic procedure to 75% in the high-performance localities (Department of Health UK, 2013; Alzheimer's Statistics, 2015). The reason for the late diagnosis of AD in the population is attributed to factors including the current diagnostic criteria (**Chapter 2.3**), which are based on assessment of biomarkers, including only two clinical phenotypes that might not be the early symptoms, therefore, insufficiently address other aspects of the presentation of the disease, like the signs and symptoms (Rohrer et al., 2012; Jones et al., 2015). The signs and symptoms are often not the same in all cases (Caselli et al., 2013) and could be misleading.

The biomarkers or signature of AD has been a low level of $A\beta\_42$ and high level of total tau (T-tau) and phosphorylated tau (P-tau) (Blennow et al., 2003; Leon et al., 2006; Galasko et al., 2009). Magnetic resonance imaging (MRI) and fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) have indicated sensitivity for AD identification at the MCI and normal cognitive stages (Leon et al., 2001; Misconi et al., 2007; Blennow et al., 2010). Even though the diagnostic value is enhanced with cerebrospinal fluid (CSF),

diagnosis of AD remains difficult mostly on clinical grounds, as there is variability in CSF collection methodology that results in variability of Aβ results (Dubois et al., 2007; Lucey et al., 2015). Access to biomarkers is restricted in some settings and the immunoassay of concern (Dubois et al., 2007; McKhann et al., 2011; Schicktanz et al., 2014; Laske et al., 2015), which has made the replication of the results difficult.

Furthermore, the low level of Aβ_42 has also been reported in plaque-free Creutzfeldt-Jakob disease (CJD) and in bacterial meningitis (Sjogren et al., 2001; Wiltfang et al., 2003; Schmidt et al., 2010), while a high level of T-tau has been reported in normal ageing and CJD. Moreover, even though Aβ_42 is said to occur before the deposition of tau pathology, neurofibrillary tangle (NFT) formation and neuronal degenerations (Jack et al., 2010; 2013; Trojanowski & Hampel, 2011), some researchers have shown that Aβ and tau occur 10–15 years before the onset of symptoms (Gustafson et al., 2007). Other researchers suggest that tau deposition precedes amyloid plaque pathology in predicting cognitive decline in healthy individuals (Braak & Braak, 1997), while Stomrud et al. (2007) states that CSF Aβ_42 reduction is more predictive of cognitive decline than high levels of tau. This variability including the inter-assay and inter-laboratory (Mattson et al., 2009; Verwey et al., 2009; Blennow et al., 2015) limits the ability to discriminate AD from other dementias and necessitates the consideration of other aspects of presentations, like the pattern in the timing and sequence of symptoms and signs of AD.

There seems to be conflicting evidence of moderate knowledge of AD among health professionals (Smyth et al., 2013; Kada et al., 2015), including the knowledge of the course or pathology of the disease. Furthermore, there is a lack of understanding of the transitional stage of asymptomatic and symptomatic AD (Paton et al., 2004; Lowe et al., 2014). An informal and interactive survey of individuals in twelve countries regarding the knowledge of the signs and symptoms of AD indicated that 5% of the surveyed individuals had a misconception of the signs and symptoms of AD with normal ageing (Alz.org, 2015) and these individuals would be unlikely to initiate or seek an intervention, hence the need to draw patterns in presentations. Moreover, there is no study that has been undertaken in the UK regarding the pattern of the signs and symptoms preceding the clinical diagnosis of the disease. Identifying the patterns that are specific to the different stages of the disease progression can improve the accuracy of diagnosis (Ganguli et al.,

2011; Lenderking et al., 2014; Johnson et al., 2015; Laske et al., 2015) for early intervention.

The researcher focusses on the limitations of early diagnosis encountered in the primary and secondary care settings and identifies patterns in the signs and symptoms at the preclinical stage, a strategy to help overcome late diagnosis that is yet to be fully researched. A better understanding of this has important clinical implications, particularly with regards to early detection (Albert et al., 2011; McKhann et al., 2014), as this period is the best time for therapeutic interventions (Reiman et al., 2009).

Critics of the early diagnosis of AD (Le Couteur et al., 2013; Lock et al., 2013) are of the opinion that early detection will mainly lead to an increase in the prevalence with unnecessary investigations, side effects from premature treatment, stigmatisation and less support (Robinson et al., 2014). However, studies indicate that the early detection of AD is beneficial (Schicktanz et al., 2014) and that the AD label is not associated with more stigmatising reactions (Johnson et al., 2015). Detecting changes that reflect disease progression in a relatively short time before the obvious/noticeable signs and symptoms emerge will obviously decrease the number of patients waiting to be diagnosed. This will also support a screening system that will predict individuals at risk and inform the intervention that is most suitable for the individual to slow progression, affording them the opportunity to make informed choices (Mittelman et al., 1996; Solomon & Murphy, 2005; Bruandet et al., 2009; Feldman et al., 2014) and delay institutionalisation. The Alzheimer's Statistics (2015) in the UK indicates that delaying the onset of dementia by five years through the early detection and diagnosis of the disease would reduce deaths directly attributed to dementia by 30,000.

Doctor's surgeries, being the primary care providers and the first point of contact for the patients, have an important role in the early detection. Indeed, 90% of data recorded at general practices during the last seven years is appropriate to enable the identification of early signs and symptoms that might suggest screening strategies for primary care to improve the prognosis of AD (William et al., 2012). This will then serve as a coordinator between the primary and secondary specialist care providers to confirm the diagnosis, as the initiation of screening is made easy with the predictive model.

1.4. Aim

To identify patterns in signs and symptoms preceding the clinical diagnosis of AD for the development of a predictive model for the early detection of the disease.

1.4.1. Objectives

1. To map, synthesise and appraise the quality of the existing evidence on the timing and sequence of signs and symptoms that will justify the clinical diagnosis of AD via a systematic scoping review.

2. To identify patterns in signs and symptoms preceding the clinical diagnosis of AD in general practice notes and patients' records, as these were presented by the AD patients before their clinical diagnosis.

3. To explore the perspectives of GPs regarding factors that may contribute to late diagnosis and recommendations for overcoming barriers to timely diagnose AD.

1.5. Description of research study plan

Objective 1

To map, synthesise and appraise the quality of existing literature on the timing and sequence of the signs and symptoms that will justify the clinical diagnosis of AD, via a systematic scoping review to inform the primary study.

Method 1 – Systematic Scoping Review

This objective was met and achieved with a systematic scoping review of research in the field of AD, which synthesised and interpreted components of the epidemiological evidence on timing and sequence of early signs and symptoms that justified a diagnosis of AD. This is an advancement to the literature review, which provided evidence and appraised findings from the entire field of study (Levac et al., 2010; Gough & Thomas, 2012). The protocol for this method is presented in section 3.1, while the method is presented in chapter four and analysed with a descriptive analysis.

Objective 2

To identify patterns in signs and symptoms preceding the clinical diagnosis of AD in general practice notes and patients' records, as these were presented by the AD patients before their clinical diagnosis.

Method 2 – Case-Control Design

This objective has been achieved with the RMRR (case-control design) which was undertaken at GP surgeries in Milton Keynes and Luton. GP surgeries were approached for the study to allow access to case notes from patients diagnosed with AD in the year 2006–2016. These notes were collected and reviewed retrospectively to identify patterns in the signs and symptoms preceding a diagnosis of AD. Probable AD met the diagnostic criteria of the NINCDS-ADRDA and screened with MMSE with a memory score of 15 and above. The signs and symptoms were measured with the Neuro-Psychiatric Inventory (NPI), which is explained in chapter three. Milton Keynes was chosen because it falls within the jurisdiction of South East England, which has the highest prevalence (n = 121,512) of people with AD (Alzheimer's Society, 2014), with a population of 16–65 year olds higher than the rest of England, while Luton has an ethnic diversity that will enrich the study results as detailed in chapter three.

Comorbidities were taken into consideration and met the standard comorbidity measurement of Index of Coexisting Disease (ICED). The ICED is a valid and reliable two-dimensional structure, measuring the severity of diseases and disability caused by comorbidity, especially useful when disability and mortality are the outcomes of interest (de Groot et al., 2003). The scores of the ICED are based on the existing signs and symptoms. The comorbidities are measured to correct confounding for internal validity, secondly to identify effect modifiers, thirdly to predict the outcome of the study and finally for statistical efficiency (de Groot et al., 2003). The statistical analysis was undertaken with the latent class (LC) logistic regression model explained in chapter three to generate subtle data patterns.

Objective 3

To explore the perspectives of GPs regarding factors that may contribute to late diagnosis and recommendations for overcoming barriers to the timely diagnosis of AD.

Method 3 – Qualitative Interviews

This objective has been met with qualitative interviews of GPs in MK and Luton exploring the perspective, seeking to elaborate and enhance the results of the retrospective medical record review and systematic scoping review studies. Analysis of verbatim transcripts was inspired by interpretive descriptive statistics and framework analysis.

1.6. The significance of the study and contribution to knowledge

The study contributes to three main areas of literature. Firstly, this study extends the existing knowledge of the signs and symptoms preceding a diagnosis of AD through the identification of patterns in the sequence and timing of these presentations. This would have a significant impact on future patients as the study could help in identifying the disease early/earlier with potential physical, social and financial benefit to patients, families and the healthcare sector.

Secondly, the diagnostic criteria are weighted more on biomarkers. The addition of an observable, non-invasive and cost-effective pattern of signs and symptoms suggest an additional early detection model that can be developed to be used in clinical settings. Thirdly, the research collected clinical data from GP surgeries, a field also underutilised, and helps fill the gap in the literature regarding the pattern of signs and symptoms preceding the diagnosis of AD, as there is no study that has been undertaken on this.

In conclusion, the study has the potential to inform future policy on the early detection of AD due to a lack of literature of this magnitude for timely and effective therapeutic intervention, to reduce the degenerative process of the disease.

1.7. Summary

This chapter has described the problems of late diagnosis, the burden of the disease to individuals and the cost of AD to the healthcare sector (11.2% of disability years in adults 60 years and above). The chapter also explained the benefits of early detection and issues that prevent the timely identification of the early signs and symptoms of AD, including confusing symptoms with other diseases (Jones et al., 2015), under-reporting of

symptoms by individuals or carers (Ording & Sorensen, 2013), high cost of diagnosis (Ording & Sorensen, 2013), lack of knowledge of the disease process (McKhann et al., 2011; Hudson et al., 2012) and issues with the diagnostic criteria (Albert et al., 2011; Zahodne et al., 2013). This chapter has identified the need for the research to enable the identification of patterns of the signs and symptoms preceding the clinical diagnosis of AD to suggest the development of a predictive model.

In order to demonstrate the need for identification of patterns, it is necessary to explore the scientific reasoning and data available, so the next chapter will proceed to view and summarise the available literature on the early signs and symptoms of the AD.

CHAPTER TWO: Review of literature

Modalities to identify AD include biomarkers, the signs, and symptoms. After an extensive engagement with the literature, this chapter identifies and provides six major themes from the literature reviewed: Firstly, the chapter provides an overview and summarizes the state-of-the-art in terms of its knowledge of AD. Secondly, the current concepts of the early signs and symptoms or rather the MCI and subjective cognitive decline (SCD), which emphasize the timing of the appearance of these presentations, are discussed. I will guide the reader to understand the early stage and manifestation of the degenerative processes which will enable early detection. Thirdly, the diagnostic criteria which incorporate biomarkers and clinical phenotypes are discussed in relation to the early diagnosis of the disease. Fourthly, the current issues surrounding the late diagnosis of AD and the benefits of early detection of the disease are explored.

The review includes a summary of individual signs and symptoms, how they relate to the stage of disease, the current debate as to which of the signs or symptoms appears first and their contribution to understanding the need to map their patterns of occurrence preceding a diagnosis of AD is also discussed. The literature is sought from a variety of different sources including magazines, newspaper articles, journals and articles, electronic databases including PubMed, MEDLINE, Web of Science, CINAHL, PsycINFO, AMED (Allied and Complementary Medicine), Scopus, Nursing Index, DH-data, King's fund, Google scholar and conference proceedings including grey literatures. The chapter ends with a summary of the literature presented, the identification of knowledge gaps in this field and the need to identify patterns of the signs and symptoms preceding the diagnosis of AD, for the development of a predictive model.

2.1. An overview of AD

AD is the most prevalent form of dementia, accounting for 60-80% of all dementias. Dementia describes a group of diseases that share a syndrome typically chronic and progressive in nature and involves disturbances of multiple higher cortical functions, such

as memory, thinking, orientation, perception and behaviours among the elderly (Alz.Org., 2014; Barnard et al., 2014).

Just like any organ in the body, brain function declines with healthy ageing but it does not lose neurons, that is, a network of communication, metabolism and repair within the brain and its environ, in large numbers. However, as stated by the National Institute of Aging (NIA, 2014), the reverse is the case in AD, with extensive damage to the neurons, characterised by the loss of connectivity with other neurons. As a result, there are neuronal dysfunction and subsequent death.

AD is characterised by the deposition of the extracellular protein fragment β- amyloid (plaques) and twisted intracellular strands of protein Tau in the brain cells (nerves), which causes a range of changes in the brain anatomy, biochemistry, genetics and functions (Selkoe et al., 2001; Jack et al., 2014). Cognitive normal individuals have AD pathology. There is amyloid deposition (Hyman et al., 2011) and neurofibrillary tangle (NFT) formation, which is almost universal in patients over the age of sixty-five, as indicated by the neuropathological studies of normal ageing, in the entorhinal cortex, as part of normal ageing or pathology (Bouras, 1994; Braak, 1995; Casselli et al., 2013). Their extension into the neocortical regions is not part of healthy ageing but attributed to AD. This might affect the ability of medical professionals to distinguish AD from normal ageing, for which fibrillary amyloid is very often detected, and other conditions with the same presentations can affect and interfere with the diagnostic algorithm. The biomarkers are thus explained.

2.1.1 Signature of AD

AD is characterised by five established biomarkers that indicate the presence of AD pathology in the brain; neuropathology that is presented by the widespread deposit of extracellular plaques consisting of amyloid βeta (Aβ) peptides and intracellular NFT consisting of phosphorylated tau (p-tau) (Serrano-Pozo et al., 2011; Hoglund et al., 2015), decreased levels of aβ42 with increased concentration of total tau (t-tau) and phosphorylated tau (p-tau), respectively in the CFS (Lewczuk et al., 2010), decrease glucose metabolism in the brain (Lowe et al., 2009) and cerebral atrophy (Dickenson et al., 2011).

2.1.1.0 Tangles and plagues

Although AD manifests clinically with progressive memory impairment and cognitive decline, the hallmarks of extracellular senile plaques of amyloid-β (Aβ) protein and intracellular hyperphosphorylated or twisted strands of protein Tau, are considered to be the main inducers and biomarkers of AD (NIA, 2014). These protein plaques signal changes in the biological processes long before the onset of cognitive symptoms (Jack et al., 2013). The involvement in tangles eventually leads to synaptic loss and nerve cell death when viewed under the microscope. Tangles and plaques are closely associated with the degree of cognitive impairment in AD individuals (Mrak & Griffin, 2001), and presence along with the cognitive impairment to warrant a diagnosis of AD.

2.1.1.1 Amyloid beta (Aβ)

Glenner & Wong (1984) were able to determine the composition of the two pathological hallmarks of AD, by isolating and identifying beta (Aβ) protein, which becomes insoluble to form neuritic plaques in the brain. Enzymes called β secretase and γ secretase in the body are responsible for producing the insoluble Aβ protein when the protein is cut sequentially; an increase in the activities of the β secretase in AD leads to overproduction of the insoluble protein that sticks together to form neurotic plaque (Sinha et al.,1999).

However, even with the strong suggestions that amyloid accumulation in the brain is responsible for AD, some researchers (Giannakopoulos et al., 2003) are of the opinion that the accumulation of the amyloid protein in the brain is not a strong predictor of the degree of cognitive impairment among adults with the disease. This is because some adults diagnosed with the disease had a low accumulation of amyloid protein in the brain (Haroutunian et al., 2008) while others with high accumulation of this protein consistent with AD, but exhibited normal cognitive function (Knopman et al., 2003; Bennett et al., 2006). This can also interfere with the diagnostic procedure, leads to misdiagnosis, and consequent late diagnosis of the disease. A supportive measure could be the observable patterns in the signs and symptoms of the disease.

2.1.1.2 T-tau and P-tau

Soon after, a number of researchers (Wood et al., 1986; Grundke-Iqbal et al., 1986; Kosik et al., 1986) identified Tau protein that makes up the NFT. Tau is a protein in the brain; a

microtubule binding protein that helps maintain the structural integrity of microtubules, by primarily promoting stability (Drechsel et al., 1992). Tau becomes saturated in AD with the chemical phosphate in a process known as phosphorylation (Goode et al., 2000), which binds together to form NFT inside the neurons (Santa-Maria et al., 2012).

The tau and tangle hypothesis by Mudher & Lovestone (2002), describes structural changes to tau and subsequent formation of NFT as being the primary cause of AD. But, this has received less support compared with the amyloid cascade hypothesis in the scientific community. However, evidence (Braak & Braak, 1991; Arriagada et al., 1992; Mitchell et al., 2002), suggests a significant relationship between the severity of the disease and accumulation of NFT compared to percentage neurotic plaques in the brain. Ironically, this hypothesis has its own limitation by the fact that genetic mutations to the tau protein do not lead to AD, but are known to cause fronto-temporal dementia, characterised by damage to the frontal and temporal lobes of the brain and changes to personality, behaviour, and language (McKhann et al., 2001).

Changes, therefore, in an unknown pathway could be the cause of AD, due to the rising debate among the scientific community about the strength and limitations of both the amyloid cascade and tau and tangle hypothesis, which needs more investigation. Moreover, cost and physical discomfort are some of the barriers and limitations to collecting these biomarkers. If there are debates about the biomarkers as signatures of the disease, the non-invasive and observable symptoms may just be the help needed to detect the disease early.

2.1.1.3 Other biomarkers

2.1.1.3a Post-synaptic protein neurogranin (NG)

Neurogranin is a postsynaptic protein involved in the regulation of synaptic signaling, through binding to calmodulin at low levels of calcium (Baudier et al., 1991). The protein is significantly increased in AD as compared to healthy individuals and correlate with rapid change in cognition in individuals at clinical follow-up (Kvartsberg et al., 2015).

2.1.1.3b Axonal cytoskeleton protein filament (NF) protein

Numerous studies (Rosengren et al., 1999; Sjogren et al., 2000; Hu et al., 2002; Norgren et al., 2003; Pijnenburg et al., 2007) have suggested an increased in CSF levels of NF light (NFL) and NF heavy (NFH), two subunits of NF consisting of four subunits (NF-light, NF-medium, NF-heavy, and Alpha-intermexin) in AD individuals. Neurofilament is a prominent axonal cytoskeleton protein found exclusively in neurons for the maintenance of neuronal caliber (Gresle et al., 2006).

2.1.1.3c Phospholipids

Lower levels of ten different phospholipids were found in older adults with impaired memory compared to adults with normal cognition, who went on to convert from normal to impaired cognition, within a five-year period (Mapstone et al., 2014) suggesting that other biomarkers may accurately identify individuals at the pre-clinical stage of the disease. A simple blood test clinically could identify those with AD in place of the most advanced biomarkers that are expensive and intrusive.

2.1.2 Stages of AD

AD was initially thought to be a disease with one phase, describing only the later stages, when dementia is already present (National Institute of Aging and Alzheimer's Association-NIA-AA, 2011). The practice was still the same especially in 1984, till the NIA-AA, for the first time in 2011, revised the clinical diagnostic criteria for AD and incorporated the three stages of AD that covers the full spectrum of the gradual changes of the disease namely:

2.1.2.1 Preclinical

The significant clinical symptoms are yet evident at the preclinical stage, with the changes in the brain including the accumulation of amyloid protein and early nerve changes potentially in progress. The risk of progression to AD is unknown and can only be detected by the presence of biomarkers (CSF analysis) and brain (positron emission tomography-PET) scan, without some of the early brain changes and outward symptoms (Jack et al., 2011; Ritchie et al., 2016). The preclinical phase of cognitive deficits precedes the clinical diagnosis of probable AD by more than six years as described by the Framingham studies (Tan et al., 2003), but might last up to 20 years before the disease is pronounced.

2.1.2.2 Intermediate stage or MCI

The intermediate stage is characterised by mild symptoms but without physical and mental incapacitation. Individuals may progress to Alzheimer's dementia (Albert et al.,2011), with the biomarkers including elevated levels of tau or decreased levels of beta-amyloid in the CSF, reduced glucose uptake in the brain as determined by PET, and atrophy of certain areas of the brain noticed with structured magnetic resonance imaging (MRI).

2.1.2.3 Dementia due to AD or Alzheimer's dementia (DAD)

This is the final stage; pronounced symptomatical and interferes with daily activities. A decline in cognition such as aphasia (word finding), hallucinations (vision/ spatial issues), and agnosia (impaired reasoning or judgment) may be the first symptoms to be noticed and the most relevant for clinicians and patients (Guy et al., 2011). Progression of the symptoms of AD takes a long time and might be mistaken for old age, which calls for more attention to the pattern at each stage of the disease, as it has been observed that individuals even at the preclinical stage could be aware that something is not right in their biological system and might constantly seek the help of their GPs to identify what is wrong with them.

2.1.3 Types of AD

The cause of AD is unknown; while the disease is associated with old age from 60years and above, scientists have discovered that AD can develop in the 30s, 40s, 50s or 60s. Although scientists have discovered the degenerative processes of disease in the brain (Ridha et al., 2006; Williams, 2013), the reason it develops and affects some individuals is unclear. While individuals sometimes mistake the disease for old age, there are considerable differences between the disease and old age (**Table 2.1**). The disease is classified into:

2.1.3.1. EOAD

This occurs in individuals 30-60 years; before 65 years, rare and might be inherited (familial AD) or sporadic without a known cause (Brickell et al., 2006; Braskie et al., 2011). Early-onset Familial AD (EOFAD) is caused by a gene in chromosomes 21, 14 and 1 that triggers the formation of abnormal and mutation of the amyloid precursor protein (APP),

presenilin-1 (PSEN-1) and presenilin- 2(PSEN-2) respectively. Each of these mutated gene products plays a role in the breakdown of APP, a part of a process that generates harmful forms of amyloid plaque, a hallmark of AD (Ridha et al., 2006; Pottier et al., 2013; Sassi et al., 2014). Presenilin-1 accounts for about two-thirds of EOFAD cases (35-70%).

2.1.3.2. LOAD

Otherwise, known as sporadic AD, LOAD is the dominant type of AD that starts at 65years and above and account for 90% of all cases of AD. LOAD had been genetically associated with the Allele types 4 apolipoprotein E (apoE) (Corder et al., 2003). The autopsies of LOAD patients indicated the presence of cytokines in the brain, a pleiotropic (more than one effect) protein involved in various immune responses, inflammatory processes and hematopoiesis (Rubio-Perez et al., 2012; Latta et al., 2015). Cytokines, a Greek word meaning cell (cyto) movement (kines), are produced by monocytes and macrophages as a proprotein and released in response to cell injury and thus lead to apoptosis (programmed cell death). The many effects of cytokines have shown to be associated with rheumatoid arthritis and AD (Refseq, 2008; Mandal et al., 2015). The proteins aid cell-to-cell communication in immune responses, stimulate the movement of cells towards the site of inflammation and link to a genetic defect in chromosomes 14 (Mandal et al., 2015; Ebbert et al., 2016). The progression, however, is similar in both the early and late onset of the disease, with the youngest onset in the UK documented as early as 27 years of age. Due to the fact that the progression is similar, establishing the different pattern of presentations in timing and sequence will help identify their differences.

TABLE 2.1: The difference between the signs and symptoms of ageing, in comparison with early and late signs and symptoms of AD.

SIGNS AND SYMPTOMS OF NORMAL AGEING	EARLY SIGNS AND SYMPTOMS OF AD	LATE SIGNS AND SYMPTOMS OF AD
Occasional memory loss of past event but not present events	Episodic memory loss	Worsening memory loss/dementia
Difficulty in finding the right words occasionally without trouble having a conversation	Apathy	Aphasia
Normal fear of frightful events only	Irritability	Phobia
Occasional pause to remember direction for unfamiliar places or to speak	Anosognosia	Hallucination and delusion
Calm except in danger	Anxiety	Opnea and restlessness
Minor decline in olfactory function due to age	Olfactory deficit	Agitation
Mobility	Disinhibition	Immobility
Independence	Aberrant motor behaviour	Loss of independence

2.2 Concepts in AD in relation to timing/stages of the disease

There has been a proposition of multiple definitions to capture the intermediate stage between healthy ageing and mild cognitive changes and dementia (**Figure 2.1**); this has been in line with the efforts devoted to diagnosing the disease early by recognising the signs and symptoms that could be used as reliable predictive markers of the disease (Flicker et al., 1991; Stephan et al., 2010).

Model of trajectory of AD
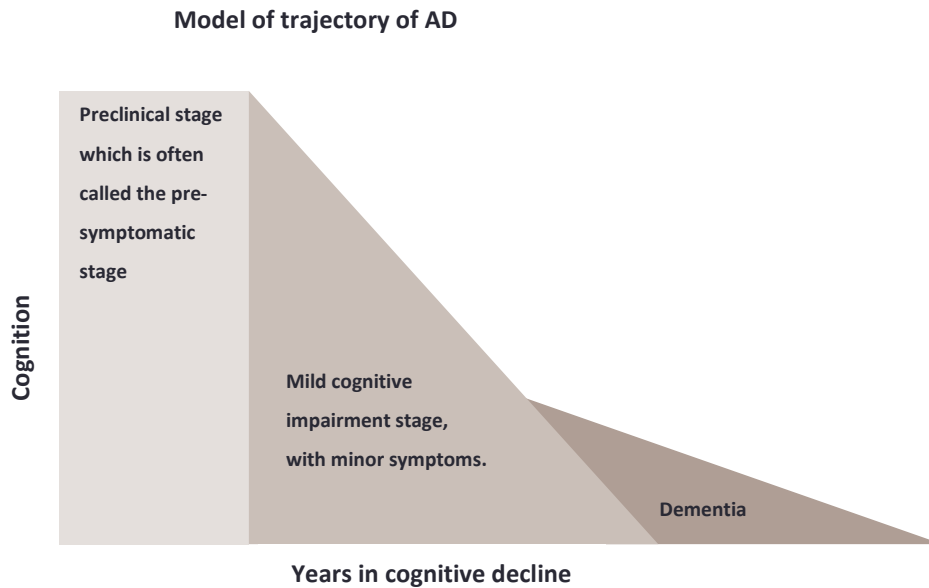
Figure 2.1: A model of the trajectory of AD. The stage of preclinical precedes MCI and encompasses the spectrum of the presymptomatic stage to the third stage of dementia. The signs and symptoms might not be present at the preclinical stage, subtle in the MCI stage and worse in dementia.

The diagnosis of AD could be viewed from two perspectives. The first is the detection of the signs and symptoms that indicate the possibility of the disease (Albert et al., 2011). The second is the diagnostic biomarkers that establish the fact that the disease in question is actually AD as suggested by the diagnostic criteria. These variables not only have a direct influence on the diagnosis but play an important role in the early intervention of the disease. Two concepts have been proposed to capture the timing of symptoms presentations, these are:

2.2.1 Concept of MCI

MCI is a transitional period between normal ageing and AD in which persons experience memory loss to a greater extent than one would expect for their age, yet they do not meet the currently accepted criteria for the clinically probable AD (Petersen et al., 2001). When observed longitudinally, individuals at this stage progress to the clinically probable AD at a considerably accelerated rate compared with healthy age-matched individuals (Busse et al., 2003).

MCI has been the more successful and longer lasting of the two concepts in AD, the other being SCD (section 2.2.2). The term MCI, introduced two decades ago by Reisberg et al. (1988), included subjects who were identified based on the global deterioration scale to be at the intermediate stage. The MCI criteria became apparent as a sizeable group of the subject in a longitudinal study of ageing, were 'in between 'and the concept was then introduced to better identify these subjects (Petersen et al., 2001). The presence of memory complaints met by objective deficits on tests of episodic memory in individuals without dementia was required for the criteria to be met, within a normal cognitive function and the ability to carry out the daily life activities.

The original concept was revised in 2003 and the international criteria for MCI became a much broader term, referring to a clinical syndrome with multiple profiles due to a variety of causes or 'aetiologies' (Winblad et al., 2004; Petersen et al., 2004). The new definition, initially directed specifically towards the detection of AD, was now restricted to a subtype of MCI (Jessen et al., 2014) and termed the Petersen criteria.

According to the Petersen criteria, an individual needed to have the following:

(A) Complain about memory by individuals or informants

(B) Impaired memory function and a test performance of more than 1 standard deviation (S.D) below age- and education-specific norms.

(C) Preservation of the general cognitive functioning.

(D) Intact ability to perform activities of daily living.

(E) The absence of dementia as assessed by the DSM-IV criteria

In the criteria, mild deficits in cognitive domains other than memory were allowed, but not the isolated deficits in nonmemory domains. The criteria are common with regards to the aim and theoretical framework, even though researchers have suggested and put to use a variety of criteria for defining cognitive impairment (Winblad et al., 2004).

2.2.1.1 Modification of the Petersen criteria

Evaluation of the current state of the condition was carried out and defined by the same criteria as the original concepts of MCI and age-associated cognitive decline (AACD), with the exception of criteria (A), memory impairment. MCI became a broader construct

meaning a clinical syndrome with multiple clinical profiles due to a variety of causes (Petersen et al., 2004) and restricted to a subtype of MCI (Petersen et al., 2014), a condition initially directed specifically at detecting AD.

MCI is a concept encompassing much more than preclinical stages of AD, useful both clinically and as a research entity (Winblad et al., 2004). The heterogeneity in aetiology, manifestations, and outcomes has been discussed as a weakness of the condition; persons followed over time with MCI have progressed to AD and other types of dementia and others became stable or even recovered (Winblad et al., 2008; Petersen et al., 2014).

The current definitions of MCI (Windblad et al., 2004; Petersen et al., 2004; American Psychiatric Association, 2013; Petersen et al., 2014) suggest that a change in cognitive ability is necessary to be classified as MCI, taking into consideration the executive functions, attention, language, memory and visuospatial skills, which can be overlapped with a diagnosis of dementia. MCI and dementia differ in the further requirement for MCI cases to have preserved independence in functional ability (Petersen et al., 2014). No gold standard as to the neuropsychological test battery to use, but it is necessary to examine all the main cognitive areas, by gathering information from the individual (subjective cognitive complaints) or the next of kin that needs to be confirmed by objective cognitive measures (Feldman et al., 2007; Petersen et al., 2014). Subsequently, SCD became a concept.

2.2.2 Concepts of SCD

Evidence suggests that subjective cognitive decline may represent the first symptomatic manifestation of AD. SCD is the self-reported decline in an individual, which may or may not be associated with AD (Mckhann et al., 2011).

Stage three of the preclinical AD is defined by biomarkers evidence for AD and subtle cognitive decline that has not reached the level of objective impairment for the diagnosis of MCI (National Institute on Aging-Alzheimer's Association (NIA-AA criteria) and difficult to detect on cognitive tests. The difficulty in detecting this subtle decline in cognitive tests does not isolate self-experience of this decline in individuals with pre-clinical AD (Jessen et al., 2014), which is a core-criteria in the definition of MCI and prodromal AD (Dubois et al., 2007; Albert et al., 2011; Sperling et al., 2011). Evidence suggests that SCD,

even at the stage of normal performance on cognitive tests at the pre-MCI and pre-prodromal stages, is linked with an increased likelihood of biomarker abnormalities consistent with AD pathology, increased risk of cognitive decline in the future and dementia due to AD (Fortea et al., 2011; Rami et al., 2011; Amariglio et al., 2012; Wang et al., 2013; Jessen et al., 2014; Rabin et al., 2015). The decline may reflect the first effects of AD pathology on cognitive functioning between full compensation and the very first decline. Intervention at this stage might preserve cognitive function at the very high level.

The subjective cognitive decline is however not specific to AD. It is related to numerous conditions like normal ageing, personality traits, psychiatric conditions, neurological and medical disorders, substance use and medication, and even the cultural background of an individual (Jessen et al., 2014). SCD is termed subjective cognitive impairment, subjective memory decline, subjective memory impairment, and memory complaints, among other terminologies (Abdulrab & Heun, 2008). However, SCD could be a simple method to assess the likelihood of memory decline among apo E carriers (Samieri el al., 2014). In a Nursing Health Study (NHS) in the US, Samieri et al. (2014) reported that individuals with the Apoe ε4 genes with self-assessed cognitive concerns appear to have worse memory with possibly accelerated memory decline than their counterparts.

The results of the current studies on SCD indicate variability and an inconclusive picture regarding the rate of decline, the risk of conversion to AD dementia and the role of biomarkers in predicting the course of the disease (Reid & Maclullick, 2006; Mol et al., 2007; Steward et al., 2012). Knowing the patterns of the self-reported declines that are reliable, present an opportunity for identifying and diagnosing the disease early, which can be achieved by a retrospective review of the patients' medical record. The second perspective is the diagnostic biomarkers which are laid open below.

2.3. The diagnostic framework

The criteria for the diagnosis of AD have been in existence for more than three decades now. In 1984, The National Institute of Neurological and Communicative Disorders and Stroke – AD and Related Disorders Association (NINCDS –ADRDA) proposed a diagnostic criterion with the following principles. Firstly, the clinical diagnosis of AD could only be made post-mortem, therefore, "probable" was the indicative diagnosis while the individual was living. Secondly, the diagnosis could only be initiated with the disease

progression to an advanced debilitative state with memory loss and cognitive impairment (Mckhann et al., 1984; Dubois et al., 2007). The 1984 criteria resulted in low specificity in differentiating AD from other dementias (Dubois et al., 2007). This was as a result of the absence of the diagnostic criteria for other dementias and their biomarkers, which in turn resulted in the International Working Group (IWG) in 2007, advancing the diagnostic criteria with the introduction of biomarkers.

 A conceptual framework was developed, which recognised AD in vivo and independent of other dementias with the presence of two requisite features (Dubois et al., 2007). The first requisite was the evidence of a specific episodic memory profile that is typical of AD patients and differs from the memory impairment observed in other dementias, Huntington's disease, normal ageing or depression. This memory profile is characterised by a low free recall that is not normalised by a reminder/ hint or cueing and was included as a specific symptom typical of AD. The second was the evidence of a biomarker through the structural MRI, molecular neuroimaging with PET (scan), and CSF analysis of amyloid or tau (total or phosphorylated). However, the 2007 diagnostic criteria focus only on typical AD with memory deficits. Surely, the biggest problem for early diagnosis is sampling, as the brain tissue cannot be sampled where the disease is causing damage, unlike other diseases. An ideal marker in this instance will be one in urine or blood.

In 2010, a refinement of the 2007 diagnostic criteria was undertaken by the IWG, which drew a distinction between the clinical disease and the disease pathology. It broadens the preclinical states in which AD pathology exists without symptoms but with biomarkers of AD (Sperling et al., 2011; Jicha et al., 2012). The refinement also included the "atypical" (unspecific and irregular) and "mixed AD" (the usual and irregular). However, no changes were made to the 2007 diagnostic criteria, except for the atypical specification, that is, the non-amnestic focal cortical syndromes that include locopenic aphasia, frontal variant AD, and posterior cortical atrophy. In 2011, the NIA-AA published a criterion to cover the full staging of the disease, with the recognition of three stages (high, intermediate and unlikely) of AD, and set diagnostic criteria for each stage supporting the diagnosis of asymptomatic AD with biomarkers information.

The IWG recently refined its criteria to include a diagnostic algorithm based on the weight of biomarkers, suggesting that Amyloid and Tau (total and phosphorylated) should be

used in combination and CSF (the AD signature) should not be used as a standalone test (Dubois et al., 2014). However, the criteria (**Table 2.2)** focus on the cognitive domain and insufficiently address other aspects of the presentation (Jones et al., 2015). Incorporating non-biomarkers (clinical manifestations of the signs and symptoms) is necessary to support the diagnosis. As indicated by a number of studies (Jack et al., 2009; Reiman et al., 2012; Villemagne et al., 2013), the recently proposed criteria do not establish diagnostic criteria that can be used easily by the primary care; rather these biomarkers remain limited to individuals, and they are expensive and invasive (Dubois et al., 2014).

TABLE 2. 2: DIAGNOSTIC CRITERIA

AUTHORS & YEAR	DIAGNOSTIC ALGORITHM	STRENGTH	LIMITATIONS
NINCDS-ADRDA, 1984	Clinical diagnosis (CD) probable CD Post-Mortem CD with the progression of the disease to an advanced debilitative stage	The first diagnostic criteria for AD The diagnostic criteria could initiate the diagnosis of AD at the advanced stage of the disease pathology, with a specificity of 70%, and sensitivity of 81%. Survived for over twenty-five years.	Absence of diagnostic criteria for other dementias without biomarkers
IWG, 2007	CD with the evidence of episodic memory not normalised with cueing CD with the presence of a biomarker	Recognised AD in vivo, and independent of other dementias Introduction of biomarkers (MRI, PET SCAN & CSF testing	Focus only on the typical AD with memory deficits
IWG, 2010	Refinement of the 2007 Algorithm to include "Atypical AD" that is non-amnestic focal syndrome including the locopenic aphasia.	Inclusion of the Atypical Non-Amnestic AD	Non-inclusion of the full stages of the disease
NIA-AA, 2011	The recognition of the three stages of AD with three subtypes including typical AD with the clinical phenotype of episodic memory impairment and behavioural changes, atypical AD with no specific phenotype but a variant of posterior cortical atrophy as indicated by visuospatial dysfunction, bi-parietal with locopenic aphasia and frontal with apathy or behavioural disinhibition A set of diagnostic criteria for each stage of the disease The of asymptomatic AD with biomarkers information	The recognition of three stages of AD Supporting the diagnosis of asymptomatic AD with biomarkers	Multitude of proposed biomarkers Cost of diagnosis. Diagnosis based on biomarkers at the expenses of other diagnostic specifications
IWG, 2014	A refinement to the previous DC, suggesting that Aβ & Tau be used in combination, and CSF should not be used as standalone tests	More advanced integration of the biomarkers, with the inclusion of memory loss for LOAD	Non- inclusion of the pattern of the signs and symptoms of AD preceding the diagnosis

2.4. Current issues in the late diagnosis of AD

The health, economic and social care burden of AD weighs heavily on individuals, society, and healthcare providers due to population ageing and increase in the prevalence of the disease. There is uncertainty in estimating the global burden of AD and growing concerns regarding the cost of the disease (Dodel et al., 2015). One of the limitations is the inadequate data available from low and medium income countries (LMIC) and Eastern Europe while the cost model relied largely on extrapolation (estimation) of economic conditions from higher to lower countries (Wimo et al., 2013). Additionally, studies are largely undertaken on all dementias, limiting the ability to quantify the burden of AD in isolation.

2.4.1. Burden on individuals

The burden of a late diagnosis of AD on individuals with the disease is associated with non-reversible symptom's progression, especially memory loss and loss of independence that leads to institutionalization and an increased mortality rate in individuals with the disease (Leifer, 2009; Hyman et al., 2011). The physical burden is even higher in individuals with comorbidities than those with only AD (Duthie et al., 2011) and may accelerate the progression towards a state of cognitive and functional impairment (Solomon et al., 2011). Having a chronic debilitating disease is daunting and adding another one could be devastating with severe consequences. Globally, it is estimated that 43% of world cases need a higher level of care equivalent to that of a nursing home (Brookmeyer et al., 2007); this estimate has yet to be updated (Dubois et al., 2016).

2.4.2. Caregivers burden

Caregiver's burden could be defined as the degree to which a carer's emotional or physical health, social life or financial status had suffered as a result of caring for their relatives (Zarit et al., 1986). This is measured by the caregiver's burden inventory (CBI) (Novak & Guest, 1989), a 24-item self-rated questionnaire on time-dependence, developmental, physical, social and emotional burden (Razani et al., 2014). Among the dementias, AD caregivers showed a higher burden level which appeared to be associated with gender (female caregivers may amplify caregiver burden significantly than their male counterparts) and length of time of care (D'Onofrio et al., 2015). Although costing informal care could be complicated and sometimes controversial (Van den berg et al., 2006), family caregivers provide 80% of the care needed by dementia individuals, which can be costly to caregiver's health (Bekhett et al., 2013). In a recent study, behavioural problems and

psychological symptoms were the primary factors associated with caregivers burden (Chiao et al., 2015), and there was a strong relationship between caregivers burden and patients' functionalities (Zawadzki et al., 2011). Caregivers' burden, therefore, could trigger symptoms similar to symptoms of AD and exacerbate the burden of health care on the health and social care sectors.

2.4.3. The burden on health care professionals

The behavioural and psychological burden of the disease not only affects families of older individuals and AD patients but also the healthcare professionals. This is because caring for the ageing population especially those with a disability is challenging due to the high demand and heavy load of gerontological caregiving (Chiao et al., 2015). In a study of the burden of AD on health care professionals, nursing staff experienced high emotional stress more likely related to contact with the resident or a relative especially in the process of care and decision making in the last phase of life and/or physical burden related to poorer clinical status of the resident (Albers et al., 2014). The earlier the disease is detected, the more individuals make sense of the disease, make lifestyle changes that improve cognition and lessen the burden on caregivers, as well as planning for a different future (Dubois et al., 2016).

2.4.4. Economic burden

As at 2009, the global costs of the economic burden of dementia was US$422 billion, translating to about $3,945 per individual annually in the lower middle income (LMI) to $12,196 in the higher income countries (HIC)(Wimo et al., 2013). The World Bank income classification of the per-capita costs of dementia varied considerably, from US$868 in low-income countries (LIC) to US$3,109 in LMI to US$6,827 in upper-middle-income countries (UMIC) to US$32,865 in HIC. In a systematic review of the economic burden of AD in France, Germany, Italy, The Netherlands, Spain, UK and the USA, the client medical costs ranged from US$5,476 in France to US$27, 380 in Spain (Takizawa et al., 2015). In the UK, the health and social care costs varied significantly by agitation, from £29,000 per year with no agitation symptoms to £57,000 at the most severe levels of agitation (NPI agitation score=12; p=0.01), equalling £2 billion a year across all in the UK (Morris et al., 2015).

2.4.5. Late diagnosis of AD and rate of general mortality

The effect of late diagnosis of AD on mortality is that AD adds 11% per year to the overall mortality rates, once the disease has progressed to the late stage of neurodegeneration (Brookmeyer et al., 2007; Phelan et al., 2012). The survival rate for the late-onset AD ranges from 3.3-7.9 years for the

male gender and 4.3-9.1 years for females (Brookmeyer et al., 2007; Dodel et al., 2015). In 2015, AD and other dementias replaced ischaemic heart disease as the leading cause of death in England and Wales, with about 11.6% of the 529,655 registered deaths (National Statistics, 2016). This is in individuals eighty years of age and above. The implications of this report need to be carefully considered to give individuals the opportunity to be diagnosed early for timely intervention. HIV individuals have a high survival rate due to the fact that the disease can be detected early and intervention met early to avoid the condition developing to AIDS; this is desirable in AD, as early diagnosis could slow the conversion to AD dementia and promote longer, quality lifespan without much stress.

2.5. Benefits of early detection and diagnosis of the disease

Even with the few studies that have explored the benefits and risks of an early diagnosis of AD in the UK, an advantage of a diagnosis at the early stage, is the opportunity to reduce the neurodegenerative processes through timely intervention with disease-modifying therapy (Dubois et al., 2015). Hence, there is a need to develop an acceptable early detection model that is cheap, non-invasive and applicable to the primary care setting. There is a relief and subsequent improvement in the quality of life once an individual is diagnosed, due to access to support services or pathways of care, and planning for the future. If AD is detected and diagnosed early and therapeutic strategies lead to just a small delay in the onset and progression of the disease by a modest one year, there would be nearly 9.2 million fewer cases of the disease in 2050 globally (Brookmeyer et al., 2007; Sperling et al., 2011). In the UK, in comparison with the scenario without early assessment or pharmacological treatment, early diagnosis reduces health care costs by £3,600 and societal costs by £7,750 per patient yearly (Getsios, 2012).

Some critics of the early diagnosis have opined that there are risks or challenges associated with the timely diagnosis of AD, including ethical issues, discrimination, stigmatisation, competence issues (Mattsson et al., 2010; Gauthier et al., 2013; Gaugler et al., 2013), misdiagnosis and increased economic burden. In the UK, substantial misdiagnosis of AD among patients with dementia has been recorded, which resulted in substantial excess cost (Happich et al., 2015). However, research has indicated that the benefits of an early diagnosis outweigh the challenges (Schicktanz et al., 2014) and that an AD label is not in fact, associated with more stigmatizing reactions (Johnson et al., 2015). Delaying the onset by an average of two years, will globally decrease the prevalence of the disease by 22.8 million and even without therapeutic effect, that is whether the treatment is

beneficial to the patient or not, but just detecting the disease early, will reduce the prevalence by 5.2 million (Brookmeyer et al., 2007). In summary, the burden of late diagnosis of AD is quite substantial and the benefits of early detection outweigh the challenges, which call for early detection and subsequent intervention to slow the progress of the disease.

2.6. General symptoms and signs of AD

A symptom could be defined as a subjective experience that depends not only on physiological process but also on patient recognition and the interpretation of this process (Teel et al., 1997; Cook et al., 2011). In contrast, a sign is an objective indicator or characteristics of a condition or disease, detected by the physician in the process of examination. AD is a slowly progressing disorder with no fixed events before its onset (Albert et al., 2011; McKhan et al., 2011; Sperling et al., 2011). This makes it particularly challenging for clinicians to identify transition points of asymptomatic to symptomatic pre-dementia phase for individual's patients (Albert et al., 2011). The disease begins with the preclinical phase in which the neuropathology of AD starts to accumulate, although the cognitive performance might be normal (Vos et al., 2013). The symptoms of the disease are, therefore, suggestive to result when the threshold of the neurodegeneration is reached (Ringman et al., 2015), and increases with the progression of the disease (Seidl et al., 2009; Ringman et al., 2015). Auguste D., the original patient of Dr. Alois Alzheimer, showed several cardinal features of the disease that are still being observed in patients today. These symptoms include progressive memory impairment; cognitive function decline; behavioural alteration including paranoia, hallucinations and delusions; and progressive aphasia (Wilkier et al., 2013).

Bateman et al. (2012) study showed an increase in brain atrophy, which was detected 15 years before the onset of symptoms; cerebral hypometabolism and impaired episodic memory were observed 10 years before expected symptom onset. The global cognitive impairment as measured by the Mini-Mental State Examination and the Clinical Dementia Rating scale was detected 5 years with patients meeting the diagnostic criteria for dementia at an average of 3 years after expected symptom onset (Bateman et al., 2012). The individuals' alertness, motoric and sensory functions are well preserved at the early and middle stages of the disease slow progressive process (Selkoe et al., 2001; McKhann et al., 2011). However, as cognitive decline continues, motoric functions decline (slow gait and coordination), which often resembles extrapyramidal motor disorders like Parkinsonism (Selkoe et al., 2001).

2.6.1. Early onset / late onset signs and symptoms

EOAD and LOAD are the two descriptions of AD with the same neuropathological characteristic hallmarks. However, EOAD may clinically present differently than LOAD, with higher biomarkers found in EOAD frontal and parietal lobes of the brain (Palasi et al., 2015). The neuropsychiatric symptoms might differ between EOAD and LOAD (Takizawa et al., 2015; Shoemark et al., 2015). The rate of progression of symptoms is difficult to predict for each individual, especially those with an infection or on medication, with a distinction between those patients with EOAD that begins from 30-60 years of age and LOAD that typically starts at age 65 years and above (Imitiaz et al., 2014).

A cognitive assessment of 172 AD patients, with the mean age of EOAD being 60 plus or minus four years (54% female) and the mean age of the LOAD 72 plus or minus five years (52% female), indicated that the EOAD presents with a different cognitive profile and the disease course seemingly different (Smit et al., 2012). The majority of EOAD present with non-amnestic presentations (Mendez et al., 2012) and performed significantly worse in attentional, verbal learning and imitational praxis (theory plus action) tests than the LOAD (Palasi et al., 2015). In LOAD, worse and frequent napping has been mentioned and associated with amyloid deposition, but it is unknown whether this is present in the earliest stages of the disease (Ju et al., 2013; Peter et al., 2015).

Diagnosis of EOAD is often a challenge because of the frequency of atypical presentations (Smits et al., 2012) and less hippocampal memory presentations (Klimkowilz et al., 2014), which includes behavioural disturbance, dementia, involuntary movements, pyramidal signs, epilepsy and family history of early onset. A recent study (Joubert et al., 2016) on EOAD/LOAD discovered that both groups were affected in most cognitive domains including episodic, semantic (worldview) and working memory, executive functions, language, praxis and Visio constructional abilities. However, the LOAD group was substantially more impaired than the EOAD group on the test of semantic knowledge.

2.6.2. Early symptoms

The early symptoms of AD are those of MCI, although the stage of the preclinical precedes the MCI and encompasses the spectrum of pre-symptomatic autosomal dominant mutations carriers (Leifer, 2009). The early signs include apathy, memory loss, agitation, anxiety, irritability, dysphoria, hallucination, aberrant motor behaviour and disinhibition (Casselli et al., 2013). In a cross-sectional study with proxy informants, behavioural and psychological symptoms (BPS) in particular apathy,

depression, anxiety and agitation frequently occurred in the early stage of AD (Harwood et al., 2000; Geda et al., 2013; Li et al., 2014). Results of these studies indicate that some non-cognitive symptoms could relate to the cognitive dysfunction in AD, without indicating the sequence and timing of these symptoms.

Consequently, the Alzheimer's Association came up with ten pre-clinical signs and symptoms of the disease include amnesia (memory loss), challenge in planning and solving problems, difficulty in completing tasks, confusion in time and space, trouble understanding visual images and spatial relationships, words and speaking difficulty, decrease or poor judgement, withdrawal, and change of mood and personality (Alzheimer's Association, 2014). However, as there is heterogeneity in studies on the signs and symptoms, knowing their sequence and timing preceding the clinical diagnosis of AD might help with the early detection of the disease.

2.6.2.1. Memory loss

In the early stages, the initial symptom of AD is memory lapses (Arshavsky et al., 2010; Bateman et al., 2012), especially the episodic memory (short-term memory of events at a particular place and time, or about "what", "where "and "when" (Didic et al., 2011). Difficulty in recalling names of friends or recent events is also common in normal elderly individuals, but to a certain extent (Mayeux et al., 2010). This is due to the fact that the hippocampus and the medial temporal lobe of the brain are the sites of early pathology underlying the initial memory impairments (Britton et al., 2011), and the disruption of one of the anatomo-functional system (the brain) at the earliest stages of the disease, relates to the clinical symptoms experienced by individuals with the disease. In an earlier structured interview of close family members of individuals with AD, memory loss was not the earliest objective sign of change (Oppenheim, 1994). However, this could be argued that the information derives from proxies who are subject to memory loss themselves.

2.6.2.2. Episodic memory

Impairment of the episodic memory, which has also been defined as records of personal events registered within the spatiotemporal cortex, has been identified in the early stage of MCI as evidenced from Visio-spatial or verbal material (Ivanoiu et al., 2005; Belleville et al., 2014), with associative memory impairment and decline of recollection (Hudon et al., 2009; Belleville et al., 2011), and hippocampal dysfunction. MCI is no longer considered to be an intermediary between

normal ageing and AD (Cortex-Canteli et al., 2014). Therefore, the episodic memory might well not be the earliest symptom.

2.6.2.3. Working memory

The working/procedural memory is impaired in MCI, especially involving tasks such as online manipulation of information like sentence span (Gagnon et al., 2011; Belleville et al., 2014). The visio spatial working memory (VWM) for reading and navigational space is affected, which is one of the earliest symptoms of AD (Tales et al., 2011). In a cross-sectional longitudinal study with healthy control (Bianchini et al., 2014), topographic disorientation (TD), a form of navigational disorders, was common among individuals that developed AD. Besides the memory problems including the VWM other deficit may be present at the early stage of AD such as attention control and executive function deficits (Pereira et al., 2014). In a cross-sectional analysis of clusters in a cognitive profile testing, 15% of the patients (atypical) presented with non-memory impairment, but with behavioural symptoms including seizures (Peter et al., 2014). This indicates the differences in early presentations of the symptoms and signs.

2.6.2.4. Seizures

Unprovoked seizures have been recorded in 10% to 22% of patients with AD, with higher rates in the familiar and early onset of the disease (Imfeld et al., 2013). In LOAD, it is speculated to precede cognitive impairment (Picco et al., 2011) and could be an early mechanism. In a transgenic mouse model, unprovoked seizures were recorded at a higher rate among the familial and early-onset AD, suggesting a cognitive impairment (Palop et al., 2009; Vossel et al., 2013). The activity in human has been widely interpreted as a secondary process resulting from advanced stages of the neurodegeneration. However, recent findings of the disease suggest that this could be a primary upstream mechanism and could rightly be attributed to humans (Vossel et al., 2013). This is because, the sporadic incidence of AD has a higher rate of seizures independent of the disease stage, and higher in the early-onset AD, autosomal dominant early-onset, and those with the major known genetic risk factor APOE E4 (Palop et al., 2009; Imfeld et al., 2013). The amyloid β peptide may contribute to the cognitive decline by eliciting similar aberrant behaviour in humans.

2.6.2.5 Anosognosia

At risk of AD individuals have been discovered to underestimate the cognitive dysfunction. Anosognosia (the denial of illness), has also been identified as a characteristic symptom at the mild

stage of AD, but not MCI (Kalbe et al., 2005). It is correlated with age, the age of onset and duration of illness (Kashwa et al., 2005). The symptom is a potential and a significant predictor of apathy in AD (Starkstein et al., 2014). The definition of anosognosia across AD domain is not well defined (Leicht et al., 2010), as a recent study (Lindau et al., 2014) indicates that anosognosia is present in AD but not in the preclinical or MCI stages. The symptom seems to increase with the disease progression to dementia, due to the right hemispheric alterations. However, if the symptom is a significant predictor of apathy in AD (Starkstein et al., 2014), then, this could be an early phenomenon.

The symptoms and signs currently used to define the preclinical stage of AD are not always present in persons who develop the disease (Palmer et al., 2008; Hudson et al., 2012). Other signs including acalculia (acquired impairment that leads to difficulty in simple mathematical calculations), alexia (reading disorder) and anomia (inability to remember nouns) which are part of the semantic memory, are common in the early stage of AD (Tang et al., 2004), especially when there is posterior cortical atrophy in the atypical presentation. Mood disorders, anxiety, and agitation have been mentioned in both MCI and AD (Porter et al., 2014). Apraxia (difficulty in words) was observed to be common in AD in a Chinese study (Shea et al., 2015). But whether this is present in the early stage, remain to be confirmed. In addition, a CSF marker-based study of the subgroups of the disease, the potential diagnostic predictive value of hallucination, hypokinesia, paranoia, rigidity, and tremors in aged individuals with AD have been reported (Igbal et al., 2013). Although, it is unclear if these symptoms occur early in the disease progression.

In an earlier study of AD in America to assess the frequency and severity of 10 behaviours, 80% of the subjects had measurable behavioural changes; the ten behaviours significantly increased compared with the normal subjects, with the most common behaviour exhibited as apathy 72%, agitation 60%, anxiety 48%, irritability 42%, dysphoria and aberrant motor behaviour both 38%, disinhibition 30%, delusion 22% and hallucination 10% (Mega et al., 1996); agitation, dysphoria, apathy and aberrant motor behaviours correlate with cognitive impairments.

2.6.2. 6. Apathy

Apathy (impaired ability to express emotions) has been mentioned as an early sign of AD. In a cross-sectional study of 435 patients, the most common symptom associated with the preclinical AD was apathy (75%) and delusion (19%) was the least of the symptoms (Craig et al., 2005). Depression and apathy were the earliest to appear; hallucinations (especially visual hallucinations with visual

cataracts) elation/euphoria, and aberrant motor behaviour were the latest symptoms to emerge in the study, while irritability was the most prevalent in the early stage of the disease (Craig et al., 2005; Ringman et al., 2015). The symptoms were reported without the timing from diagnosis to the first symptom presentation that will justify a diagnosis of AD. Apathy seems to appear at the earliest stage of the disease (Han et al., 2014). Although, apathy is associated with the progression of the disease from the MCI to AD in a non-depressed individual with the disease (Richard et al., 2012), studies indicate that there is no difference between MCI and AD symptoms, except the decreased metabolism in the posterior cingulate cortex in MCI individuals (Delrieu et al., 2015).

2.6.2.7. Depression

Depression is also mentioned as early symptom and a prediction for the conversion of MCI to AD (Geerlings et al., 2000; Monastero et al., 2009; Starkstein et al., 2014; Gracia et al., 2015); it has mostly been reported in younger adults (Chamberlain et al., 2011), and independently associated with cognitive impaired community-dwelling elderly people (Chang et al., 2014). Although depression in MCI signifies the progression to AD (Zahodne et al., 2013; Van et al., 2014), MCI with depressive symptoms showed more severe behavioural symptoms and more verbal agitated behaviour than AD without depressive behaviour (Stefan et al., 2012), it can occur early in the disease progression and diminish over time due to the decline in cognition and subsequent loss of insight or awareness. However, while the disease progresses and the fundamental and cognitive symptoms gradually worsen, the depressive symptoms do not, and may increase with ageing regardless of the type of dementia (Masters et al., 2015). Overall, depressive symptoms are not widespread among individuals with AD, as it remains a controversy and the result inconclusive (Chemerinski et al., 2014; Geerlings et al., 2014). Reverse causality could be the case, as the history of depression with the first onset before the age of 60 years represents a risk of developing AD in later life (Geerlings et al., 2008). Further studies to understand the neurochemical and histopathological characteristics of the AD that contributes to depressive symptoms, and different from cognitively normal individuals with depression is needed.

2.6.2.8. Olfactory deficit

Odour deficit is also identified as an early phenomenon indicating its superiority as an early marker for the detection of AD. The odour deficit proposed an initial chemosensory impairment in AD at the central lobe rather than the periphery (Nordin et al., 1998). The olfactory capacity is reported as a potential biomarker for identifying individuals at risk for the age-related cognitive decline and AD

(Sohrabi et al., 2009). Olfactory disturbance and apathy in AD might result as the disease pathology progress to a more advanced stage (Selyman et al., 2013). In a recent review, there was significant poor olfactory function associated with AD and a marker for conversion of MCI to AD (Mangliano et al., 2014; Velayudhan, 2015), and in a more recent memory study, identification of odour impairment was superior to deficits in verbal episodic memory in predicting cognitive decline in cognitively intact subjects (Devanand et al., 2015). Neurological soft signs (NSS) scores (covered by five factors: 'motor coordination', 'integrative functions', 'complex motor tasks', 'right/left and spatial orientation') and 'hard signs' are, therefore, significantly higher in the early stage of AD (Urbanowitsch et al., 2015), and provide evidence that an impairment exists and a rationale for a more formal detection and evaluation for confirmation of the disease.

2.6.2.9. Weight loss

Weight loss or low body mass index (BMI) has also been observed in patients with AD, the observation was made before and during AD dementia onset (Gustafson et al., 2012). The low BMI emphasises or predicts rapid cognitive decline (RCD) (Soto et al., 2012). Recent research by Besser et al (2014) indicates that weight changes are associated with clinical progression in amnestic MCI (AMCI) and the early stage of the disease, however, AMCI associated with high BMI indicates slower progression, and AMCI with low or no weight changes also indicate a faster progression. AD is the related outcome of impaired nutrition and weight loss; the low BMI and weight loss could be the beginning of the pathological processes of the disease (Robertson et al., 2013; Panda et al., 2014).

The signs and symptoms discussed and other factors could be present at the GP clinical records and could help initiate patterns based on the timing and sequence of appearance of these presentations in different subgroups of AD. This is because GP surgeries are the primary points of contact with patients and even without symptoms, individuals with AD sometimes seek the help of their GPs, due to their inclination that something is wrong and will want a clarification from their respective health care providers.

2.7. Summary

Findings indicate that there are inconsistencies with the biomarkers of the disease especially as they are present in normal ageing individuals; genetic mutations of tau protein do not lead to AD but to frontotemporal dementia, which is characteried by severe behavioural and personality and language changes. This indicates that tau might not be required for AD diagnosis and remained

uninformative, hence the need for clinical criteria for early detection. Accumulation of amyloid may not be a strong predictor of AD; this is because some of the individuals diagnosed with AD had a low accumulation of amyloid protein in the brain while others with the high level of the protein showed no signs of cognitive impairment. The current concepts in AD including the MCI and SCD, which are directed at finding the intermediate stage of the disease, to help identify the clinical phenotypes of these stages, have loopholes. MCI might not be the transitional stage between normal ageing and AD, as changes in cognitive ability, executive functions, attention, and language deficits are necessary to define MCI and the current knowledge in SCD are insufficient due to difficulties in detecting a subtle cognitive decline in a standardised cognitive testing.

Past literature has shown that the current diagnostic criteria are expensive, invasive and heterogeneous in their reporting while extrapolating or extending the diagnostic criteria into general practice has its challenges such as having a wider meaning at different settings (Petersen et al., 2014). Furthermore, there are differences in presentations between EOAD and LOAD. This could be attributed to genes and the initial impact of neurodegeneration and NFT in the neocortex, as opposed to onset in the Transentorhinal cortex in typical amnestic AD. Aside from the biomarkers and mini-mental state examinations, there is heterogeneity in reporting the signs and symptoms. The two clinical phenotypes (episodic memory loss for typical AD and locopenic aphasia for atypical AD) incorporated in the diagnostic criteria, might not be the earliest symptoms in some individuals, hence, a more definite clinical marker is needed. Also, while some studies (Ivanoiu et al., 2005; Bianchini et al., 2014) state that episodic memory is the earliest sign to appear in AD, others (Craig et al., 2005; Han et al., 2014) affirmed that apathy is the first sign. The result of these studies could be due to the study design, the number of participants or the age of onset of the disease.

Some studies (Kalbe et al., 2005; Starkstein et al., 2014) have shown that anosognosia precedes the diagnosis of apathy and could be the earliest symptoms, while Sohrabi et al. (2009), Mangliano et al. (2014) and Devanand et al. (2015), declared that odour deficit is superior to the verbal episodic memory deficit as the earliest symptom. The differences in the outcome of these studies, could be attributed to the sample size that ranged from forty-two to a cohort of 1417 people, individual difference and differences in studies designs; while some studies were longitudinal (Palmer et al., 2008; Yoon et al., 2014), other designed were clinical evaluations with few subjects without the testing of subtypes (Linn et al., 1995; Elias et al., 2000; Michel et al., 2010; Peter et al., 2014).

In conclusion, most of the studies were comparative studies of the stage of AD (Toyota et al., 2007; Gronning et al., 2012; Yoon et al., 2014). Some of the studies looked at individual symptoms with measurement after the establishment of the disease (Craig et al., 2005; Sohrabi et al., 2009; Selyman et al., 2013; Vos et al., 2013) and others, compared AD and other dementias (Ballard et al., 2000; Chiu et al., 2006; Fernandez et al., 2008; Thompson et al., 2010), rather than patterns in sequence and timing of these presentations preceding the clinical diagnosis of AD of which this study desired to identify. Although, the studies reviewed focus on one symptom or another; AD or dementia; EOAD or LOAD; however, none was undertaken to identify patterns of the signs and symptoms of the disease. There is little detailed statistical information on the patterns in signs and symptoms preceding the clinical diagnosis of the disease in the UK, with only a study with the title "pattern of cognitive decline" (Chen et al., 2001), undertaken prospectively after the diagnosis of AD. Determining patterns in timing and sequence of the earliest evidence signalling the onset of the disease is pertinent, as studies indicate that the preclinical phase of detectable lowering of cognitive function precedes the appearance of preclinical AD by many years (Linn et al., 1995; Elias et al., 2000; Makowska et al., 2014).

The literature review took an in-depth view of studies and theoretical perspectives on the pathophysiology and the signs and symptoms of AD. This is the foundation in identifying the early presentations of AD, which was further explored in a systematic scoping review, RMRRS and qualitative interview of GPs. The presence of biomarkers in normal ageing and their presence in AD do not prevent the discrimination of self-experience of individuals with the disease. Knowing the timing and sequence of these complaints before diagnosis will aid in suggesting a predictive model for early detection, therefore, this calls for further studies in this regard.

Prior to this, the mixed method approach is reported in the next chapter, while the protocols for each method used in the approach to identify patterns are described in detail as well as the philosophical stance for the research. This is to intimate the reader with the methodology that is applied to the realisation of the objectives of the study.

CHAPTER THREE: Methodology

3.1. Introduction

This chapter introduces the research method that adopts a mixed method approach, which fits into a three-arm study including a systematic scoping review, a qualitative interview of GPs and a RMRRS. These will individually be discussed.

3.2. The concept of epidemiology and epidemiological designs

Effort to curb the spread of disease and infection is not new to human society; epidemiology (a Greek word meaning 'study upon population' – Bhopal, 2008) is the science and study of the distribution and determinants of health-related states or events and disease, and the application of this study to the control of diseases and other health problems (World Health Organisation). The science of epidemiology involves the investigation of the causes and understanding the means to prevent and control problems or diseases (Bhopal, 2008). An individual is a unique entity with its history. Furthermore, there are unique and distinctive patterns of diseases that population groups have due to the variations in the exposure of individuals to the causes of diseases (Krieger, 2011). Some variations could, however, be due to genetic differences and the variations between individuals within the environment. Characteristics of individuals discriminate the patterns of disease in a population, with the environment (seasons, weather, and water) playing an important role in the development of problems or diseases (Bhopal, 2008). The description, understanding, and utilisation of these patterns to improve health are the presumptively inter-related ideas (Krieger, 2011), which my research seeks to achieve.

Epidemiological designs and interpretation of the results depend on the subject of the research and desired inference. The researcher had considered epidemiological designs without a rigid view of science that is inconsistent with current practice and philosophy (Rothman, 1986); for example, a cohort study, otherwise known as a longitudinal and prospective study was considered. The design has the advantage of establishing the exposure of a condition or disease and allows for the accurate collection of information of exposure or the nature of a condition (Bowling, 2009). However, a very large sample is needed, takes time and requires an extended period of contact with the subjects of research (Shekaran & Bougie, 2010), all of which are limited to the researcher. Furthermore, a cross-sectional design was considered, but because the design collects data at one point in time, which is contrary to what the study desires to achieve, a case-control was adopted, which is faster, cheaper,

more practical (Vandenbroucke & Pearce, 2012), and increasingly used in AD research (McKhann et al., 1984; Imfeld et al., 2012; Whitwell et al., 2012; Slattery et al., 2014; Beber et al., 2015). Case-control studies identify individuals with (cases) and without (control) a particular disease or condition retrospectively to compare the prevalence or level of exposure to a risk factor (Lilienfeld & Stolley, 1994). In this study, the comparison is in the patterns of the signs and symptoms preceding the clinical diagnosis of AD.

The case-control design has been selected over other observational designs including cohort and cross-sectional because the design is the best to answer the question of my study. The design offers the opportunity to identify patient's records with the disease and the disease processes (signs and symptoms) which are compared retrospectively with referents records without the disease in GP practices in Milton Keynes and Luton. It allows the flexibility to compare the pattern of signs and symptoms with or without the disease and variables can be considered simultaneously (multiple exposures). The design allows the measurement and adjustment of confounding factors (comorbidities), which was taken more efficiently by group matching the cases and controls to present the true differences between the groups.

Another reason for the choice of a case-control study is the fact that it is more cost efficient than a cohort and cross-sectional and will determine the relative importance of these presentations in drawing patterns of AD. Furthermore, the design is a more feasible option to study a disease such as AD with a long-latency period (Mann, 2003). The retrospective medical records review study (RMRRS) design is relatively cheap and uses a pre-recorded and patient focus data as the primary source of information (Wu & Aston, 1997) as the data needed for the study has been collected over time. RMRRS is a good design for generating patterns and behaviour. Although, the design could be labour intensive (Pope et al., 2000) and limit in scope; for example, the data might have been collected for a different purpose, and might not have captured the desired variables (Matt & Mathew, 2013), the design has pre-established degree of validity and reliability if the data is collected systematically (Jick et al., 1992; Sari et al., 2007; Boslaugh et al., 2007). Additionally, the data needed for this study is primarily collected in the GP surgeries and the desired conclusion is about the course of the disease.

3.3. Philosophical framework

The philosophical framework considered in this research is less rigid, based on blended rules of deductive and inductive reasoning (Bowling, 2009). Deductive reasoning is where the conclusion is logical, beginning from general to specific, reached from the premises that knowledge is based on what is already known and applicable to objectives one and two (RMRRS), and inductive reasoning in which a generalisation is argued on the basic statement that derived directly from sensory experience, from the specific to general statements, applicable to objectives one, two and three (qualitative interview) (Crotty, 1998; Karl, 2004).

3.3.1. Pragmatic worldview

The researcher also extends the views of the current rational philosophical framework and looks at the world through the eyes of a pragmatist, as this view does not ignore the relevance of epistemology and other concepts from the philosophy of knowledge (Morgan, 2008). The value of maintaining attention to epistemology issues in research methodology can easily be preserved with a pragmatic approach. Morgan (2008) further opined that the pragmatic approach concentrates on methodology as an area that connects issues at the abstract level of epistemology and mechanical level of actual methods. It builds on prior accomplishments in order to draw liberally from both the qualitative and quantitative assumptions of this research, which arise out of the consequence and application of what works best in this research. No wonder, many researchers (Harasty et al., 1999; Canon-Flinterman et al., 2005; Gao et al., 2006; Janzen et al., 2006) in the field of AD have assumed this worldview to draw from the qualitative and quantitative realities with success.

Pragmatic philosophy as a worldview arises out of actions, situations and consequences rather than antecedence conditions of postpositivism (Creswell, 2013); researchers emphasises the problem of research and apply all approaches available to understand the problem rather than focusing on the methods (**Figure 3.1)**, hence, the choice of pragmatism. The theory uses a pluralistic approach to obtain solutions to problems and provides a philosophical basis for research (Creswell, 2013). The quantitative and qualitative approaches are applied to solve the problem at hand; my research assumes the same approach by combining the qualitative interview and quantitative RMRRS to identify patterns and develop a predictive model.

Additionally, researchers have freedom of choice of methods, procedures and techniques that are suitable for their research. The qualitative and quantitative data together, provide an excellent

understanding of a research problem. Pragmatism believes in the external world dependent and independent of the mind, and thus, opens the door to multiple methods (Creswell, 2013). Hence, the mixed methods approach to undertake this study.

PROBLEM SOLVING
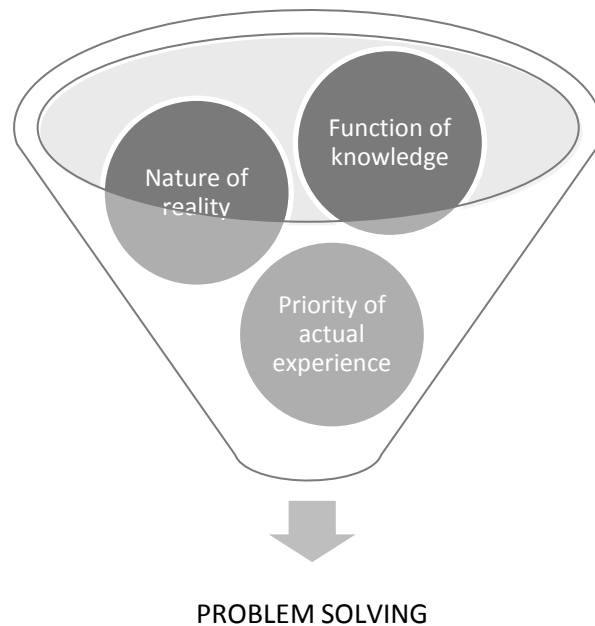
FIGURE 3.1 Pragmatic worldview. The figure points out the empirical emphasis on actual experience over a priori (non-experience) and fixed principles and combining different methods to solve problems.

3.4. The research approach

The research follows a mixed method approach, an approach that involves the use of more than one research method (scoping review, RMRRS and qualitative interview), theoretical perspectives (Denzin, 1978) or data collection (Denzin, 1997; Creswell, 2013), and helps to improve confidence in the result and outcome of the study, to overcome research bias (Murray et al., 1999). Multiple viewpoints allow for greater accuracy of research findings and can be used as complete information to inform theory and practice, through the unity of thoughts, logic and goal (Creswell, 2013). Still within the mixed method approach, a methodological triangulation, the between-method triangulation has been chosen, which employs techniques agreeing with both the qualitative and

the quantitative research traditions in the same study (Denzin, 1970; Thurmond, 2001; Bekhet, 2012; Hussein, 2015).

The concept of triangulation dates back to the work of Campbell and Fiske (1959), and the term derived from Navigation and military strategy in which multiple reference points are used to locate objects exact positions (Jack, 1979), and has been extended to the field of research. This approach has been chosen based on evidence from previous knowledge from the literature review and past researchers in the field of AD (Paton et al., 2004; Duggleby et al., 2011; Beard et al., 2013; Stone et al., 2013; Randhawa et al., 2015), who have adopted the same approach, that have produced good results.

Similar to other designs, these researchers experienced some limitations including application of the design that can be problematic especially with the unit of analysis, lack of weighted clarity as to which method weigh more, theoretical paradigms that can amplify sources of error and bias (Begley et al., 1996; Greene & Caracelli, 2003; Sandelowski, 2010), and replication problems from mixed methodology (Jick, 1979). However, these limitations were overcome with the knowledge of the variables of study, a complementary test for convergence dissonance of ideas, decision rules to guide the analysis of data. Secondly, the analysis assumed the procedural approach, in which documents are compared, in each comparative step to ensure transparency and replicability (Meijer et al., 2002).

Another challenge to this design is that I needed specialist training in both the quantitative and the qualitative arm of this research, which was time-consuming and expensive but enabled demonstration of how the three studies fit together to form a paradigm. I was well aware of this and acquired training in both the quantitative and qualitative methods of inquiry. Other challenges could have been information bias, the moderate reliability of data and hindsight bias ("knowing it all–along"), as new technologies for visualizing and understanding data, could heighten these challenges (Barnes et al., 2009). However, piloting and screening improved the quality of data used.

Convergence coding matrix was applied to summarise the similarities and differences between the two sets of data. Comparison of findings with respect to meanings and interpretations of themes, the frequency, and prominence of themes, and specific examples was given while the convergence coding identified themes from each data. The dissonance of findings and similarities was assessed to review all compared segments and document different perspectives. Identification of key

differences in scope was assessed by comparing methods in order to enhance the completeness of findings (Farmer et al., 2006; Lewis, 2015).

The strength of this design lies in the variations in themes provided, enabling each data set to provide part of a story for the research, by contributing to achieving a complete picture of the research study. The quantitative part of the design aimed at understanding the best predictors of an outcome and to test a theory deductively to generalize and replicate findings; while the qualitative interview looked at the subject of the research inductively. The combination of the deductive and the inductive reasoning is a scientific rationale; a reasoning that distinguishes the natural sciences of chemistry, metrology, and geography from mathematical subjects of set theories (Crotty, 2005). The quantitative approach enabled the researcher to study a large sample that is validated statistically and accurately reflects the population where the research was carried out (Vanderstoep et al., 2010; Punch et al., 2013).

3.5. Research design

The design of this research is methodological triangulation (**Figure 3.2)**; consistent with the chosen approach of a mixed method. The design includes a systematic scoping review, retrospective medical record review study (RMRRS) and a complementary qualitative interview that falls within a three-arm study and each component extensively discussed in the following sections (section 3.5.1, 3.5.2 and 3.5.3).
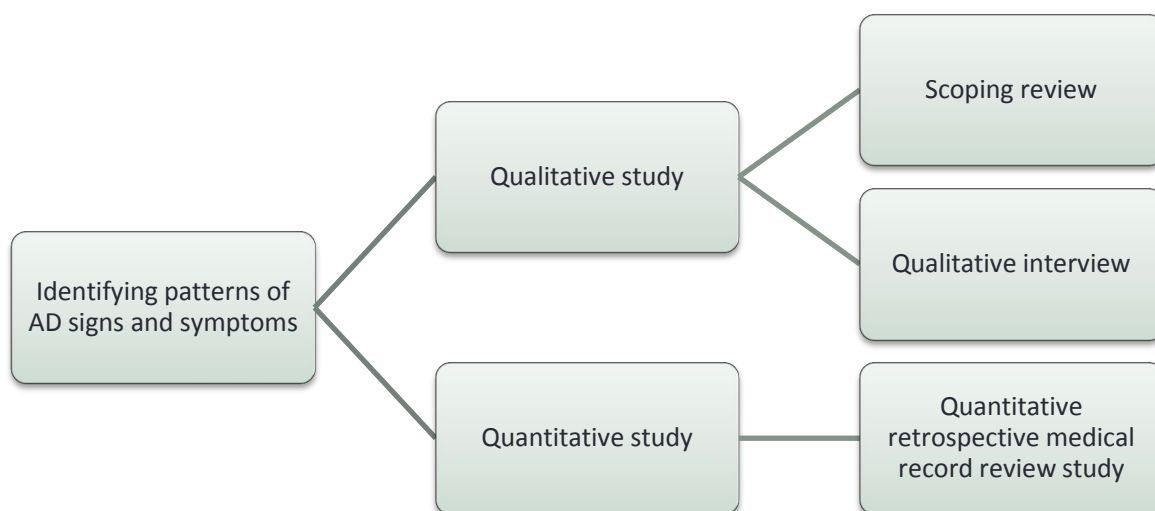
Figure 3.2: Mixed methods methodological triangulatory design. The aim of the study has been met by the combination of the scoping review, qualitative interview and the RMRRS.

3.5.1. Systematic scoping review of empirical studies

The first arm of the research design is the systematic scoping review. This section collects data systematically and synthesizes evidence on sequence and timing of the signs and symptoms, that is, the first symptoms reporting that justified a clinical diagnosis of AD, to draw patterns.

Scoping reviews are described as a process of mapping the existing literature in the field of interest, in terms of the volume, nature, and characteristics of the primary research (Arksey & O'Malley, 2005). They are particularly useful when the subject of the research has not extensively been reviewed or a complex or heterogeneous in nature (Mays et al., 2005). They are used to identified research gaps, summarise findings and identify the potential scope of systematic reviews (Davis et al., 2009). In this research, the scoping is useful as the topic of research has not been extensively reviewed and heterogeneous in nature. Just like a systematic review, scoping review can be used as a standalone project (Arksey & O'Malley, 2005); they both share the same processes of using rigorous and transparent methods to comprehensively identify and analyse relevant literature of the research topic (DiCenso et al., 2010; Hardwick et al., 2015). Their difference lies in the purposes and aims of the review, and while scoping maps out the body of literature from potentially large and diverse literature, systematic review sums up the best available studies of the specific question,

from research on the topic (Arskey & O'Malley, 2005; Daudt et al., 2014). Although, scoping reviews are a relatively new approach for which there is not yet a universal study definition or procedure (Arskey & O'Malley, 2005; Levac et al., 2010; Daudt et al., 2013), they have become increasingly adopted approach and have been published across a wide range of discipline (Davis et al., 2008).

This review was undertaken using the protocol for a systematic review but within a large and diverse literature. This was to map and appraise the existing literature by systematically searching so as not to miss any relevant literature and to bring meaning to the result (Armstrong et al., 2011; Pham et al., 2014). A detailed systematic scoping review protocol is provided (**Appendix XII)**, with a clarification on the types of AD and theatres or field used to identify studies.

3.5.1.1 Aim

To map, appraise and synthesise the quality of existing evidence on the signs and symptoms preceding the clinical diagnosis of AD.

3.5.1.2 Objectives

1. To identify the sequence and timing of the presentation of signs and symptoms at the early stage of AD, to inform a primary study.

2. To understand how far back from diagnosis the first symptoms that will justify a diagnosis was reported.

3.5.1.3 Methods

Criteria for considering evidence for this review includes:

3.5.1.4 Inclusion criteria

3.5.1.4a Types of studies

Qualitative and quantitative empirical evidence undertaken in developed countries and relating to the early signs and symptoms in the early detection and diagnosis of AD were synthesised systematically.

3.5.1.4b Participants

Individuals aged 30-85 years of age, diagnosed with AD, were reviewed. The age restriction was because the pathophysiology takes between 10-30 years. The incidence of the disease among those 30-40 years is rising (12.7% in 2009) (Harvey et al., 2003; Alzheimer's Association Europe, 2009)

hence the inclusion of these group. The early-onset begins at age 65 and below while the late onset begins at age 65 and above. Studies of individuals with the mixed diagnosis were considered as long as the outcomes were reported separately.

3.5.1.4c Index symptoms

The majority of individuals with AD present with multiple signs and symptoms that begin years before the diagnosis of the disease. Studies have been carried out on the early signs and symptoms but few undertaken on the sequence and timing of these presentations. The index symptoms were utilised as patterns to suggest the development of a predictive model for early detection of AD in the primary care centres to complement the biomarkers examinations.

The review included combinations of signs and symptoms alone, while studies restricted on single sign and symptom were excluded.

3.5.1.4d Target condition

All types and stages of AD were included in the review.

3.5.1.5 Outcomes

1. The sequence and timing of presentation.

2. The timing between diagnosis and first symptom reporting that justify a diagnosis.

3.5.1.6 Language of publication

No language restriction was applied to the search so as not to miss relevant articles. Moreover, the University provides an environment where individuals from different countries with diverse languages, are available to translate if an article is not published in the English language.

3.5.1.7 Exclusion criteria

Studies focusing on developing countries, other neurological conditions, and non-empirical studies were excluded. Also, studies on other dementias and late stages of AD where it was not possible to separate data on early stage of AD were also excluded.

3.5.1.8 Search strategy

This implies the specific terms used in searching the database and the global approach to searching including the specific database to search.

3.5.1.9 Research evidence

RefWorks was used as the referencing software.

The databases used included but not limited to:

- Specialist literature databases: Ovid MEDLINE (1946), PUBMED (1996), CINAHL (1937) (Ebsco), Psych INFO (1967), Web of Science, Scopus, Nursing Index (1994) and Health Technology Assessment Database (HTA). We searched each database from early inception in other to capture all evidence on the early signs and symptoms of AD. Hand searching of the reference list of systematic reviews, conference proceedings from Alzheimer's Association and Dissertations Express were also undertaken.

- Specialist systematic review databases: Cochrane register of diagnostic test accuracy studies.

Other literature sources included Google and Google Scholar. This approach uncovered literature to use in the review. There was a different search term for each database as their parameters were different (Jefferson et al., 2011).

3.5.1.10 Publication status

Published articles from a bibliographic database, specialists journals and reference lists from articles were considered. Unpublished (grey or fugitive literature) or informally reported studies as full papers, including theses, reports, book chapters and conference abstracts, were included as long as the full study details were available (Song et al., 2000). The studies were carried out in primary care centres, memory clinics, hospitals and community populations to capture and established a diagnosis of AD.

3.5.1.11 Country of focus

Countries classified as developed countries due to a high human development index (HDI) by the World Bank, were included. This was to ensure that the population from the review studies were the same as the study population in terms of economic status, standard of living, infrastructures availability, provision of amenities and locality.

3.5.1.12 Keyword included

In this research, I included both EOAD and LOAD. Early detection or diagnosis is different from the early-onset AD. The definition is based on the timing of the disease process when the neurodegenerative process has not or slightly began. The early term is used rather than the late-

term that allowed me to find studies undertaken at the early stage of AD and report signs and symptoms before the full manifestation of the disease or dementia (the final stage of AD). These studies should have been undertaken retrospectively or prospectively, within a period of 10 years before diagnosis, as the neurodegenerative process takes between 10-30 years before the manifestation of these presentations(Bateman et al., 2012), while the early stage is approximated to be six years before diagnosis. Also, the disease theatre was the main theatre, followed by the timing theatre, then the basic theatre including country, onset and combination theatres, before duplicate was removed. This procedure was followed to systematically capture the desired data required for this review.

Search one:

Alzheimer's disease AND Early detection OR early assessment OR early diagnosis OR early signs OR early symptoms OR early intervention OR dementia OR cognitive imbalance OR MCI OR subjective cognitive decline OR biomarkers OR biological markers OR brain pathology OR neuropsychological tests OR neuropsychological index OR tomography OR CSF analysis OR MMSE OR screening OR magnetic resonance imaging OR MRI.

Search two:

Alzheimer's disease AND (Early detection OR early assessment OR early diagnosis OR early signs OR early symptoms OR early intervention OR dementia OR cognitive imbalance OR OR subjective cognitive decline OR behavioural symptoms OR psychiatric symptoms OR clinical presentations OR clinical features OR preclinical manifestations OR clinical presentations OR early manifestations OR early presentations OR early detection OR biomarkers OR biological markers OR brain pathology OR neuropsychological tests OR neuropsychological index OR tomography OR CSF analysis OR mini-mental state examination OR screening OR magnetic resonance imaging OR MRI) AND (Andorra OR Argentina OR Australia OR Austria OR Bahrain OR Belgium OR Bermuda OR Brunei OR Canada OR Chile OR Croatia OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Faroe Islands OR Finland OR France OR Germany OR Greece OR Holy See (Vatican)OR Hong Kong OR Iceland OR Ireland OR Israel OR Italy OR Japan OR Korea South OR Kuwait OR Latvia OR Liechtenstein OR Lithuania OR Luxembourg OR Malta OR Monaco OR Montenegro OR Netherlands OR New Zealand OR Norway OR Poland OR Portugal OR Qatar OR SanMarino OR Saudi Arabia OR Singapore OR Slovakia OR Slovenia OR South Africa OR Spain OR Sweden OR Switzerland OR Turkey OR United Arab Emirates OR United Kingdom OR United States).

3.5.1.13 Data collection and analysis

3.5.1.13a Quality assessment

The criteria to assess the data quality included the Quality Assessment Diagnostic Accuracy Studies (QUADAS-2), which contains the assessment domain with signaling questions to select patients, index symptoms and timing (Whiting, 2011). The risk of bias was assessed with the QUADAS standard risk of bias template that rates studies based on good quality paper, poor quality paper or uncertain for bias (selection). The results were summarised in **Table 4.1, Figures 4.3 & 4.4**.

3.5.1.13b Missing data

I understand that missing data could be pervasive. Statistical analysis based only on complete case subsamples could introduce biased estimates and standard error, while the impact of the missing value will reduce the sample size and concomitant loss of statistical power based on comparative datasets. However, there are conditions under which missing data can be ignored (Eff & Don, 2009; Stekhoven et al., 2012), which depend entirely on the relationship between the variable of interest missing and the available variable to help explain the missing value.

Authors of empirical studies (Devier et al., 2010; Fox et al., 1998) with missing data were contacted for the full study reports while being clear as to the nature of data required (mean, median or standard deviation value). One author (Fox et al., 1998) was re-contacted again when there was no answer the first time and all correspondents were logged in (**Appendix XIII).** I made sure that there were no publications missed from the search that contains the data missing; perhaps a study had been published after the search was completed, without limiting the language of publication, to avoid language bias. If the full data could not be retrieved after all these, the papers were excluded. This was stated as part of the challenges faced while undertaken the study.

3.5.1.13c Study selection

The screening process included title screening and abstract screening of primary studies on AD. This was based on the inclusion criteria to identify relevant articles and reduce waste of time and resources in reviewing articles that do not meet the necessary inclusion criteria. Title and abstract screening form was developed (**Appendix XIII)** and was pretested before the scoping review. The second level of review included the review of the full articles deemed relevant. Articles that were only available in an abstracts format and meet the inclusion criteria were included at the second level of review while acknowledging their inclusion limitations, to avoid missing out on recently

reported studies available only in abstract format (Boland, 2014). All other articles that did not meet the eligibility criteria were excluded.

3.5.1.13d Extraction of data

The data extraction forms and tables have been devised and were supposed to be piloted from the first five to ten studies, to know if the data extraction approach is consistent with purpose and questions. However, due to the dearth in data, the researcher piloted it in two studies under the guidance and approval of my supervisors and proceeded to use it as it was consistent with the aim of the study.

3.5.1.14 Data synthesis

Although data synthesis (collating, summarising and reporting) is minimal in a scoping review, quality assessment of the studies included was undertaken, to apply meaning to the results (Armstrong et al., 2011) and consider the implications of the findings within the broader research, policy and practice. This is because I intend to publish the result for use by a wider audience and reduction of duplication of effort that will guide in future research.

There was no quantitative data plotted in (i) forest plots and (ii) ROC plots. Hence, a synthesis using the weighted meta-analysis estimates where there is compatible design and heterogeneity was not considered reasonably (data quality as evidenced by CASP tools used across different designs including CASP cohort study checklist). Heterogeneity among the study results was examined using the sub-group analysis (Pham et al., 2014) in a descriptive analysis. The narrative synthesis was carried out with a summary of each study under the themes provided. Reporting the results of the study assumed a two dimension 1) descriptively on study characteristics and 2) analytical on outcomes of the study (Boland, 2014).

3.5.1.15 Assessment of reporting bias

Formal assessment was reported based on symptoms interpretation with or without biomarkers examinations and PET scans.

3.5.2. Retrospective medical record review study (RMRRS)

The RMRRS used pre-recorded patient focus data as the primary source of information to answer the research question. The study design has guided research (Wu & Ashton, 1997) and is common in epidemiological investigations (Jansen et al., 2005). The source of information included physician

recorded notes prior to the diagnosis, by considering the types of the signs and symptoms preceding the diagnosis of the disease (Webb & Bain, 2010), to ascertain patterns. A clear definition of these variables and understanding of the health records is an essential prerequisite to developing the standard chart review abstraction instrument (Gearing et al., 2006).

Additionally, RMRRS is a suitable design for the chosen topic of this research and an important design with a distinct advantage and valuable research opportunity (Gearing et al., 2006; Matt et al., 2013). The study attempted to answer the research question that cannot be answered prospectively; as prospective studies are impractical to address studies on the pattern of disease or behaviour (Worster & Haines, 2004). The design has been reported to comprise 25% of all scientific articles in emergency medical journals (Woster & Haines, 2004). Moreover, notable researchers related to AD (Calder et al., 2002 -UK; Zeppegno et al., 2009 -Italy; Zonneveld et al., 2014 -Amsterdam; Pankratz et al., 2015 -USA), have assumed the same methodology. The data was collected within a fixed period of four months. Although, the preparation and analysis of GP case notes are labour intensive (Pope et al., 2000), structured case notes are reliable and could detect adverse events that the research desired (Jick et al., 1992; Sari et al., 2007).

3.5.2.1 Method: case-control study

The methodological steps of conducting a RMRRS begin from the conception of the idea to the data abstraction, analysis and interpretation of result (**Figure 3.3).**

A retrospective case-control study has been chosen. This is a population based study with cases matched with controls by age, gender and practice. The design has been chosen over other observational studies including cohort and cross-sectional because the design is the best to answer the question of my study. The design offers the opportunity to identify patient's records with the disease and the disease processes (signs and symptoms) which are compared retrospectively with referents records without the disease in GP practices in Milton Keynes and Luton. It allows the flexibility to compare the pattern of signs and symptoms with or without the disease and variables can be considered simultaneously (multiple exposures). The design allows the measurement and adjustment of confounding factors (comorbidities). The approach to drawing a pattern is to examine the profile of the signs and symptoms of AD in individuals preceding their (current) formal diagnosis.

Another reason for the choice of a case-control study is the fact that it is cost efficient than a cohort and cross-sectional. Furthermore, the design identifies individuals with (cases) and without (control)

a particular disease or condition retrospectively to compare the prevalence or level of exposure to a risk factor (Lilienfeld & Lilienfeld, 1979). In this study, the comparison is in the patterns of the signs and symptoms in sequence and timing preceding the clinical diagnosis of AD.

Figure 3.3: Methodological Steps for conducting RMRRS. The table indicates the conceptual framework for the data collection and analysis.

Conception	
Aim of study	Question of study

Litterature review	
Published & unpublised literature	More than one boeleen database

Proposal development	
Definition of study variable	Selection of data collection method

Sampling to determine the right sample size for the study

Ethics application and approval from the institutional review board

Development of data abstraction instruments with the use of soft ware to parallel the data

Conduct piloting to determine the feasibility of planned study and reliability of instruments of data collection

Develop protocol of coding manual with clear guidelines on data collection

Data abstraction using the site set standard procedure for data collection and analysis.

Even though confounding variables and bias could be an issue with this research, the researcher took steps to sample the medical record of cases and control from the same GP practices to overcome sampling bias. A sample from a specific register with AD was taken; however,

randomisation was not achieved for the cases due to few cases available and a non-probability sampling was assumed including all cases. My original plan of individual matching was not possible due to the few prevalences and I needed to maximised the opportunity, hence, more controls were added based on the matching criteria. The controls were constructed by selecting age and gender-matched individuals from the same population to improve the external validity (Mann et al., 2003).

Although, there are quite a number of instruments as checklists for the behavioural disturbances in AD, like the Revised Memory and Behavioural Problems checklist (RMBPC) (Teri et al., 1992), the signs and symptoms of AD are measured based on the Neuropsychiatric Inventory (NPI), which is a standardised measure for the behavioural disturbances in AD, obtained from caregivers familiar with patient's behaviour (McKhann et al., 1984; American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington DC, 1994). The instrument is valid and reliable, and distinguishes between aetiologies, severity and frequency of behavioural changes, and minimise administrative time (Cummings et al., 1997).

The prevalence rates of these signs and symptoms in AD are presented below; however, it is worthy to note that though they are present in cognitively healthy individuals at a less severe level (Lyketsos et al., 2002), they do not pose any disturbance to the individual. In MCI, the score of the prevalence of agitation is 11.3%, depression 20.1%, anxiety 9.9%, euphoria 0.6% apathy 14.7%, disinhibition 3.1%, irritability 14.7%, aberrant motor disturbance 3.8%, sleep disturbances 13.8% and eating disturbance 10.4% (Lyketsos et al., 2002). The prevalence is however higher in dementia due to AD, with a score in agitation of 30.3%, depression 32.3%, anxiety 21.5%, euphoria 3.1%, apathy 35.9%, disinhibition 12.7%, irritability 27%, aberrant motor disturbance 16%, sleep disorders 27% and eating disorders 19.6%. In MCI, the most frequent and clinically significant symptoms with a disturbance score of more than 4% are sleep disturbance 8.8%, irritability 7.5%, and depression, apathy and eating disturbance scoring 6.3% each. More than 80% of AD patients exhibit any symptom from the onset of the cognitive impairment (Lyketsos et al., 2002), indicating that there is always a sign or symptom to indicate the presence of an abnormality and that these signs increase in severity as the disease progresses. In an earlier study (Mega et al., 1996) to assess the psychopathology in dementia patients, the prevalence of these symptoms were high with apathy scoring 72%, agitation 40%, anxiety 48%, irritability 42%, dysphoria and aberrant motor disturbance 38%, disinhibition 22%, hallucinations and euphoria 10%.

The outcome measure (AD) is classified according to the international statistical classification of disease and Related Health Problems with Revision ten (ICD-10), World Health Organisation Version for 2016. The codes are FOO.0* for AD with early onset, FOO.1* for AD with late-onset, FOO.2* for atypical or mixed AD and FOO.9* for the unspecified AD. The code classification is a medical classification list that contains codes for disease, signs and symptoms, abnormal findings, complaints, social circumstances and external causes of injuries or diseases; it permits tracking of many new diagnoses with a codes set of more than 14,400 different codes. The disease was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) for dementia and National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA).

3.5.2.1a Inclusion criteria

CASES-: Records of adult patients diagnosed with AD in MK and Luton GP surgeries, from 2006-2016.

Control: Records of adult individuals without AD disease in GP surgeries in MK and Luton.

Group matching was restricted to gender, locality, ethnicity, comorbidities and age (18-100 years plus or minus one year difference).

3.5.2.1b Exclusion criteria

Records of individuals with diagnosis outside AD were not included and those outside MK and Luton or below 18 years of age and above 100 years of age.

3.5.2.2 Data collected

Data collection is an important and integral aspect of a research study (Neuman, 2005). The accuracy of data collection can affect the research positively if adequately collected or negatively if not collected properly, which can lead to invalid results (Bowling, 2009). Simplicity and clarity were maintained for uniformity in the collection of data while maintaining a logical order. Data was collected by consulting medical records of participatory GP surgeries and assigning codes to variables. A variable was paired with a response section to capture the required information. This is to standardise the data and enhance internal validity (Jansen et al., 2005). The data abstraction instrument was electronic (case report form and excel), which reduces input error and allows for generalization and access to data. The electronic data retrieval method also assists with the management of data statistically and quality control (Woster & Haines, 2004).

Each data was listed and captured in the data abstraction instrument, describing where the data is located in the health records, with a clear protocol for extraction. This is to increase the inter-rater reliability (the rate or percentage of agreement among the observers of the data abstraction), which was calculated using the Cohen's Kappa (κ) that has the value of -1 (perfect disagreement) to 1 (perfect agreement) (Cohen, 1960; VonKoss Krowchuk et al., 1995). The GP surgeries' established guideline for data abstraction was adhered to.

Before the commencement of the study, consideration was taken into account as to who may access the data charts, space available to read the charts, operation hours, policies regarding the use of computers and clarification met before commencement (Gearing et al., 2006). The 10% proportion of the abstracted data was randomly checked for accuracy of abstraction, as the recommended percentages. Although confounding variables and bias could be an issue with this research, the researcher has taken steps to sample the medical record of cases and control from the same GP (convenient sampling) practices to overcome sampling bias.

The signs and symptoms that are presented before the diagnosis, were evaluated and assigned a specific checklist in terms of present and not present, type of symptom (locopenic aphasia, episodic amnesia, visual hallucination etc.) if stated, and a subscale in order to classified two categories; "presence of reported symptoms" and "presence of unreported symptoms". The desired medical record data was recorded in such a way that the patients cannot be identified (i.e by the researcher or others), via linkage codes assigned to the data directly or indirectly. This means that the names, National Health Service numbers, or any other patient identifiers cannot be associated or linked to the data set. Consequently, the resulting research data set was subsequently and completely anonymous and once the data was collected from the patient's record, the researcher could not add or subtract information from the records.

It is understood that each patient's data is composed of different interpretations of different scenarios, and that the free–text format commonly used in collecting patients' record is challenging both with the legibility and interpretation (Wu & Aston, 1997; Woster et al., 2005; Pourasghar et al., 2008) and leads to validity and reliability problems with the recorded information. However, the quality of data used in RMRRS is not always inferior, especially if the data is recorded essentially without subjectivity and the introduction of electronic medical recording in place of paper recording (Zhan & Miller, 2003; Matt et al., 2013). Medical records were reviewed to collect the following data: A register with a ten year demographic (age, age of onset of AD, gender, ethnicity, onset and

type of first symptoms, comorbidities), behavioural (dietary habits including water intake and physical activities), and health and developmental (environmental factors, education, MMSE) factors were also considered (Suresh et al., 2011).

To draw a pattern and a distinction, the researcher considered the fourteen signs and symptoms previously reported and unreported, covering dimensions of AD and taking into consideration gender and comorbidities. These signs and symptoms included apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, dysphoriaa, irritability, hallucination, olfactory disturbances and weight loss. Gender, age of onset, education/occupation and comorbidities were included as concomitants (association/ occurring to predict class membership).

Although, there are quite a number of instruments as checklists for the behavioural disturbances of AD, like the Revised Memory and Behavioural Problems Checklist (RMBPC) (Teri et al., 1992), the signs and symptoms of AD are measured based on the Neuropsychiatric Inventory (NPI), which is a standardised measure for the behavioural disturbances in AD, and could also be obtained from caregivers familiar with patient's behaviour (McKhann et al., 1984; Guelfi, 2004). The instrument is valid and reliable, and distinguish among aetiologies, severity and frequency of behavioural changes, and minimise administrative time (Cummings et al., 1997).

3.5.2.3 SAMPLING TECHNIQUE

The sampling of the RMRRS is based on the fact that data has been collected retrospectively over time and this is an advantage as the information can be accessed once (Zhan et al., 2003). The commonly used sampling methods in a retrospective medical record review studies include the convenient, quota and systematic sampling (Gearing et al., 2006). The choice of each method depends on a number of factors including epidemiological nature and prevalence of the disease, importance of probability sampling, population size, research budget and time constraints (Gearing et al., 2006) all of which have been taken into consideration.

Probability sampling was intended to be used in this study as it gives the opportunity for all cases to be included in the study and selection can be implemented to categories (Saunders et al., 2011). Furthermore, a feature that distinguishes the quantitative from the qualitative approach is probability sampling (Sandelowski & Margarete, 2000; Neuman, 2005). Notable RMRRS researchers (Rubin et al., 2012; Flower et al., 2013; Hunter et al., 2013; Schuetz et al., 2014; Hooper et al., 2015)

that have researched on the symptoms of diseases, have assumed the probability sampling for their sample selection. However, and as stated in the constraints for RMRR sampling, only three GP surgeries signed up for the study with a low prevalence of AD in the participating GP surgeries. Therefore, all cases available were included as a consecutive sampling, which is the best sampling method next to the probability sampling as all eligibility is included. The limitations in this sampling strategy lie in the fact that the sample might be similar in ethnicity, street and house, or have a seasonal and terminal trend, which this study is devoid of, as the sample includes individuals from diverse ethnic and socio-economic conditions.

3.5.2.4 SAMPLE SIZE

Every retrospective medical record review requires a statistical power analysis to determine the appropriate sample size (Abel Ickowicz, 2006; Kadam et al., 2010; Naiji et al., 2013). This is to provide valid and robust conclusions and permits the generalisation of the results of the study. Retrospective chart review sampling usually uses the number of variables of the study to calculate and determine the sample size, that is, ten charts to a variable. The larger the sample size, the greater the precision and power to detect an effect/difference between the means and proportion of cases and controls (Gogtay, 2010). Means (u1 and u2) in numerical data is the average of data that can be measured or calculated in numbers, while proportion (p1 and p2) in a categorical data, is the characteristic in a group with or without mathematical meaning. Simply put, it is the difference between the signs and symptoms in patients with AD and those without AD; a shift from the conventional to the unconventional.

Although the concepts underlying most methods of sample size calculation are similar, they are not the same in all research approaches. The concepts are based on the primary research question and whether the data is numerical (quantitative), which requires large sample size or categorical (qualitative) requiring small sample size (Nakagawa & Cuthill, 2007). In this research, the data is both numerical and categorical; hence, a larger sample size is required. The formula engaged will determine the minimum sample of cases and controls required to draw distinct patterns of the signs and symptoms in AD and control group. This will require power and two side type 1 error probability α (alpha)- usually set at an industrial standard of 5%, or α = 0.05. The power of statistical procedure is the ability to show that the null hypothesis (H0) is false when it is actually false (Kasiulevicius et al., 2006; Charan et al., 2013). It is related to effect size/true events which are a statistic estimate of the magnitude of an effect (e.g. mean difference, regression coefficient, Cohen's d, and correlation

coefficient), sample size and significance level (Nakagawa & Cuthill, 2007). In my research, the effect measure to identify patterns is the odds ratio and a generalisation of the odds ratio will be undertaken with the LC regression, a quantifying measurement for investigating and identifying patterns. The usual values for power are 80%, 85%, 90% & 95%, with the formula as $\beta=1$-power.

Results from previous studies (McKhann et al., 1984) indicate that the diagnostic accuracy of these signs and symptoms range from 65% - 96% sensitivity (percentage of individuals with the signs and symptoms that are true positive) and 23% - 85% specificity (percentage of individuals without the signs and symptoms that are true negative). The standard, however, of the diagnostic accuracy is not the same in all studies and therefore, the accuracy has not been fully established (Lim et al., 1999; Petrovitch et al., 2001; Kazee et al., 1993; Dubois et al., 2007). In a more recent study (Dubois et al., 2014), the sensitivity test ranged from 46% - 88% and specificity of 37% - 90% of MCI cases. While an earlier cohort study (Jicha et al., 2006) indicated 70% sensitivity and 30% specificity. I will use the 95% CI to draw a pattern.

Based on the previous reports of the prevalence of the signs and symptoms of AD, the researcher estimates the percentage in the control group to be 20% (**Table 3.1).**

The odds ratio (OR) provides a relative measure of effect, which allows the comparison of the signs and symptoms in patients with AD relative to the control group. This sample size has 95% CI to detect a true event size (OR) of 4.89%, for the majority of the signs and symptoms of AD and a 95% confidence level that repeatedly; the result will be the same.

Table 3.1: Sample size calculation: calculated according to Sullivan et al (OpenEpi, 2009).

Sample Size for Case-Control Study		
For:		
	Two-sided confidence level (1-alpha)	95
	Power (% chance of detecting)	95
	Ratio of controls to cases	1
	Hypothetical proportion of controls with exposure	20
	Hypothetical proportion of cases with exposure	55
	Least extreme odds ratio to be detected:	4.89
		(Fleiss with CC)
Sample size – cases		53
Sample size - controls		53
Total sample size:		106

However, due to the low prevalence in the GP practices that participated in the research, the sample size consisted of 37 cases and 72 controls; assuming the ratio of controls to cases is 2:1, hypothetical proportion of controls with signs and symptoms is 16% and that of the cases is 40%, the least extreme odds ratio to be detected will be OR=3.5 for all signs and symptoms. The prevalence of the signs and symptoms is variable and not the same in all cases, hence the variation in the result presented in chapter five, which could also be a bias.

3.5.2.5 INCLUSION CRITERIA

Case notes of adult patients in the GP surgeries with AD (cases) and without AD (controls) were included in the study; EOAD case ever recorded in the UK was aged 27 years (Zoe Bottrell story; Mail online - health, 2015), while the late-onset begins at 65 years and above. The age restriction is to enable the researcher to detect changes at the earliest onset, by examining and analysing data ten years before the diagnosis of the disease, to understand the prevalence and pattern of neuropsychiatric symptoms. The neurodegeneration progresses 20 - 30 years before the signs and symptoms appear; the data will also reflect the preceding signs and symptoms of AD (Mann, 2003; Hennekens & Buring, 1987).

Case notes of patients with a diagnosis of other neurological conditions, accident cases, an inconclusive diagnosis, and/or are outside the age bracket.

3.5.2.7 DATA ANALYSIS

The literature review reveals that the population of AD is divided into five groups namely: the early onset group, the late-onset group, the typical presentation group, atypical presentation group and AD with comorbidities. In this arm of the research, the analysis assumed the logistic regression which is ideally suitable for a study as this, an analysis that uses the concomitant variable to predict class membership. In recent years, they have become increasingly popular strategy for quantifying measurement in investigating and generating patterns from signs and symptoms of disease (Severo et al., 2012; Smart et al., 2012; Baumert et al., 2014; Birkeflet et al., 2014; Simpson et al,. 2014; Lawrence et al., 2015), and have reported plausible results. The LC analysis explains the relationship among categorical variables stating the existence of a latent or unobserved classifier to conditionally make them independent and items are treated as fallible indicators of unseen true states (Chung et al., 2006); class is the probability that indicates the chance that the variable takes on certain values. Covariates predict class membership through binary or polytomous logistic regression by the extension of this to traditional LC models, and logistically predict the value of the categorical outcome. The dependent variable (AD) is categorical with a number of possible values, which is either yes or no (Bandeen-Roche et al., 1997).

Signs and symptoms-predict AD (binary diagnosis)

The LC model is written as:

$$p_{i1,i2,\ldots,iN} \approx \sum_t^T p_t \prod_n^N p_{i_n,t}^n,$$

Where T is the number of latent classes

Pt is the unconditional probability that should sum up to one

A pint is a conditional probability.

Initially, descriptive statistic and analysis were applied to describe variables, before the final and more advanced analysis with the logistic regression model.

3.5.2.8 PILOTING

Piloting is undertaken in this research to assist with the clarification of the data abstraction protocol, the reliability of the data abstraction sheet, the process of pulling charts and evaluate of any sampling concerns (Smith, 1996; Wu & Ashton, 1997; Jansen et al., 2005). Moreover, piloting is the most effective method to determine the development of any problem with missing data. The research, therefore, commenced with the piloting, with five charts, according to the standard guidelines of piloting (Wu & Ashton, 1997; Perry, 2001), without concern. Although, there is no universal method for tackling the issues of missing data, a protocol to address this issue is the piloting to determine the development of issues with missing data. The issue of missing data is clarified in chapter five.

3.5.3. QUALITATIVE INTERVIEW

3.5.3.1 BACKGROUND

This section of the thesis is the protocol for a qualitative interview. The study fits into a three-phase research study; adopting the qualitative approach, focusing on creating patterns of the signs and symptoms of AD and reflecting the perspective of professionals. Although AD researchers (Paton et al., 2004; Somme et al., 2013; Brorsson et al., 2013; Cuijpers et al., 2014; Chaney et al., 2015; Gambina et al., 2015; Forsgren et al., 2015) have adopted the same data collection design, this study provides the first insight from the GP's view of the preceding signs and symptoms before the diagnosis of AD, perception of late diagnosis and recommendations to tackle the issue of late diagnosis. This is because the GPs are the primary point of contact with the service user, and are in the best position to know the presentation of the disease prior to an official diagnosis.

A sample of 16 GPs was initially proposed out of the general practices in Milton Keynes and Luton area. However, seven GPs agreed to participate which coincided with the saturation point. All have attended to individuals with AD or related disorders, with the recurrent theme of (1) identifying early clinical symptoms, which occur prior to diagnosis, as early signs of AD (2) the reluctances to formally diagnose AD (issues around labelling and "putting off a formal diagnosis" and (3) future recommendations against barriers to early detection. The interviews were semi-structured respectively for numerical and verbatim excerpts. The results of the interview complemented the retrospective study, which focuses on patient notes, and suggested guidelines for the early screening and subsequent earlier diagnosis of the disease.

3.5.3.2 OBJECTIVES

To explore the perceptions of the GPs, explore their definition of the signs and symptoms that precede the diagnosis of AD, determine the problem of late diagnosis and identify the current barriers to early diagnosis.

3.5.3.3 RESEARCH DESIGN

This is a complimentary (embedded) interview that adopts a qualitative technique, seeking to elaborate and enhance the results of the first study that looks at patients' notes for pre-diagnosed common signs and symptoms that may indicate the early onset of AD.

3.5.3.4 PARTICIPANTS

Participants are GPs from the surgeries in Milton Keynes and Luton who have worked within the GP surgeries in the city, between 2006-2016, without consideration of their age, gender, ethnicity or specialty. They were purposely a self-selected group based on their desire to participate in the interview and enable the study.

3.5.3.5 SAMPLE SIZE

Sixteen GPs were proposed but only seven were able to participate based on availability for interview. This gave the research student the experience of planning and structuring interviews, conducting and transcribing. Additionally, the saturation, quality and depth of data, matter more than the quantity in qualitative interviews (Burmeister & Aitken, 2012; Fusch, 2015). This view is supported by Baker et al (2012), who opined that one respondent is all you need, that is, your person of interest.   Generally, however, the four thumb rules is ideal that you keep asking the question as long as the responses keep coming differently and reporting fully, how the question can be resolved.

3.5.3.6 ANALYSIS

A framework analysis was used to analyse the interview data based on the content of the data that had cases and codes that needed a flexible approach to a content analysis, and as a way of getting closer to the data and developing a deeper appreciation of its content; the summary was in a matrix output of rows and columns. Furthermore, it offers an accessible and theoretical, flexible approach to qualitative data analysis, and not attached to any particular epistemology or ontological positions (Joffe & Yardley, 2004).

In a framework analysis, the steps to follow are transparent and bring forth highly structured outputs of summarised data (Gale et al., 2013). The framework analysis is part of a broad method of analysis termed thematic or qualitative content analysis; it identifies commonalities and differences in qualitative data before focusing on the relationship between different parts of the data (Gale et al., 2013). Defining its feature is the matrix outputs which are rows (cases), columns (codes) and cells of summarised data, providing the means for systematic analysis of the case or coded data (Ritchie & Lewis, 2013). According to Gale et al. (2013), the method seeks to draw conclusions descriptively and/or explanatory around themes and is widely employed in health research. It is seductive in nature, as its methodical processes and 'spread sheet' approach aligned more closely with quantitative paradigm (Pope & Mays, 2009). The clear steps to follow, the ability to combine different data and identify themes from the data, has influenced the choice of the framework analysis.

Due to the nature of the framework method, that is a highly systematic method of organising and categorising cumbersome quality data, qualitative research skills are needed to adequately and appropriately interpret the data set while hastening the generation of descriptions, categories, explanations, and typologies. As with other methods, the framework method requires reflexivity, rigour, and quality analysis to succeed (Gale et al., 2013); the researcher is well aware of this and took steps to minimise this by gaining the desired knowledge and experience for the framework analysis. As the analysis presents the systematic element of content analysis (quantitative in nature), permitting the combined analysis of frequency of codes with analysis of meaning; it will be approached inductively (coding and themes are generated and directed by the content of the data), and deductively (coding and themes are pre-selected and directed by the existing concepts) (Joffe & Yardley, 2004; Braun & Clark, 2006). This is in relation to the research question, rational scientific framework and objective of the interview. The difference lies in how themes are selected.

Qualitative data analysis including grounded theory, discourse analysis and ethnomethodology (pays attention to language and its use in social interaction) as well as phenomenology and narrative method (experience, meaning and language are important) are based on philosophical ideas that shaped the analysis process and associated with specific disciplines (Crotty, 1998). However, the framework analysis is not affiliated with any epistemological, philosophical or theoretical approach, but can be adapted with many qualitative analyses, due to its flexibility. The framework analysis

facilitates constant comparative techniques through the review of data across matrix and not necessarily concerned with generating social theory (Gale et al., 2013).

The Graneheim & Lundman (2004) framework analysis description that is thematic in nature was adopted which includes:

Transcription: This is the verbatim (word-for-word) transcription of the content of the interview, which should have adequate line spacing and large margins for subsequent coding and notes making. The process is an opportunity to immerse in the data.

Familiarisation: This is the process of emersion in the data by listening to the recording several times, to become familiar with the contextual or reflective notes.

Coding: This is the phase of generating labels (codes) succinctly that identify data that is relevant to the research question, and involves coding the complete dataset, collating all the codes and relevant data for the analysis stage.

Development of analytical framework: The next step is the process of abstraction and comparing labels on a set of codes to the transcripts. Codes should be categories and clearly defined using a tree diagram if needed. The researcher will consider the use of the 'other' code under each category, to include data that does not fit.

The analytical framework: A detailed analysis of each theme based on the scope and focus of each theme, to determine the story of each theme (Braun & Clark, 2006). Categories were refined to informative name for the analysis before charting began (Ritchie et al., 2002). Indexing of transcripts was undertaken using the existing categories and codes, and assigning a number or abbreviation to codes for easy identification. Particularly useful at this stage to speed up the process of transcription and ensure easy retrieval of data is the Computer Assisted Quality Data Analysis Software (CAQDAS). This is an effective way of data storing and organising for accessibility and analysis.

Charting data into framework matrix: Information from the recording was finally charted according to the codes and indexes. A spreadsheet was used to generate the matrix. This is a process of summarising the data by category from each transcript and includes references to illustrative and interesting quotations using CAQDAS or NVIVO that generated the framework matrix. The researcher is aware that an hour interview can generate between 15-30 pages of text and that it takes approximately half a day per hour-long transcript to be charted, which might take longer in some cases.

Mapping and interpretation: Data was finally mapped according to themes and the result interpreted.

Interviewer effect, which is a drawback of the qualitative interview was minimised with consistency in the collection of data, and the delivery of the questions provided in the same format and order to every respondent (Esterberg, 2002; Payne, 2016). The interview was conducted while considering the location, balance of control, good rapport, respect, active listening and probes.

3.6. Study location

This research study was undertaken in Milton Keynes in Buckinghamshire and Luton in Bedfordshire Counties, United Kingdom. Each city is introduced individually as follows:

3.6.1 Milton Keynes

Milton Keynes is located in the southeast of England and became a new town on the 23 January 1967, as a result of the British Government decision to generate new housing to relieve housing congestion in London. The city encompasses the existing towns of Wolverton, Stony Stratford, and Bletchley (**Figure 3.4**) with a population of about 229,941 in 2011 (Census, 2011), and an area of about 34 square meters (m^2). Recently, the Joint Strategy Need Assessment (JSNA, 2013) estimated the population to be about 255,700, with 274,383 individuals registered within the twenty-seven GP surgeries in 2014, a university hospital in the Eagle's Stone district of the council, and a small private hospital known as the Saxon clinic. The Milton Keynes University Hospital is an NHS general hospital with Accident and Emergency unit and associated with the University of Buckingham medical school for medical teaching purposes. The GP surgeries include: Ashfield Medical Centre, Grove Surgery, King Fisher Surgery, Parkside Surgery, Watling Vale Medical Centre, Dulverton Drive Surgery, Newport Pagnell Medical Centre, Bedford Street Surgery, Sovereign Medical Centre West Field Road Surgery, Bur chard Crescent Surgery, Cobbs Garden Surgery, Griffith Gate Surgery, Stony Medical Centre, Stone Dean Practice, Hilltops Medical Centre, Water Eaton Health Centre, Neath Hill Surgery, Purbeck Surgery, Purbeck Health Centre, Oakridge Park Medical Centre, 2 Solar Court Surgery and Milton Keynes village practice.

Figure 3.4: Map of Milton Keynes. The map indicates the different areas of MK where the research was undertaken; the surgeries were based in Fisher mead which is in the central MK and Middleton areas. Source: Free media repositories, accessed 05/06/2016.

The name of the city was taken from the existing village of Milton Keynes on the site and was deliberately located with the distance equally from London, Birmingham, Leicester, Oxford, and Cambridge, to be self-sustaining and become a regional centre in its own right (JSNA, 2013). Milton Keynes was chosen for the following reasons: Firstly, it is located in a region (south-east) with the highest prevalence of AD (121,572) among the nine regions of England (Alzheimer's Society, 2014). Secondly, even though the Isle of Wright Clinical Commissioning Group (CCG) has the highest prevalence of dementia (46.4%) and the Tower Hamlets with the lowest (15.5%), Milton Keynes has a very high growth rate, that is, the second fastest growth rate of all local authority within England

(HSCIS, 2014; MK Clinical Counselling Group, 2015). The city has a population that consists of 65.3% 16-64 years olds compared with 63.8% of England as a whole; this is the population at risk of developing dementia. To plan ahead for the anticipated incidence in this group will be ideal.

In 1990, migration accounted for 80% of the city population, with the highest number of the population within the 25-39-year-old age group (39,600 out of the population of 145,800) (Kerswill & Williams, 2000). Those within this age would be in their late fifties or early sixties now and this population (60-65 years) is ageing faster than the national average and forecasted to increase to about 95% from 3,635 in 2010 to 7,060 in 2026, with an increase in long-term illnesses including AD (JSNA, 2015). However, the demography of MK is not evenly distributed in terms of age; the deprived areas are skewed toward the younger population when compared to the affluent areas. Thirdly, the disease diagnosis rate of 53% has been achieved within the last year, and there is a focus on the identification of people at risk of dementia and the offering of a memory assessment in their GP surgeries. This study supports the identification of patterns prior to the current point of diagnosis of AD and I aimed to develop a predictive model for early detection. This will subsequently be used to identify those who might benefit from more expensive or invasive diagnostic testing. Finally, the researcher's prospect of negotiating access to the study sites is taken into consideration, as the researcher is local to the area.

3.6.2 Luton

Luton is a large city/ town situated in the South of England, in Bedfordshire County (**Figure 3.5**). The town was founded by the Anglo Saxon in the sixth century and had a population of 214,700 in mid-2015 (National Statistics, 2015). It shares borders with Aylesbury in the east; Stevenage in the west; west of London in the north and Milton Keynes in the south. According to the 2011 census (Luton Census Demographics, UK 2011), the average age of individuals living in Luton was 35, with a median age of 32, consisting of 67% white, 6.3% Pakistanis, 3.1% Bangladesh, 2.6% India, 2.3% Irish, 1.2% Scottish, 0.9% Jamaican, Nigerians and Zimbabweans and 0.7% Kenyans.

Figure 3.5: Map of Luton. The map indicates the areas within the metropolis, with Luton in the center; an area where I carried out the research, which is large and diversified (Google maps, 2017).

In 2015, Luton's population was approximately made up of 35% Black and Minority Ethnic (BME) groups including Pakistani, Bangladeshi, Indian and African Caribbean and has an annual growth rate of 1.8% faster than the national average with 0.8% (Luton Demography, 2016). This population is serviced by thirty-seven GP practices including Lea Vale Medical Group; Barton Hills Medical Group; Bell House Medical Centre; Blenheim Medical Centre; Bramingham Park Medical Centre; Bute House Medical Centre; Castle Street Surgery; Conway Medical Centre; Dr A Zaman's Practice; Dr Mirza & Partners, Gardenia & Marsh Farm Practice and Lea Vale Medical Group with two surgeries each; Hochwell Ring Med Pract-Mirza; Kingfisher Practice; Kingsway Health Centre; Larkside Practice; Leagrave Surgery; Lister House Surgery; Medici Medical Centre; Medina Medical Center; Moakes Medical Centre; Neville Road Surgery; Oakley Surgery; Pastures Way Surgery; Stopsley Village Practice; Sundon Medical Centre; Sundon Park Health Centre; The Ashcroft Practice; The Link Surgery; Town Centre GP Surgery; Wenlock Surgery; Whipperley Medical Centre and Woodland Avenue Practice.

Even though Luton has a younger population than the national average due to international migration, with a net migration of 1,700 in 2015, the population of those between the ages of 30-64 is quite high, about 43.5% of the entire population. This is the population at risk of EOAD as well as LOAD and as expected this population will double in the next decade.

Dementia Luton (2015) has recognised that there is an increase in the prevalence of dementia in the black community, which the significant and diverse BME community in Luton could lend itself due to the diminished recognition of dementia as a condition in this group and the South Asian community. Additionally, there is a misunderstanding and sometimes, lack of knowledge of the symptoms of dementia as well as issues within the older people's mental health; language barriers, the stigma surrounding mental issues and risk of misdiagnosis and delayed treatment among these communities could present issues regarding the prevalence of the disease. Moreover, the prevalence is not really established, as the number of individuals on GP registers with dementia is 560, while the national data figure is approximated to be 900 (Dementia Luton, 2015) per all the registered patients in the GP surgeries. Even though the prevalence of early-onset AD is much smaller, the needs and circumstances of these young adults could be different from the older counterpart. Careful planning with regards to early diagnosis, treatment and support, and total commitment is needed in anticipation of the rise in prevalence of the disease in the near future.

3.7. Ethical issues.

The first ethical concern of a researcher is the respect for the dignity and autonomy of participants. Four principles or moral commitments are linked with data sharing (Gillion, 1994; Beauchamp & Childress, 2001). These principles include respect for autonomy (respecting the decision-making capacities of autonomous individuals); non-maleficence (refraining from causing harm); beneficence (to do good) and justice (the fair distribution of benefits, risks and cost). These principles have been described as "prima facie "principles (Ross, 1939), meaning that they are binding unless they conflict with others. The principles help researchers to make informed decision regarding moral and ethical issues in research (Brakewood & Poldrack, 2013). Morality here refers to norms about right and wrong and standards of conduct that are generally acknowledged by those in the medical and healthcare profession (Ross & Stratton-Lake, 2002). Good ethical practice is an obligation to shared data, however, the decision to be morally right lies solely with the researcher. It is with this moral obligation that the researcher sought ethics approval from the regulating authority to enhance the validity and gain trust with the research.

One of the designs of this research collects and analyses patients' anonymised data and seeks the opinion of GPs through a qualitative interview; the National Health Service (NHS) data is increasingly being used for medical and health research, which include data from approximately one million

individuals treated every 36 hours (William et al., 2012). The research had to be undertaken in an ethical way to maintain the trust of patients and individuals.

Ethics was subsequently sought and approved by the IHR Research Ethics Committee (REC) of the University of Bedfordshire, my alma mater and the first responsibility for making sure that the research is undertaken within the good ethical practice. Furthermore, approval was sought from the institutional review boards (NHS REC, North of Scotland and London) and HRA for the GPs interview and RMRRS through the Integrated Research Application System (IRAS). The process, which is long and overwhelming for the committee and investigators alike is necessary due to the standardisation of the application to local RECss (Jamrozik, 2004; William et al., 2012), and is geared towards overcoming the inconsistencies in paperwork required by different committees (IRAS, 2016). Even with the frustration experienced due to delays in gaining approval from the NHS REC (Dixon-Woods et al., 2016) and issues of publication and outcome reporting bias in the UK (Begum & Kolstoe, 2015), the system is highly regarded in ensuring patients' safety and confidentiality of data sharing in medical research. There was no issue regarding consent and withdrawal from participating GPs and surgeries, deception, confidentiality and anonymity.

3.7.1. Consent

For the qualitative interviews, GPs were informed verbally and provided with an information sheet (Appendix VII). All of their questions were answered to their contentment before the commencement of the research. Participants were also told that they are under no obligation to decide or to participate and that they could withdraw personally from the research at any time. Anonymised data from interviews and the RMRRS is used in this research, after ethics approval from the ethics review board and participating GP surgeries.

3.7.2. Confidentiality

This research does not involve analysing sensitive data that is protected by civil right like personal information. The researcher adhered to both the data protection Act, 1998 (Act, D.P., 1998) and the Health and Social Care Act 2001 (Act, H.S.C.A, 2001). The code of the confidentiality of the participating GP surgeries was adhered to, for confidentiality of all held data. The data was held on a password protected and non-networked computer which could only be accessed by the researcher, under lock and key. All data is anonymised and pseudonyms or codes assigned for the collection and analysis of data. Nothing is attributed by name or any personal identifier but by codes

or pseudonyms. Also for the quantitative data, the researcher reduced the precision of variables that might be identifiable like postcode while being careful for distorting the qualitative data and emphasising access restriction through a password protected and non-networked computer, accessed only by the researcher.

While this chapter discussed the methodology in detail, the next chapter mapped, synthesised and appraised the evidence available on patterns in signs and symptoms of AD through a systematic scoping review of literature. The synthesis is provided to highlight the current evidence and the need for more research in this regard.

CHAPTER FOUR: Systematic scoping review

4.1 Background

Owing to the diversity of presentations among the AD groups, it is pertinent for a systematic scoping review of previously reported symptoms and signs, as well as their sequence and timing to increase awareness for early diagnosis and for timely intervention. Even though there are studies on the frequencies and prevalence of the symptoms of AD, to date there is no systematic review of the timing and sequence of the early symptoms and signs of AD. This review will therefore encourage researchers to undertake such research to produce studies that will enable the generalisation of the results. Similarly, it is supplemented with a literature review to synthesise and produce the best available evidence on patterns in the presentations of AD.

4.2 Objectives

The objectives of this review are: (i) to identify the sequence and timing of the presentation of signs and symptoms at the early stage of AD to inform a primary study and (ii) to understand how far back from diagnosis the first symptoms that will justify a diagnosis were reported.

4.3 Search methods

This is extensively explained in the protocol in **chapter 3.5.1.9**.

4.4 Selection criteria

The reviewer included all empirical evidence as explained in the protocol.

4.5 Data collection and analysis

The outcomes of this review were: (i) the sequence and timing of signs and symptoms preceding the clinical diagnosis of AD and (ii) the timing from the report of the first symptom that justified the clinical diagnosis of AD to the clinical diagnosis of the disease. Only one study by Devier et al. (2010) reported on outcomes related to this review. Even though there were limitations in the studies on

the sequence and timing of the signs and symptoms preceding the diagnosis of AD, I identified three additional studies with outcomes of interest from the 3,528 unique citations reviewed at the title and abstract level; these were: (a) emergence of first clinical symptoms to dementia phase, (b) from first assessment to appearance or symptomatic assessment and (c) clinical onset of symptoms and signs to case fatality or death. However, the data on these outcomes was also limited.

A descriptive/narrative analysis was undertaken due to the heterogeneity in the objectives of the included studies. A quality assessment was conducted with the QUADAS-2 assessment tool.

4.6 Main results

Four articles (Amieva et al., 2008; Devier et al., 2010; Fox et al., 1998; Schmidt et al., 2010) were used in this review, which reported data from 593 individuals diagnosed with AD; one study (Amieva et al, 2008) was conducted in a community setting and three others in secondary/specialist settings. The overall quality of studies was good, except for the heterogeneity in review objectives.

4.6.1 Outcome I:

Of the 148 participants in the study by Devier et al. (2010), 39 (26%) converted to AD and all the converters were 55 years at baseline indicating EOAD. There was heterogeneity in first symptom reported, which included memory loss and depression.

4.6.2 Outcome II:

The timing from the report of the first symptom to the diagnosis of AD ranged between 19–176 months, with an average of 62 months.

4.6.3 Outcome III:

Amieva et al. (2008) reported the timing from the report of the first clinical symptom to dementia. Cognitive decline was the first to appear 12 years before dementia in the measure of semantic memory and conceptual formation, closely followed by depressive symptoms and verbal memory decline two years later. Four years after the cognitive decline, converters became more dependent on their activities of daily living (ADL), subsequently visual disturbances were recorded which worsened until the stage of dementia.

4.6.4 Outcome IV:

Outcome four was the timing from the first assessment to the symptomatic assessment of individuals at risk of FAD. Out of the 63 subjects in the study by Fox et al. (1998), 15.9% converted to AD with a mean time (± SD) from initial assessment to symptomatic assessment of 3.1 ± 1.5 years. Episodic memory loss was the most common and noticed on average 6 months before symptomatic assessment. The only subject with a MMSE score of 25 in the study remained stable for 2 years, consistent with family members with the same score that remained healthy throughout.

4.6.5 Outcome V:

Schmidt et al. (2010) investigated rapidly degenerating AD that indicated additional focal symptoms consistent with a form of prion disease, CJD. The outcome measure was the timing from symptoms, median life span from clinical onset of the disease to case fatality or death. In total, 35 distinct neurological, psychiatric and autonomic symptoms and signs were reported, with the sequence and timing (in months) in the early stage between 2.0–51.1 months.

4.6.6 Author's conclusions

Further studies regarding the timing and sequence in presentations of AD are needed because there is a paucity of data regarding this topic and research on the presentations has been on the prevalence and most common signs and symptoms of AD. Therefore, this review has insufficient data to make recommendations on the timing and sequence of these presentations to aid the early detection of AD. However, it is worthy to consider the additional focal symptoms of rapidly progressive AD and an MMSE score of 25 in the inherited dominant familiar AD in discriminating the disease from other dementias.

4.7 Plain language summary

This review aimed to identify the sequence and timing of early presentations of AD (please refer to **chapter 2.1**) to inform a primary study. The early signs and symptoms have been identified from previous epidemiology studies (Mega et al., 1996; Cumming et al., 1997; Palmer et al., 2008; Igbal et al., 2013) as the characteristics of the early stage of AD. The early stage here means the stage at which the pathology of the disease is just beginning and at the lowest threshold; the preclinical phase of detecting cognitive deficits which is estimated to be about five years (Linn et al., 1995; Forstil & Kurz, 1999). These signs and symptoms include those mentioned in chapter 2.1; they are

not always present in an individual, with their timing and sequence in appearance different in each type of AD. The reviewer searched a wide range of resources and found 3,219 unique citations reviewed at the title and abstract level. Forty academic papers were reviewed fully; thirteen articles deemed fit, however, after further review, four were finally included in the review. The review included studies in the community (people living in the community with AD) and secondary institutions (specialist clinics for referrals).

4.8 Scientific summary; Background

4.8.1 Target condition under review

The target condition for this review is AD (please refer to **chapter 1.2** for the prevalence and **2.1** for description of the disease). The early stage of AD is characterised by the pathology of biomarkers (Villemagne et al., 2015; Mufson et al., 2016) rather than observable signs and symptoms and is known as the preclinical or asymptomatic phase. As stated in **chapter 2.1**, the heterogeneous nature of the disease presentations leads to challenges in the early diagnosis, which can result in late diagnosis or misdiagnosis with a potentially inappropriate intervention that could worsen the prognosis.

4.8.2 Index symptoms

The index symptoms as described in **chapter 2** (Mega et al., 1996; Albert et al., 2011; Dubois et al., 2014; Morris et al., 2014; Hirao et al., 2015) have different scores across studies and individuals (Mega et al., 1996; Kang et al., 2004; Craig et al., 2005; Ringman et al., 2015). The timing and sequence of the presentations are not clearly defined, with few studies undertaken on timing from the first symptom manifestation to diagnosis (Palmer et al., 2008; Devier et al., 2010; Shea et al., 2015), which deserve research attention, as they have clear potential to impact on early diagnosis of AD to inform timely intervention that will slow down the degenerative processes of the disease.

4.8.3 Objectives

Scoping reviews map and appraise the quality of existing evidence (Arskey & O'Malley, 2005) and are similar to systematic reviews but with broader and more comprehensive objectives (Sandelowski et al., 1997; Glasziou et al., 2001). This has been undertaken using the protocol for a systematic review but within a large body of diverse literature and guided by specific objectives. This was to understand the whole of the literature by systematically searching so as not to miss any

relevant articles and to bring meaning to the result. It is therefore neither a diagnostic nor intervention study but a study to identify the sequence and timing of the signs and symptoms preceding the clinical diagnosis of AD to inform a primary study.

4.9 Methods

Criteria for considering studies for this review

4.9.1 Types of studies

All studies were considered where participants were assessed with the index symptoms and reference standard diagnostic assessment within any health care setting. No study design was excluded if the study was empirical and appraised as good quality.

4.9.2 Participants

Participants in studies undertaken at an early stage with the signs and symptoms of AD were included if they were between the ages of 30–85 years, with the study in primary care, memory clinics or secondary care settings. The objectives of this review were to identify the sequence and timing of presentations at the early stage of AD, therefore studies on presentations in the late stage of AD (AD dementia) were excluded. The rate of progression and timing in this group can be reviewed separately. Also, other dementias and neurological conditions were excluded, as well as studies that were undertaken in developing countries.

4.9.3 Index symptoms

The reviewer considered fourteen symptoms which have been identified at the early stage of the pre-clinical and MCI (details in background and **chapter 2.1**).

4.9.4 Comparator tests

There are no comparators or alternate tests, as the review is not about testing diagnostic tools but reviewing the sequence and timing of the signs and symptoms preceding the clinical diagnosis of AD.

4.9.5 Target condition

AD and any subtypes including early onset and late onset AD.

4.9.6 Reference standard

Studies that used the reference standard set out in the protocol for this review, which is the standard for diagnosing AD, were included. The reference standard used in this review was the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA), a commonly used criteria for AD dementia. NIA-AA criteria, more recent criteria that use biomarkers to support the diagnosis, Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV, American Psychiatric Association, 1994), DSM-5 (Freedman et al., 2013) were considered. A study on post-mortem verification was included because of the timing of presentations at the early stage of the disease.

4.9.7 Exclusion criteria were:

- Participants with other dementia or neurological conditions
- Inaccurate diagnostic criteria
- Single reference symptom
- Late stage AD dementia

4.9.8 Search criteria for identification of studies

The researcher searched OvidSP MEDLINE (1950–May 2016), PsycINFO (1806–May 2016), Nursing Index and the Cochrane register for diagnostic and intervention studies.

Terms describing the sampling frame or setting of studies are not standardised, hence, there was no attempt to restrict the search to studies, which would have lessened the sensitivity of the search. No language or publication restrictions were applied. The researcher used theatres to standardise and improve the search; a disease theatre as the main, followed by a basic theatre including timing/onset and country, and the combination of theatres before duplicates were removed.

4.9.9 Searching other sources

Manual searching of studies was undertaken, even when there was little evidence to support this (Glanville et al., 2012), with reference lists of relevant papers. Also, the Health Technology Assessment (HTA) database via Cochrane Library, Database of Abstracts of Reviews of Effects and the Grey (Science Citation Index, Thesis and Conference Proceedings) literature through the Web of Science were searched. No unpublished data was found.

4.10 Data Collection and analysis

4.10.1 Selection of studies

Studies were selected based on the inclusion criteria. Titles of articles identified were scanned by the reviewer to exclude irrelevant articles. The reviewer and librarian independently scanned the titles and abstracts of the studies deemed relevant with an agreement; the reviewer reviewed the full text versions, then together with one of her supervisors, considered the studies to be included (**Figure 4.1**). There was no disagreement.

The reviewer independently extracted data on the study characteristics (study design, participants' characteristics, inclusion and exclusion criteria, recruitment period, country of study, health care settings, diagnostic criteria and clinical signs and symptoms). A two by two table was not possible due to the nature of the data reviewed; however, any discrepancy was resolved with the supervisors. The data abstraction form as well as the title and abstract form (Appendices XIII &XIV) were piloted and reviewed by my supervisors before the final abstraction was undertaken.

4.10.2 Assessment of methodological quality

The reviewer independently assessed the quality of included studies using the QUADAS tool. Details of the quality assessment tool and coding criteria based on the QUADAS tool (Whiting et al., 2011) is outlined in Table 4.1; assessment of methodological quality.
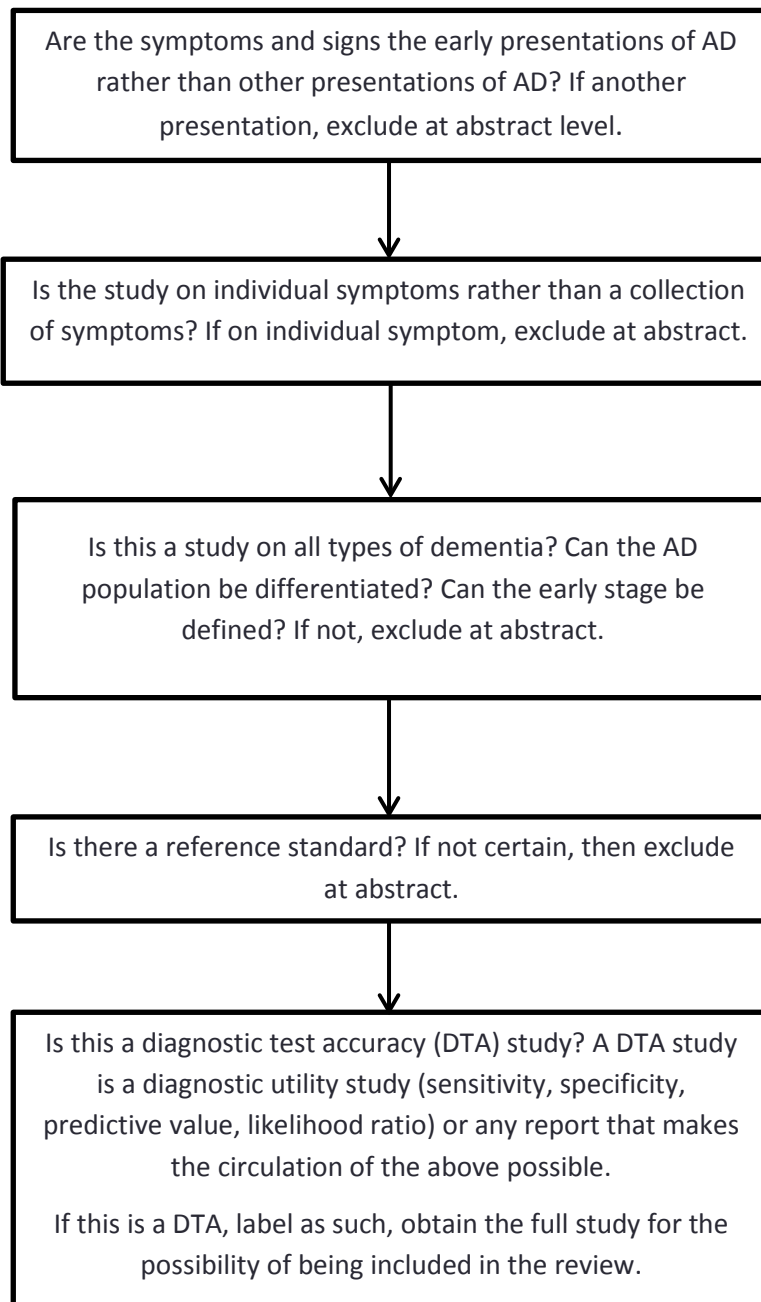
Figure 4.1: A flow chart of the inclusion criteria. The reviewer reviewed the title, abstract, and full text of studies included.

Table 4.1: Quality assessment with the QUADAS tool.

DOMAIN	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of participant selection: Description included participants (prior testing, presentation, intended use of index test and setting)	Describe the index test (symptoms and signs) and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any participants who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (Yes/no/unclear)	Was there a consecutive or random sample of participants enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard? Did all participants receive a reference standard? Did all participants receive the same reference standard? Were all participants included in the analysis?
Risk of bias (High/low/unclear)	Could the selection of participants have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the participant flow have introduced bias?
Concerns regarding applicability: (High/low/unclear)	Are there concerns that the included participants do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.10.3 Statistical analysis and data synthesis

Due to the heterogeneity in the objectives of studies included, statistical analysis was not possible. Instead, a descriptive analysis was undertaken and the studies presented individually accordingly. QUADAS-2 was used to assess the study quality to determine the overall risk of bias and strength for each study.

The data was extracted from the four distinguished studies that reported on the early and late stages of AD and presented in the study. A bivariate random-effects approach is appropriate if the threshold of sensitivity and specificity was reported and was consistent (Reitsma et al., 2005).

4.10.4 Heterogeneity investigations

Heterogeneity in the included studies was assessed with the QUADAS-2 tool.

4.10.5 Assessment of reporting bias

Formal assessment of reporting bias was not undertaken in this review as the objective of the study was not the accuracy of tests, but the timing and sequence. Moreover, there are uncertainties in the assessment of reporting bias in diagnostic test accuracy reviews (Deeks et al., 2005).

4.11 Results

4.11.1 Search results

A total of 3,210 articles were identified, screened and selected for the review including duplicates (318), nine others were identified bringing the total to 3219. Of these, 3,179 were excluded based on titles and abstract alone (**Figure 4.2**). Forty full text versions were reviewed, 13 were initially included but 9 later excluded due to technical reasons, finally 4 were selected for review. The agreement between the reviewer and the supervisors on the full text screening was good.
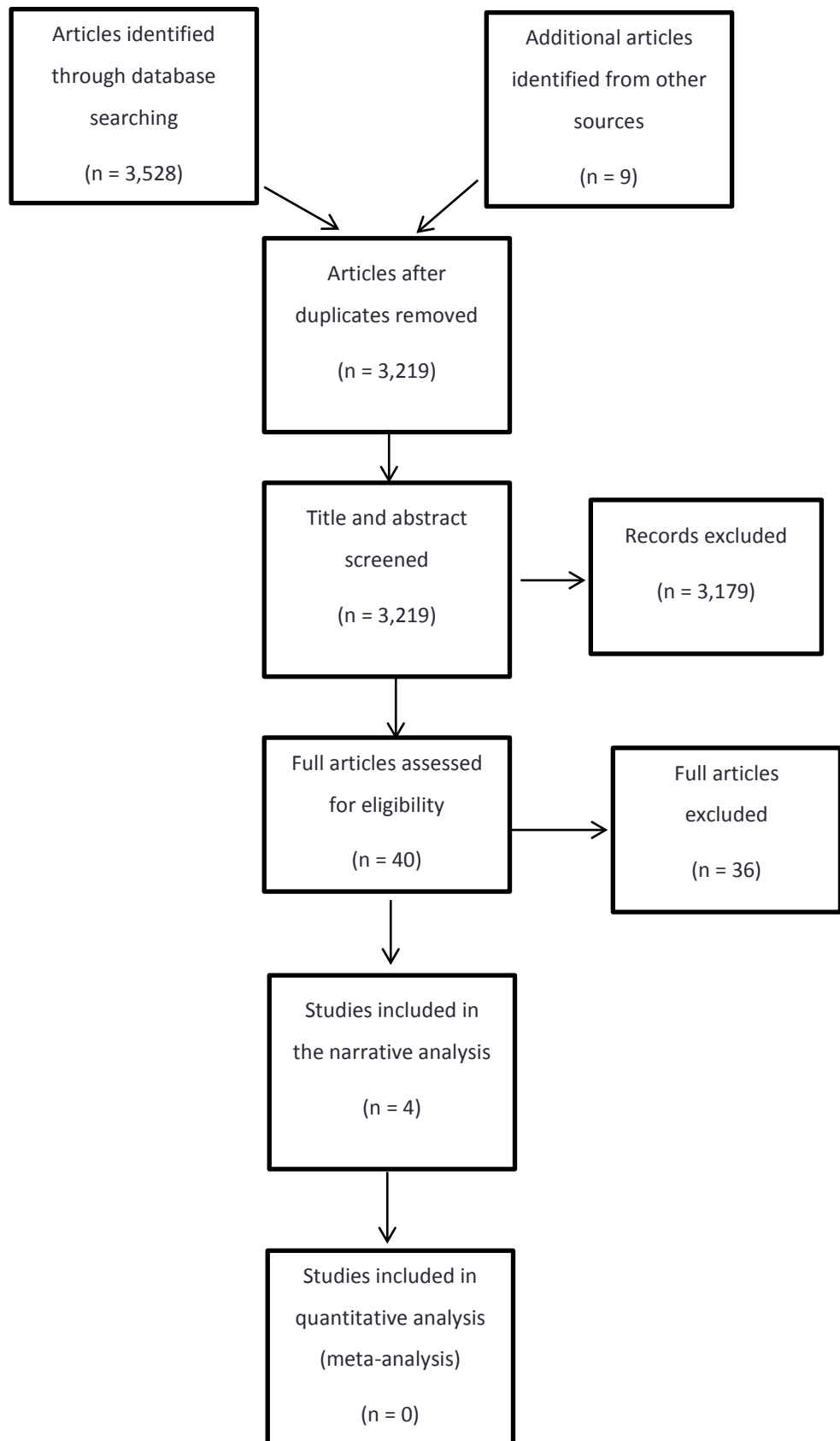
Figure 4.2: Flow diagram indicating the articles included in the study.

4.11.2 Reasons for exclusion

Exclude discussions on reliability and timing of presentation 2; Interviews 2; looking at commonality of symptoms 5; Establish diagnosis 1; Comparing VAS and AD 2; Retrospective survey of symptoms between AD dementia 1; Prediction of extrapyramidal signs 2; Behavioural syndrome study 2; Single symptoms studies 2; Accuracy of diagnosis 1; Clinical clips 1; Association studies 3; Cognitive profile 1; Data research dissertation 1; Trajectory of cognitive decline1. Studies that were reviewed in detail but excluded have fully been referenced (n = 9).

- Exclude discussions on reliability and timing of presentation 2;
- Interviews 2; Looking at commonality of symptoms 5;
- Establish diagnosis 1;
- Comparing VAS and AD 2;
- Retrospective survey of symptoms between AD dementia 1;
- Prediction of extrapyramidal signs 2;
- Behavioural syndrome study 2;
- Single symptoms study 2;
- Accuracy of diagnosis 1;
- Clinical clips 1; Association studies 3;
- Cognitive profile 1;
- Data research dissertation 1;
- Trajectory of cognitive decline 1;

Initially, thirteen studies met the inclusion criteria and were reviewed in full. However, four studies on dementia (Yoon et al., 2014; Masters et al., 2013; Kang et al., 2004; Di Ilio et al., 2010), one study undertaken in a developing country (Lopera et al., 1997), another on caregivers' distress (Craig et al., 2005), one single case study (Shea et al., 2015), one study with incomplete data (Jost et al., 1996) and one without a reference point for the diagnosis of AD (Palmer et al., 2008) were then excluded, so that four studies were included in the final review. The excluded studies are presented in the characteristics of excluded studies table.

Summary of findings 1: Four studies were included and had a total of 593 participants with AD (Amieva et al., 2008; Devier et al., 2010; Fox et al., 1998; Schmidt et al., 2010). One study was conducted in a community setting (Amieva et al., 2008) and three in secondary care

settings (St Mary's Hospital, London, Fox et al., 1998; memory clinic, Devier et al., 2010; a post-mortem retrospective analysis in the National CJD Surveillance Unit in Germany, Schmidt et al., 2010).

4.11.3 Methodological quality of included studies

The methodological quality in each domain was assessed individually, with two authors contacted for more information on the methodological quality. The QUADAS-2 scores for each domain of the studies included in the review are shown in **Figure 4.3 and 4.4** respectively. This review aimed to identify the sequence and timing of the early symptoms and signs preceding the clinical diagnosis of AD disease therefore patient selection was based on the best available options. With regards to the protocol, there was no discrimination on design as long as it was empirical within the inclusive criteria. The studies included a nested case-control with random sampling (Amieva et al., 2008), longitudinal follow-up of MCI (red-flag) patients (Devier et al., 2010), longitudinal prospective study of individuals at risk of autosomal dominant familial AD (ADFAD)(Fox et al., 1998) and a retrospective case study (post-mortem)(Schmidt et al., 2010). For the case studies (Devier al., 2010; Fox et al., 1998; Schmidt et al., 2010), there was no inappropriate exclusion and sample selection was consecutive, which reduced the risk of selection bias. However, applicability could be a risk as these were case studies with few samples, even though underestimation of diagnostic accuracy could result from the exclusion of red-flags of the target condition or those easier to diagnose (QUADAS-2 tool).
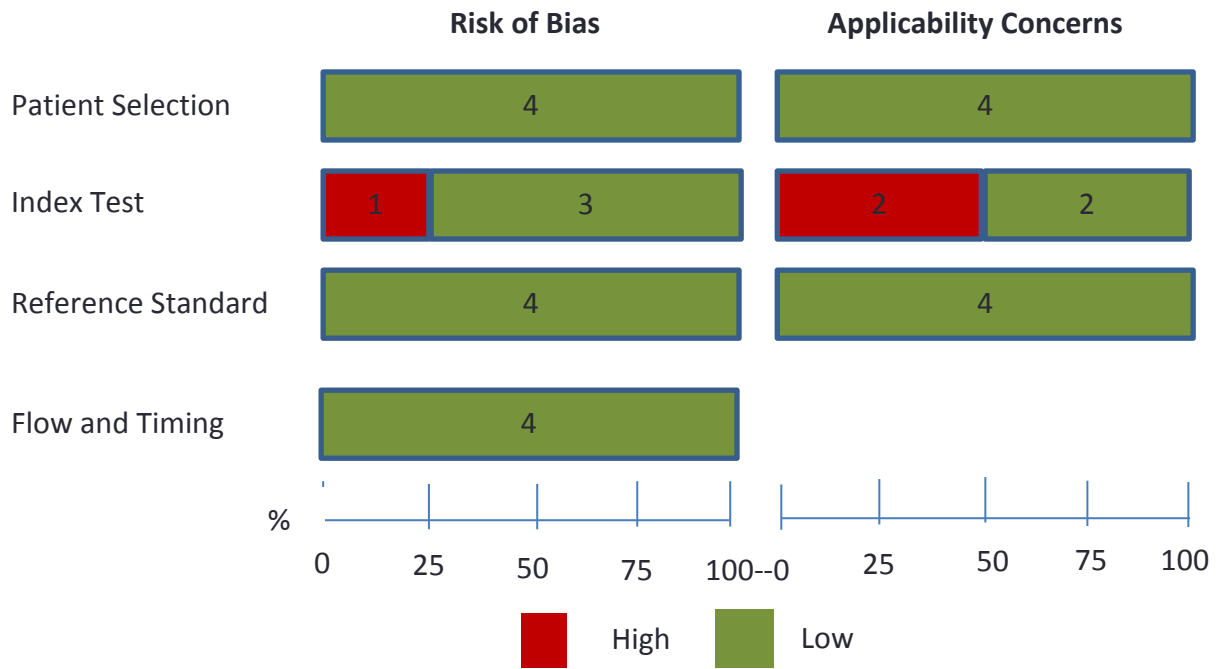
Figure 4.3. Graph representing the risk of bias and applicability concerns. Each domain is represented as a percentage across the included studies, red indicates high risk, green indicates low risk, but no studies had an unclear risk of bias and applicability concerns (QUADAS-2 tool).

Figure 4.4. Summary of the risk of bias and applicability concerns: reviewer's judgement on each domain for the included studies is shown with a high risk of bias and applicability concerns on index test.

The interpretation of the index tests (signs and symptoms) was not influenced by the knowledge of the reference standard in three studies (Amieva et al., 2008; Devier et al., 2010; Fox et al., 1998). The index test domain was judged at a high risk of bias in the study by Schmidt et al. (2010) due to the fact that the index tests (symptoms and signs) was interpreted based on the knowledge of the disease (post-mortem). Regarding applicability, the conduct and interpretation were different from the review question in Fox et al. (1998) and Schmidt et al. (2010); the Fox study identified the mean time from first assessment to the report of the appearance of symptoms, while the Schmidt study determined the symptoms median time span from clinical onset of the disease to the fatal end point.

With regards to the reference standard domain, all studies were undertaken using an internationally recognised standard reference that could correctly classify the condition with masking in all. The Schmidt et al. study (2010) on rapidly progressive AD was undertaken post-mortem, the gold standard of diagnosing AD. However, none of the studies reported how the reference standard was applied, so they were assessed as being at low risk of concerns about applicability.

Concerning the flow and timing domain, there was an appropriate interval between the appearance of symptoms and signs and the reference standard, as the aim of this review was to identify the timing from diagnosis to the report of the first symptoms that justified a diagnosis. However, these symptoms varied across participants. There was no mention of treatment in between the timing and all the participants received the same reference standard except in Schmidt et al. (2010), which was a post-mortem diagnosis, the gold standard of AD diagnosis.

4.12 Findings

The outcomes for this review are stated in **chapter 4.5.** Only one study (Devier et al., 2010) reported on the review objectives, however, three studies with outcomes of interest were included. These outcomes included: timing in presentation of symptoms from MCI to dementia stage (Amieva et al., 2008), timing in presentations from first assessment to symptomatic assessment (Fox et al., 1998) and timing of clinical presentations to case fatality or death (Schmidt et al., 2010). Consequently, this review had five outcomes of interest.

4.12.1 Setting

I) Community setting: Participants 65 years and older (LOAD) were sampled in the PAQUID population study in France, with a mean age at diagnosis of 86.2 (SD, 5.6) years. The symptoms were reported in the following sequence: memory loss, followed by a cognitive decline, depression visual disturbance and verbal memory loss. ADL scores followed two years later. MMSE scores slightly declined (0.05% point/year) from 11 years. Throughout the fourteen year longitudinal study, memory loss was experienced 12 years before clinically defined AD dementia, cognitive decline in semantic memory was observed 12 years before dementia, the MMSE score started to decline in the fifth year of the study, visual disturbance occurred at 5–6 years and ADL score declined 8–9 years into the study before dementia.

II) Memory or secondary care setting: This refers to specialist units. Three studies were carried out in secondary care settings Devier et al. (2010), Fox et al. (1998) and Schmidt et al. (2010) in the US, UK and Germany respectively. However, as mentioned previously, the study by Schmidt et al. (2010) was a post-mortem retrospective case analysis.

4.12.2: Outcomes

OUTCOME 1

Of the 148 participants in this study, 39 (26%) converted to AD and all converters were 55 years at baseline indicating an early onset AD (EOAD) and had a lower MMSE score compared with non-converters. In the early stage, memory decline was reported first in 118 (80%) of the cases, depressed mood in 13 (9%), change in language in 6 (4%), change in performance of higher order/cognitive activities in 4 (3%), disorientation in 3 (2%) personality changes and behavioural changes in 2 (1%), with no group difference in reporting of symptoms. Sequentially, memory decline was the first, followed by performance changes, changes in language, disorientation, personality changes, depressed mood, behavioural changes and psychosis consecutivel

Outcome II

The timing in reporting the first symptom to diagnosis was as follows: memory decline was experienced in 38.5 months before diagnosis, depressed mood in 37.4 months, performance in 36.8 months, personality changes in 32.5 months, behavioural changes in 31.1 months, language difficulties at 29.2 months, disorientation in 29.1 months and psychosis at 14.0 months prior to the diagnosis.

Outcome III

Amieva et al. (2008) reported the timing from the report of the first clinical symptom to dementia and the presentations in timing and sequence. Cognitive decline was the first to appear 12 years before dementia in the measure of semantic memory and conceptual formation. Depressive symptoms appeared concomitantly with the cognitive decline, followed two years later with verbal memory decline. Two years later, converters became more dependent on their activities of ADL, subsequently visual disturbances were recorded and worsened until the stage of dementia.

Outcome IV

This outcome was the timing from first assessment to the symptomatic assessment of individuals at risk of familial AD (FAD). Of the 63 subjects in the study of Fox et al. (1998), 10 probably converted to AD and the mean time (±SD) from first assessment to the appearance of symptoms was 2.6 ± 1.4 years. Episodic memory loss was the most common and observed on average 6 months before symptomatic assessment. The study suggested that cognitive decline is present 2–3 years before symptoms and 4–5 years before individuals fulfil the criteria for probable AD. There was no distinction in presentations with regards to age, gender and handedness and verbal memory was superior to semantic memory in differentiating AD and normal ageing, with the lowest MMSE score of 25 in a subject remaining stable for 2 years consistent with family members with the same score that remained healthy.

Outcome V

The study by Schmidt et al. (2010) on rapidly progressive LOAD indicated that the additional focal symptoms were consistent with CJD, a form of prion disease. The outcome measure was timing from symptoms median life span from clinical onset of the disease to case fatality or death. Thirty-five distinct neurological, psychiatric and autonomic symptoms and signs were reported, with the sequence and timing (in months) in the early stage as follows: disinhibit ion 51.1, spasticity 31.1, dysphagia 21.6, akinetic mutism 20.0, significant weight loss 20.0, apraxia 19.5, apathy 17.0, sleep disorder 16.0, delusions 15.0, myoclonus, hallucinations, seizures 13.0, impaired concentration 4.5, depression 4.0 and disorientation 2.0, with others following after. The study identified additional early focal symptoms consistent with CJD including myoclonus and seizures. A third of RPAD experienced rapid weight loss and sleep disorder indicating their significance in discriminating the disease from other dementias.

4.12.3 Symptoms

A pooled estimate was not possible due to the heterogeneity in the objectives of the studies. Of the 148 participants in the study by Devier et al. (2010), 39 (26%) converted to AD and the hazard of conversion increased with age; in the < 60 year old participants, 6% (2/35) converted, 15% (6/39) converted in the 60–67 year age group, 31% (11/36) converted in the 68-74 year group and 53% (20/38) converted to AD in the ≥75 years age group. MCI was required at baseline in this study, with memory complaints 6 months to 10 years prior to enrollment. The study began long before the MCI criteria definition by Petersen et al. (2004). Memory loss was observed on average at 38.5 months, depressed mood at 37.4 months, performance at 36.8 months, personality at 32.1 months, behaviour deficits at 31.1 months, language deficits at 29.2 months, disorientation at 29.1 months and psychosis at 14.0 months prior to enrollment in the study.

The study by Fox et al. (1998) of autosomal dominant inherited AD pedigree, an EOAD, measured the time between the first initial assessments to first symptoms assessment. For the 10 converters in the study, the mean time (± SD) from initial assessment to first symptomatic assessment was 3.1 ± 1.5 years (range 1–5 years). The most common presentations were symptoms of very mild episodic memory. Two of the ten subjects already had deficits in verbal memory and were the first to be symptomatic, verbal memory deficit was observed 1–5 years during the symptomatic phase indicating early sensitivity than the semantic memory and cognitive changes 2–3 years before the symptomatic phase. Individuals fulfilled the criteria for probable AD 2–3 years later without the data for the timing to diagnosis provided. There was no difference observed between cases and non-converters in terms of age, gender, handedness or MMSE at initial assessment and symptomatic assessment.

Schmidt et al. (2010) conducted a post-mortem examination of rapidly progressive AD, a LOAD. The median disease duration was 26.4 months and the median age at clinical onset was 73 years. The time measurement was from clinical manifestation to disease fatal end point and the symptoms were presented as the median time to symptoms onset in months. The reviewer was unable to obtain a summary of the data from the onset of the symptoms to disease diagnosis.

All the studies scored the recommended points to AD diagnosis (**Table 4.2**) and were carried out with standardised diagnostic criteria. The measurements of the thresholds were undertaken with the recommended measurement with diagnostic accuracy.

Table 4.2: Summary of findings 1. Overview of studies and population characteristics

Populations/participants	Participants met the inclusion criteria in four populations: 1. general population (PAQUID STUDY), regardless of a perceived problem with memory 2. participants that presented in the memory clinic with MCI 3. familiar dominant inherited EOAD 4. rapidly progressive LOAD
Settings	Community study but measurements were undertaken in the secondary care settings; secondary care settings
Index tests	Clinical symptoms and signs of early stage of AD
Reference Standard	The National Institute of Neurological and Communicative Disease and Stroke-AD and Related Disorders Association (NINCDS-ADRDS) diagnostic criteria for AD, with the use of additional laboratory tests, CSF analysis and MRI. Post-mortem brain examination for the rapidly progressive AD
Target condition	All types of AD
Included studies	4 studies (593 participants)
Quality concerns	All the studies were at low risk of bias and applicability of patient selection, reference standard, flow, and timing. However, one study was a high risk of bias in the index test and two studies in applicability
Heterogeneity	Considerable differences due to settings, participants, countries, index test and timing

INCLUDED STUDIES

Author, year	Amieva et al., 2008	Devier et al., 2010	Fox et al., 1998	Schmidt et al., 2010
Population and setting	community setting in France	memory clinic in the US	secondary setting in the UK	secondary setting in Germany
Sample size	350	148	63	32
Age (mean)	86.2	67.1 ± 9.9	44.7 ± 8.1	73 (median)
Education	42% had no diploma, 40.6% with primary diploma, 17.4% with higher education	15.1 ± 4.3 years	not stated	not stated
Index test	early signs and symptoms of AD	early signs and symptoms of AD	early symptoms of FAD	symptoms reporting rapidly progressive AD to fatality stage
Target condition	AD dementia	AD	AD	AD fatality
Reference standard	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA	Post-mortem examination
Comparison group	AD vs normal group	a longitudinal follow-up with no control group	longitudinal prospective case study with no control group	AD vs rapidly progressive dementia

4.13 Discussion

4.13.1 Summary of findings

The search to identify studies on the sequence and timing of AD at the early stage, how far back from diagnosis, symptoms and signs that will justify a diagnosis, yielded four studies with heterogeneous objectives and a total of 593 patients followed for conversion to AD. All studies assessed the timing of the signs and symptoms but with different time points. Only one study (Devier et al., 2010) had outcomes similar to those in this review. However, they only recruited MCI

patients without a control group and reported four domains (memory, personality changes, disorientation, behaviour) and four symptoms. The symptoms in the domains were not specified as there was no data provided. Due to the paucity of data and heterogeneity in all the studies, the researcher could only provide a description without a formal evaluation of the signs and symptoms nor factors such as follow-up time, sequence, threshold and types of AD. Furthermore, methodological differences and small sample sizes, only one study had 350 participants (Amieva et al., 2008), while the others (Devier et al., 2010; Fox et al., 1998; Scmidt et al., 2010) had 148, 63 and 32 participants respectively, made statistical analysis impossible.

Furthermore, there were few studies conducted on the review question. In a disease with high prevalence, high mortality and a high financial burden, all avenues should be explored to reduce the burden rather than channelling the energy in one direction. Research is needed to identify the timing and sequence from diagnosis, the first symptoms to justify a diagnosis, to complement the current diagnostic criteria.

4.13.2 Strengths and weaknesses of the review

One of the strengths of this review was its comprehensive search strategy and detailed protocol (appendices 12 and 16) to identify articles for review. In order not to overlook articles, the disease theatre was used as the main field, followed by the timing theatre, then basic theatres like the type of AD or onset, country of study and combinations before removing duplicates. Multiple databases were searched with a single-concept search without language restriction and reference list, as well as group registers to locate as broad a range of studies as possible. Studies were assessed methodologically with the QUADAS-2 tool and the process was overseen by the supervisors. Authors of original articles were contacted for more information regarding insufficient data. Furthermore, studies were assessed with the standard reference standard for the diagnosis of AD with the NINCDS-ADRDA and post-mortem examination, which is the gold standard. In this review, the NINCDS-ADRDA, the NIA-AA and the DSM tool were considered, as AD could be adequately diagnosed with these diagnostic tools.

Regarding the signs and symptoms of AD, even though there were differences in timing, objectives and participants, the FAD study by Fox et al. (1998) identified a participant with a MMSE score of 25/30, the lowest in the converters group that remained the same for two years, similar to family

members that remained well in this group. Furthermore, there was no difference between the converters and non-converters in terms of age, gender, handedness or MMSE at initial assessment. Memory disturbances remained the predominant predictor of early AD from normal ageing in all studies and verbal memory was more vulnerable than non-verbal in the EOFAD (Fox et al., 1998) as the memory test for words indicated significant differences in scores between 1–5 years before becoming symptomatic against the semantic memory vulnerability.

Depressed symptoms appeared at the same time as cognitive symptoms and each of these was the first symptom to appear in some individuals with LOAD (Amieva et al., 2008; Devier et al., 2010). The rapidly progressive LOAD presented predominantly with myoclonus (75%), disturbed gait (66%) and rigidity; these were also early in presentation, even before apathy. This review is the first to identify the sequence and timing of the presentation of the early stage of AD; how far back from diagnosis the first symptom that will warrant a diagnosis. This is a period recognised as important for timely intervention, as the degenerative processes have not progressed to a severe cognitive and functional decline.

The main limitation of this review is the dearth of data and heterogeneity in methodology and findings. Moreover, a pooled estimate was not possible with the differences in participants; sequence and timing, with fewer symptoms were reported in some studies. Several other potential sources of heterogeneity like the age of onset, gender and education could not be investigated with the paucity of data. Only one study (Amieva et al., 2008) reported the sequence and timing in line with the review question, with fewer symptoms than the review. Another limitation was the exclusion criteria. The researcher excluded studies on individual symptoms and signs, due to the aim of identifying sequence and timing, had these been included, the results may have been different. Studies on all types dementia were also excluded, which may have resulted in the paucity of data. Even though the researcher and the librarian independently identified articles at the title and abstract level without disagreement, the researcher reviewed the full articles independently. The identified full articles were then reviewed by my supervisor with an agreement on the four articles that were included. The review of full articles independently by the researcher might have introduced bias and could be a limitation; nonetheless, the search was undertaken rigorously with the librarian.

This review is useful to GPs, health policy makers and the public, especially if there was enough data to draw definite conclusions on the timing and sequence of the early presentations of AD, as the potential diagnostic value of the signs and symptoms are documented.

4.13.3 Applicability of findings to the review question

Based on the current diagnostic criteria, the absence and presence of two clinical features could aid the diagnosis of AD. There is also a distinction between the early and late presentations of the disease, but without a clear definition of the timing and sequence of these presentations. In addition, the presentation of these signs and symptoms varied according to the age of onset. Memory loss presents early and mostly in the LOAD (Amieva et al., 2008), while neurological and depressive behavioural presentations are an early occurrence in the EOAD (Devier et al., 2010). Another group of LOAD (rapidly progressive AD) presented early with myoclonus, rigidity, depressed mood and addition focal neurological symptoms consistent with CJD; the disease was diagnosed as CJD until the Schmidt et al. (2010) post-mortem study isolated AD as the cause of the presentations. The findings of this review may not be applicable to draw conclusions, as this is a single study with few subjects with bias in objectives. Further studies are required to identify the sequence and timing of the early signs and symptoms preceding the diagnosis to aid the early detection and subsequent diagnosis of AD.

4.14 Conclusions

4.14.1 Implications for practice

There is a proposition of multiple definitions to capture the intermediate stage between ageing and mild cognitive changes, which is in line with the effort in diagnosing the disease early, by recognising the signs and symptoms as reliable predictive markers of the disease (Flicker et al., 1991; Stephan et al., 2010). There is currently insufficient published data on the sequence and timing of the early presentations to aid diagnosis of AD. The role of these presentations to aid diagnosis is not in dispute because they are incorporated in the current diagnostic criteria to indicate the possibility of the AD (Albert et al., 2011; Dubois et al., 2014). In this review, recommendations cannot be made on the sequence and timing of the early signs and symptoms of AD due to insufficient qualitative and quantitative data. The researcher is advocating for more research to identify the sequence and timing for the detection of the disease.

4.14.2 Implications for future research

Due to the paucity of data in this area, further high quality and quantitative research are required to identify the sequence and timing of the early presentations to aid in the early detection of AD. Even though the information included in this research is insufficient, it is essential to note the differences and subsets in AD, as this information will help to confirm the particular type of AD based on the type of sequence and timing of the presentations. A detective model with the type, timing and sequence of the signs and symptoms preceding the clinical diagnosis of AD could be more useful to determine the therapeutic effect of interventions.

4.15 Data

All the data analysed in the tests (symptoms) used in this review are detailed in **Table 4.3.** It has been explained previously that all studies included in the review had different objectives to this review's objectives except for one study. However, the majority of the symptoms and signs presented in this review are from a single study (Schmidt et al., 2010). The data presented from other studies were the cognitive, behavioural, personality and disorientation domains, without indicating the specific signs or symptoms of the domain. Other symptoms and signs of this review including olfactory disturbances, anosognosia, acalculia, alexia, anomia and irritability were not mentioned in all studies.

Table 4.3: Data for all the signs and symptoms in the study

Test	No of studies	No of participants
Memory loss	4	593
Apathy	1	32
Anxiety	1	32
Depression	3	520
Disinhibition	1	32
Hallucination	2	32
Weight loss	1	32
Aberrant motor disturbance	1	32

4.16 Differences between the protocol and review

Initially, it was intended to review studies on the sequence and timing of presentation of the early signs and symptoms of AD to understand how far back from diagnosis the first symptom that will justify a diagnosis was reported. However, due to the paucity of studies of this kind, differences in study objectives, design and timing in the studies included, a comparison and meta-analysis were not possible, so a narrative review was undertaken instead.

CHAPTER FIVE: A retrospective medical record review study.

5.1 Introduction

The previous chapter systematically mapped the existing literature on the sequence and timing in early signs and symptoms of AD and paved the way for the retrospective record review in this chapter. The RMRRS   capture the patterns in the signs and symptoms as these were presented by the patients before the diagnosis of AD. Consequently, this the whole aim of identifying patterns in the presentations at the early stage of the disease.

Substantial scientific discovery has been made about AD including the definition and manifestation of the phases of the disease (NIA-AA). The manifestation of AD includes the wide range of neuropsychiatric symptoms (NPS); the association of these symptoms and AD have widely been reported elsewhere (Jost et al., 1996; Cummings et al., 1998; Lyketsos et al., 2011; Zhao et al., 2016). The type and association with the deficits in the structure of the brain mechanism have also been stated (Jeste et al., 2000; Rosenberg et al., 2015), hence their importance in discriminating AD from other diseases (Schmidt et al., 2010). However, there is no clear pattern of the timing and sequence of these signs and symptoms at the early stage that will support the early diagnosis of AD in the primary care. There is also very little evidence of what signs and symptoms occur at the preclinical stage, which needs clarification (Dubois et al., 2016). Until now, the evidence pertaining to the timing of these presentations is debatable.

AD remains the highest cause of mortality and replaces ischaemic heart diseases as the number one cause of mortality. AD accounts for 11.6% of the registered death in 2015 (National Statistic, 2016) and part of its high associated morbidity can be accounted for because the disease is diagnosed late. Episodic memory loss, anxiety, olfactory disturbances, depressed mood, irritability and hallucination are all signs and symptoms seen in a variety of conditions including AD. The lack of a distinct and AD-specific pattern of signs and symptoms has resulted in late diagnosis and misdiagnosis of the disease leading to its' confusion with other conditions. The current diagnostic criteria (Dubois et al., 2015) emphasise the importance of the early signs and symptoms in aiding the correct diagnosis of AD. Results of several studies (Monto et al., 2000; Gordon et al., 2002; Zhang et al., 2014) have shown how important the pattern of signs and symptoms are in aiding the diagnosis of the disease.

Patterns in signs and symptoms have been used to develop predictive models in other diseases, enabling early detection and diagnosis of diseases (Ambrosy et al., 2013; Nijman et al., 2013; Van et al., 2013). Yet the studies on the early signs and symptoms of AD are limited in content and lack the ability to predict the early stage of AD, the stage at which clinical intervention would work best (Alzheimer's Association, 2013; de Vugh & Verhey, 2013; Barnett et al., 2014). Given the rise in morbidity and mortality of AD and the devastating effect of worsening cognitive impairment, providing GPs with a predictive model for early detection could potentially improve the lives of patients and decrease the burden associated with late diagnosis of the disease.

In this research, the focus is mainly on identifying the signs and symptoms and their patterns before the diagnosis of the disease, which will subsequently inform the suggestion of a predictive model. The model establishes the significant relationship and the strength of impact between the dependent variable (AD) and independent (s) (signs and symptoms). The predictive model assume the logistic regression model based on the fact that the dependent variable (AD) is binary (present/absent), takes the value of Y with a range of 0 to 1 and represented by the following equation:

Odds= p/ (1-p) = probability of event occurrence / probability of event not occurrence

ln (odds) = ln (p/ (1-p))

Logit (p) = ln (p/ (1-p)) = b0+b1X1+b2X2+b3X3....+bkXk.

P is the probability of the presence of AD.

5.2 Purpose

The study was undertaken to identify the patterns in signs and symptoms, as reported by patients ten years preceding the clinical diagnosis of AD.

5.3 Methods

5.3.1 Study participants, recruitment and logistics.

This study is a retrospective pooled analysis of signs and symptoms that appear in patients notes in the ten year period preceding the clinical diagnosis of 109 adults patients (cases n=37 and control n=72). These patients were each diagnosed between the year 2006-2016 with LOAD (FOO.1*) in

three GP surgeries in Milton Keynes and Luton. These surgeries are integrated primary health care that served about 7,000- 30,000 patients. From these clinics, 109 patient records including 37 AD cases were selected and evaluated by the GPs with MMSE (a score of 4-29 was recorded) and subsequently diagnosed with AD in the memory clinics with the NINCDS-ARDRA diagnostic criteria, a validated diagnostic tool. Others included 72 controls, matched according to age (+ or – 1 year) and gender in the same GP surgeries without AD.

To ensure concurrences and reliability, the files with the data collected were first reviewed and assessed by a professional in the GP surgeries before being handed over to the researcher. My supervisors subsequently assessed the data collected. The procedure for the study and anonymity of the records was approved by the NHS-REC, HRA, University of Bedfordshire and each GP surgery (Appendices 2, 3, 4). Even though there are conditions under which missing values can be ignored (Eff & Don, 2009; Stekhoven et al., 2012), which depend entirely on the relationship between the variable of interest missing and the available variable to help explain the missing value; in this study, which was missing completely at random was replaced by multiple imputations. The result of the logistic regression is provided for the original data and imputed data in **Table 5.8**.

Tables 5.1 - 5.3 show the distribution of the cases and controls according to location, gender and ethnicity. The socioeconomic characteristics of the patients could not be established, as this information was not collected at baseline; 70.6% of the sample had no education or employment status, 8.3% were retirees and 21.1% were a mixture of professionals including consultant, pharmacist, engineers, nurses, carers and a dentist. The demography of participants was as follows: Luton had the highest prevalence of 77.1% and Milton Keynes 22.9% (**Table 5.1)**. The ethnicity of participants indicated that majority of individuals were white (69%). However, the Asians, the Caribbean and the Middle Ease ethnic groups, were the least with 9% respectively. The demographic result of could be due to the fact that these towns are mainly Caucasians with a diverse ethnic minority.

Table 5.1 Demographic characteristics of participants**.**

Frequency	Cases	Control	Total	%
Milton Keynes	5	20	25	22.9
Luton	32	52	84	77.1
Total	**37**	**72**	**109**	**100.0**

The frequency table indicates the number of samples in the two areas, with 77% of samples in Luton.

Table 5.2 Gender characteristics of participants**.**

Gender	Cases (%)	Control (%)	Total (%)
Male	12 (32.4)	32 (44.4)	44 (40.4)
Female	25 (67.6)	40 (55.6)	65 (59.6)
Total	**37 (100)**	**72 (100)**	**109 (100)**

The majority (65) of the samples were females representing 59.6% of the total sample.

5.3.2 Variables

5.3.2a Signs and symptoms

I initially set out to identify patterns in fourteen signs and symptoms previously identified as early presentations of the disease as described in **chapter 2** (section 2.6.2) and to identify novel signs and symptoms not yet identified in the literature. These signs and symptoms were presented by the patients and confirmed by the GP during their consultations. A computation was made on the timing and sequence of the presentations, i.e. from the time of reporting to the official diagnosis of the disease. The analysis was undertaken on the frequency of four or more individual signs and symptoms.

Table 5.3 Ethnicity of participants

Ethnicity	Cases	Control	Total	%
White	25	44	69	63.3
Mixed	11	14	25	22.9
African	1	2	3	2.8
Caribbean	0	1	1	.9
Asian	0	1	1	.9
Middle East	0	1	1	.9
Undeclared	0	9	9	8.3
Total	**37**	**72**	**109**	**100.0**

The ethnicity table arranges the samples according to groups, with 63.3% among the white ethnic group, 22.9% mixed, 2.8% Africans, 9% Caribbean, Asian and the Middle East respectively. However, 8.3% of the controls did not declare their ethnicity.

5.3.2b Confounding factors

The signs and symptoms might be influenced by other factors which might be associated with AD. The factors identified as confounders linked to AD include comorbidities, age and socio-economic factors such as poor diet, lack of education and physical activities (Katz et al., 1997; de Groot et al., 2003). These factors were collected and comorbidities including hypertension, diabetes and other conditions were identified with the sample. The comorbidities were diagnosed separately from AD and met the standard measurement of ICED.

5.3.2c Ethical consideration

Ethics protocol was observed following the approval from NHS-REC, HRA, GP surgeries and the University (UREC), which stressed and ensured that non-identifiable data was collected and processed. The data protection Act of 1998 was observed, which ensured that the data was used for the academic purpose and destroyed immediately after the research was completed. Data was stored without passing it to anyone else, apart from the research team.

5.3.2d Data management

I undertook the task of managing the data by collecting each variable into the data abstraction sheet and made sure the timing and sequence of presentation of the signs and symptoms were collected. I also specified the differences between classes of some symptoms such as episodic memory loss. These were undertaken to prepare the data for analysis. The data was collected with a validated case report form, a specialised document in clinical research and included the covariates used (gender, age at diagnosis, ethnicity, type of AD and education), comorbidity and medical history.

5.3.3 Data analysis

The main outcome measure was the patterns regarding the sequence and timing of signs and symptoms associated with AD, measured with the OR and associated 95% confidence intervals (CI). The researcher initially estimated the prevalence and distribution of these signs and symptoms in both groups (cases: patients with AD and controls: age and gender-matched individuals without AD) after the data was cleaned and variables checked for accuracy. The timing of presentations, up to ten years before diagnosis was established and followed by the sequence and timing of presentations in relation to the ultimate diagnosis of AD. This was followed by calculating the mean ($\bar{x}$ "x-bar") in timing in years between the reporting of the signs and symptoms and a diagnosis of AD, which is the average of set value in years of the presentations, calculated by adding the sum value in time and dividing by the number of the values or subjects. The data analysis was undertaken with SPSS and MedCalc software. The binary logistic regression was the standard of measurement, as it was the suitable measurement for my data with a dependent variable with two categories. This was against Poisson regression for counting and multinomial regression that could be used for dependent variables with more than two categories, to determine the OR in respect to the cases and controls. The OR and 95% CI determined the association of the signs and symptoms to AD, by coding 1 in association with cases, and 0 for the control respectably. The analysis was undertaken for gender, ethnicity and locality for all the samples, while reporting the OR and p values. However, the bivariate models analysis for the cases could not be established using the logistic regression, as the Hosmer and Lemeshow test indicated that the model was not a good fit (.032) for the small sample size in cases. The ideal score will be .05 and above in order to follow a chi square distribution with $g\text{-}2$ degrees of freedom (Hosmer Jr et al., 2013); a small p-value indicates a poor fit. The exact logistic regression would have been the perfect model; a valid analytical technique for a small, sparse, skewed or heavily tied data, which was unavailable for this analysis.

5.4 Results

5.4.1 Descriptive analysis

The overall prevalence of these symptoms and signs were higher in cases than control (**Table 5.4**), however, individually, there was heterogeneity in their prevalence. There was a higher prevalence of these symptoms among white women especially those between the ages of 70-75 and 80-85 years (16.21% respectively). Episodic memory was the symptom with the highest prevalence in the entire sample (26.6%) and more frequent in the cases (75.6%) than controls (1.38%). This was followed by depression with 13.76% in the entire sample. Symptoms that were identified in cases only included abdominal pain (8.1%), agoraphobia (2.7%), dehydration (2.7%), excessive sweating (2.7%), hallucinations (8.1%), poor appetite (2.7%) and tiredness (5.4%). The Chi-square test also written as $\chi 2$ test, which differentiates between the expected frequencies and observed frequencies in one or more independent variables, was inappropriate for my study as the frequencies in some signs and symptoms were less than 1. More than 20% of the frequencies in these signs and symptoms are less than 5, hence the Fisher's Exact test (Pr <= P) was undertaken. The test was insignificant for all variables, i.e., the null hypothesis that there is no relationship between these variables and AD could be accepted, except episodic memory with a p-value of 0.00% (**Table 5.4)**

Table 5.4 Prevalence (%) of the signs and symptoms in cases and control

Signs and symptoms	Total N	%	Cases N	%	Controls N	%	Pr <=P
Abdominal pains	3	2.75	3	8.10	0	0	
Agoraphobia	1	0.91	1	2.70	0	0	
Anxiety	5	4.58	2	5.40	3	4.16	.24
Auditory disturbances	14	12.84	8	21.6	6	8.33	.21
Backache	7	6.42	4	10.8	3	4.16	.17
Constipation	4	3.66	2	5.40	2	2.77	.41
Dehydration	1	0.91	1	2.70	0	0	
Depressed mood	15	13.7	7	18.9	8	11.1	.16
Dizziness	3	2.75	1	2.70	2	2.77	.71
Drowsiness	2	1.83	1	2.70	1	1.38	.71
Episodic memory loss	29	26.6	28	75.6	1	1.38	.00
Excessive sweating	1	0.91	1	2.70	0	0	
Flatulence	2	1.83	1	2.70	1	1.38	.71
Hallucinations	3	2.75	3	8.10	0	0	
Headache	5	4.58	3	8.10	2	2.77	.21
Indigestion	4	3.66	2	5.40	2	2.77	.21
Irritability	2	1.83	1	2.70	1	1.38	.56
Leg cramps	1	0.91	1	2.70	0	0	
Olfactory disturbances	1	0.91	0	0	1	1.38	
Poor appetite	1	0.91	1	2.70	0	0	
Tiredness	2	1.83	2	5.40	0	0	
Visual disturbances	1	0.91	1	2.70	0	0	
Weight loss	4	3.66	2	5.40	2	2.77	.11

N = number; χ2= Fisher's Exact test.

Among the previously identified signs and symptoms of AD, only anxiety, depression, episodic memory loss, hallucinations, irritability and weight loss were identified in the study, out of which irritability was only identified in one sample of the control group. Other signs and symptoms identified with considerable frequency included backache, headache, constipation and indigestion.

However, agoraphobia, dehydration, dizziness, drowsiness, excessive sweating, flatulence, poor appetite and leg cramp were identified in single measures respectively. Out of the symptoms identified in the cases, episodic memory was presented as the first symptom in 16 (43.2%) of the 37 cases, auditory disorders in eight (21.6%), depression in five (13.5%) and headache in one (2.7%).

5.5 Individual symptoms and signs in cases

The mean in the timing of the signs and symptoms as reported in cases is shown in **Table 5.5**. The table shows the means in years of the symptoms. Headache had the highest mean in cases (mean=26.8%) and was presented 68 years before diagnosis, followed by depression presented 60 years before diagnosis (16.4%) and was not associated with medication or comorbidity. However, the symptom was presented in the control group 56 years before the pseudo-diagnosis with a high prevalence (53.3%) in this group than the cases (46.3%).

Auditory disturbance that has not been fully identified with AD was the third symptom sequentially presented 30 years (mean=14.5%) before the diagnosis of AD with a prevalence of 21.6% in this group. Backache followed with a means of 9.2% and a prevalence of 10.5%.

Table 5.5 Means of signs and symptoms in years before diagnosis in cases and controls

Symptom	Mean in years (SD) cases	Mean in years (SD) controls	p-value
Anxiety	1 (0)	17.3 (15.5)	0.70
Auditory disturbance	14.5 (8.94)	4.8 (3.1)	0.05
Backache	9.25 (10.7)	6 (2.6)	0.19
Depression	16.4 (21.1)	12.5 (17.8)	0.20
Episodic memory	3.48 (3.42)	11 (4.3)	0.0001
Headache	26.8 (36.1)	5.5 (4.9)	0.20
Weight loss	0.5 (0.14)	3 (2.82)	0.0001

 SD: standard deviation.

When analysing for the correlation **(r)** of the signs and symptoms, represented in a correlation matrix; the univariate analysis **(Table 5.6)** indicates a positive correlation at < 1% significant level between episodic memory and AD (0.475**). For auditory disturbance, there was a positive correlation with AD (0.587**) and episodic memory (p=0.586*); which means that individuals with auditory disturbances are likely to have episodic memory loss and AD. There was also a positive correlation but a weak one between the female gender and AD (.116**) at the two-tailed level.

Table 5.6. Correlations Matrix of variants.

		Group	Gender	Epi. Mem. Loss	Audi. Dist.
GROUP	Pearson Correlation	1	.116**	.475**	.587**
	Sig. (2-tailed)		.003	.000	.000
	N	109	109	109	109
GENDER	Pearson Correlation	.116**	1	.017	-.007
	Sig. (2-tailed)	.003		.658	.949
	N	109	109	109	109
EPISODIC_MEMORY_LOSS_YEARS	Pearson Correlation	.475**	.017	1	.586**
	Sig. (2-tailed)	.000	.658		.000
	N	109	109	109	109
AUDITORY_DISTURBANCE	Pearson Correlation	.587**	-.007	.586**	1
	Sig. (2-tailed)	.000	.949	.000	
	N	109	109	109	109

**. Correlation is significant at the 0.01 level (2-tailed).

Episodic memory, which is the chief symptom linked with AD especially the late onset, was presented six years before diagnosis with a means of 3.4% and had the highest prevalence in this group. Hallucination was next and presented three years (mean = 1.8%) before the diagnosis of AD. Constipation and tiredness were presented five years respectively before diagnosis. However, tiredness was not associated with the control group. 46.4% of the prevalence of episodic memory was among the white females and 17.8% for white males **(Table 5.7)**. The table further indicates that individuals with auditory disturbances, a symptom that has not been reported in AD, have threefold (3.03) increased odds for associating with AD, with a p-value of ≤ 0.050. Other signs and symptoms with increased odds but not significant are abdominal pain and hallucination, with p values of ≤ 0.07 respectively. The table also shows that individuals with backache had 88%, headache 58% and depression 19% increased odds of association with AD, however, with p values > than 0.1.

Table 5.7 Odds ratio of symptoms reported by cases and control

Variable	Odds Ratio	95% CI
Anxiety	1.31	0.20 - 8.20
Auditory Disturbance	3.03	0.96 - 9.53
Backache	2.70	0.58 - 1.31
Depression	1.01	0.96 – 1.07
Episodic memory	2.77	1.52 – 5.02
Headache	3.08	0.49 - 14.4
Weight Loss	1.31	0.20 - 8.20
Ethnicity	1.18	0.56 - 4.20
Gender	1.15	0.44 - 3.01

The 95% CI indicates the lower and upper limit.

Ethnicity and gender have an influence on the outcome of cases (**Table 5.7**). The Wald statistics and the all-important OR Exp (B), shows that the variables ethnicity and gender were not very significant

and positive in the overall effect. However, when controlling for gender, the OR indicates that the female gender has 61.8% increased odds more likely to be associated with AD compared with men (full report in **Appendix XVII**). Similarly, the OR shows that the mixed ethnic group had more than two-fold (0R = 2.1) increased odds of developing AD, followed by Caucasians with a 93%, increased odds. Even though the Wald statistic was significant for Luton locality, the OR was not significant and could be excused due to the limited samples. However, for the other ethnic groups, the result was insignificant.

The majority of the signs and symptoms were diagnosed at age 70-80 in both the cases and controls, followed by those within 80-90 years. For the original data, **Table 5.8** indicates that individuals with episodic memory loss had more than two fold (OR = 2.77) increased odds for developing the disease as indicated by the high prevalence in cases than controls (28 to 1). The table indicates the significance of gender for episodic memory loss and auditory disturbances; however, the CI was less than 1 for gender and auditory disturbance**. When considering the sequence of the appearance of the signs and symptoms in years prior to diagnosis of AD, it was found that headache was the first symptom to be reported 68 years before diagnosis. This was reported as early as 14 years into the life of the patient. In comparison to the control group, however, the symptom was presented 11 years before the pseudo (non-AD conditions) diagnosis. The symptom was followed by depression at 60 years, auditory disturbance 30 years, backache 25 years, hallucination 15 years and episodic memory six years before diagnosis (**Table 5.9**).

The result of the imputed data was considerably the same as the original data for episodic memory; while the p-value remained p<0.001, the CI was slightly different for gender and ethnicity (**Table 5.7**). When adjusted for gender and ethnicity, there was more than two fold increase in the odds for episodic memory. For auditory disturbance, however, the result was similar when adjusted for gender and almost the same for the crude model and the model adjusted for gender and ethnicity. For depression, the results were insignificant. The slight difference in the odds ratio results of episodic memory loss in the current and imputed data could be due to the fact that the symptom was presented in only one individual in the control group; the results are still significant. Generally, there were few differences across the imputed results.

Table 5.8: Adjusted odds ratio for gender and ethnicity.

Original data	Model 1	Model 2	Model 3
Variable	OR (95% CI)	OR (95% CI)	OR (95% CI)
Audi. disturbance	3.03*** (0.96-9.53)	2.12*** (0.90-5.03)	1.71*** (0.76-3.86)
Depression	1.01*** (0.96-1.07)	1.02*** (0.96-1.09)	1.07*** (0.95-1.07)
Episodic memory	2.77*** (1.52-5.02)	2.71 ***(1.48-4.96)	2.54*** (1.41-4.57)
Imputed data			
Audi. disturbance	1.68***(1.24-2.28)	2.12***(0.90-5.03)	2.11*** (0.90-4.98)
Depression	1.01***(0.96-1.07)	1.02***(0.96-1.09)	1.01*** (0.9.5-1.07)
Episodic memory	2.77***(1.52-5.02)	2.71***(2.07-3.55)	2.70***(1.47-4.94)

Model 1: crude: model 2 adjusted for gender; and model 3 adjusted for gender and ethnicity*. The crude model considers how individual symptom/sign is associated with AD affects the outcome measure while ignoring other variables; model 2 adjusts to incorporate gender, while model 3 incorporates ethnicity as a covariate. **Significant difference at $p<0.01$.*Significant difference at $p<0.05$

Table 5.9 Timing of signs and symptoms in patient notes prior to a diagnosis of AD

Symptom/sign	Cases Mean in Years (SD)	Controls Mean in Years (SD)	Mean Difference	95% Confidence Interval (CI)
Headache	26.8 (37.2)	5.5 (4.94)	-21.3	-32.5 to -10.0
Depression	16.4 (21.1)	12.5 (17.8)	-3.90	-25.5 to 17.7
Auditory disturbance	14.5 (8.94)	4.83 (3.18)	-9.67	-18.8 to -1.28
Backache	9.25 (10.7)	6.00 (2.64)	-3.25	-19.9 to 13.4
Episodic memory loss	6 (3.48)	0	0	0

The table shows that headache was reported with a mean age of 26.8 years before diagnosis. Only one person reported the symptom of episodic memory in the control group.

When I considered episodic memory and gender, I found that 62% of those cases in which episodic memory loss was recorded was in the female gender (**Table 5.10)**, with an overall prevalence of 26.6 in the whole sample **(Table 5.4).** Only about 3.4% of the prevalence of the symptom was recorded in the control group. The 34 males representing 31.1% of the total sample and 46 females (42.2%) were symptom-free.

The distribution of auditory disturbances in the sample was found to be 85.7% in the female, with 75% in the cases, indicating a female predilection for developing the disease (**Table 5.11;** see **Table 5.4** for the prevalence).

Table 5.10 Distribution in years of the reporting of episodic memory loss and its association with gender.

Sample	GENDER	Prevalence---Years before the diagnosis of episodic memory loss				Total
		N (%)	0.5	5-10	10 & Above	
Cases	Male	3 (2.7)	7 (6.4)	3 (2.7)	0 (0)	13 (11.9)
	Female	6 (5.5)	13 (11.9)	5 (4.6)	0 (0)	24 (22.0)
Control	Male	30 (27.5)	0 (0)	0 (0)	1 (0.9)	31 (28.4)
	Female	41 (37.6)	0 (0)	0 (0)	0 (0)	41 (37.6)
	Total	80 (73.3)	20 (18.3)	8 (7.3)	1 (0.9)	109 (100)

N: number

Table 5.11 Distribution in years of the reporting of auditory disturbance and its association with gender

Sample	GENDER	Prevalence---Years before the diagnosis of auditory disturbances				Total
		N (%)	0.5	5-10	10 & Above	
Cases	Male	11 (10.1)	0 (0)	0 (0)	1 (0.9)	12 (11)
	Female	18 (16.5)	1 (0.9)	3 (2.7)	3 (2.7)	25 (23)
Control	Male	31 (28.4)	0 (0)	1 (0.9)	0 (0)	32 (29)
	Female	35 (32.1)	3 (2.7)	2 (1.8)	0 (0)	40 (37)
	Total	95 (87)	4 (3.7)	6 (5.6)	4 (3.7)	109 (100)

Of the 29 samples with the symptom of episodic memory loss, 75.8% were Caucasians and 75% in cases (**Table 5.12**). However, this symptom was not recorded in the Asians or the Caribbean, with only 3.4% being noted in the African community. This indicates that the Caucasian ethnic group with the symptom were three times more likely to be diagnosed with AD than any other ethnic groups.

Table 5.12 Episodic memory and ethnicity in cases and controls

Ethnicity		Years (%)			
Cases	N (%)	0-5	5-10	10 & Above	Total
White	4 (3.7)	15 (13.7)	6 (5.5)	-	25 (22.9)
Mixed	5 (4.5)	5 (4.5)	-	1 (0.9)	11 (10.1)
African	-	1 (0.9)	-	-	1 (0.9)
Control= White	43 (39.4)	-	-	1 (0.9)	44 (40.3)
Mixed	14 (12.8)	-	-	-	14 (12.8)
African	2 (1.8)	-	-	-	2 (1.8)
Caribbean	1 (0.9)	-	-	-	1 (0.9)
Asian	1 (0.9)	-	-	-	1 (0.9)
Middle East	1 (0.9	-	-	-	1 (0.9)
Undeclared	9 (8.3)	-	-	-	9 (8.3)
Total	80 (73)	21 (19.2)	6 (5.5)	2 (1.8)	109 (100)

Data is the number of sample that presented with episodic memory years before diagnosis (percentage of population).

Out of the 14 samples with the auditory disturbances, 57.1% were Caucasians, followed by a 35.7% for the mixed race (**Table 5.13**). However, the symptom was not recorded in the African, Asian or the Caribbean ethnic group. This shows that the white female ethnic group with auditory disturbance were twice likely to be diagnosed with AD than any other ethnic group. While the Africans, Asians and Caribbean were less likely to be diagnosed with AD despite having the symptom.

The Hosmer and Lemeshow Test suggested that the binary logistic regression was a good fit to the data with a p-value of 0.684 (>0.05), and could correctly classify the outcome of the cases in 68.6% of the time, indicating an improvement over the null model (**Appendix XVII**). The result indicates that the logistic regression is reliable and valid for this data, with a higher rate of correctly classifying the outcome.

Table 5.13 Auditory symptom and ethnicity of cases and control.

Ethnicity	Years (%)				
Cases	No	0-5	5-10	10 & above	Total
White	19(17.4)	-	3 (2.7)	3 (2.7)	25 (22.9)
Mixed	9 (8.3)	-	1 (0.9)	1 (0.9)	11 (10.0)
African	1 (0.9)	-	-	-	1 (0.9)
Control: White	41(37.6)	1 (0.9)	2 (1.8)	-	44 (40.4)
Mixed	11 (10.0)	1 (0.9)	2 (1.8)	-	14 (12.8)
African	2 (1.8)	-	-	-	2 (1.8)
Caribbean	1 (0.9)	-	-	-	1 (0.9)
Asian	1 (0.9)	-	-	-	1 (0.9)
Middle East	1 (0.9)	-	-	-	1 (0.9)
Undeclared	9 (8.3)	-	-	-	9 (8.3)
Total	95 (87.1)	2 (1.8)	8 (7.3)	4 (3.7)	109 (100)

Data is the number of sample that presented with episodic memory years before diagnosis (percentage of population).

5.6 Comorbidities

Concomitants health conditions have been associated with AD, which can act as confounders or effect modifiers. In this study, multiple comorbid conditions were isolated with AD including hypertension with the highest prevalence and tremor with the least. The number of comorbidities per individual was between zero and nine (**Table 5.14**). 14 cases had one comorbid condition each, while the controls had 0-4, with seven controls having one each.

Table 5.14 Comorbidities identified in cases and controls

N of individuals Cases	N of comorbidities Cases	N of individuals Control	N of comorbidities Control
1	9	0	9
4	4	3	4
7	3	8	3
6	2	7	2
14	1	7	1
5	0	47	0
Total=37	Mean= 3.8 (3.1 SD)	Total=72	Mean=2.5 (1.2 SD)

The most frequently reported comorbid condition was hypertension, reported by 20 cases (40.5%), chronic kidney disease followed with 10.8%, high cholesterolemia and ischaemic heart attack with 8.1% respectively (**Table 5.15**). Asthma, depression, biventricular heart disease and sciatica were reported by 5.4% of cases respectively, while others including osteoarthritis, gastritis, adnexia, tinnitus, paresthesia, gallstones, hyperthermia, ocular hypertension, cataract, cardiovascular accident, asthma, bilateral fine drusen, cerebral atrophy, diverticular disease and hypothyroidism were reported in one individual respectively. The frequently reported comorbidities had a mean of 3.8 (3.1 SD).

Table 5.15 Numbers of comorbidities per individuals in cases and control

Comorbidity	Number of cases (%)	Number of control (%)
Hypertension/Essential	15/5 (40.5)	9 (12.5)
Chronic kidney disease	4 (10.8)	1 (1.38)
High cholesterolemia	3 (8.1)	0
Ischaemic heart disease/ attack (TIA)	3 (8.1)	2 (2.8)
Asthma	2 (5.4)	3 (4.2)
Depression	2 "	1 (1.38)
Osteoarthritis	2 "	6 (8.3)
Biventricular heart failure	2 "	1 (1.38)
Sciatica	2 "	0
Adnexa	1 (2.7)	0
Atrial fibrillation	1 "	1 (1.38)
Bilateral fine drusen	1 "	0
Cardiovascular disease	1 "	2 (2.8)
Cataract	1 "	1 (1.38)
Cerebral atrophy	1 "	0
Diabetes mellitus	1 "	7 (9.7)
Diverticular disease	1 "	2 (2.8)
Gallstones	1 "	0
Gastritis	1 "	0
Hyperthermia	1 "	0
Hypothyroidism	1 "	3 (4.2)
Macular degeneration	1 "	0
Ocular hypertension	1 "	0
Paraesthesia	1 "	1 (1.38)
Tinnitus	1 "	1 "
Tremor	1 "	0
Chronic obstructive pulmonary disease (COPD)	0	8 (11.1)
Otitis external	0	2 (2.8)
Lacunar infarction	0	1 (1.38)
Total number of Comorbidities reported	26	29

5.7 Discussion

This study explored the possibility of identifying patterns in signs and symptoms preceding the clinical diagnosis of AD. The researcher discovered that individuals with AD have higher odds of auditory disturbances. This finding to my knowledge is novel and cannot be compared with other studies, as this is the first study that has reported auditory disturbance apart from auditory hallucination, which is considered to be frequent psychotic symptom of AD (El Haj et al., 2017). There could be biological plausibility that could be investigated with a large sample, as the result is a borderline significance due to small sample size.

The three most distant presentations included headache, which was presented more than two decades before diagnosis, followed by depression and auditory disturbances before episodic memory loss. Weight loss, however, presented less than a year before diagnosis, closely tailed by anxiety and hallucinations. Opining and supporting literature stating that these presentations are late mechanisms and indicate the progression of the disease (Soto et al., 2012; Besser et al., 2014; El Haj et al., 2017). The result is contrary to literature stating that anxiety is an early presentation (Casselli et al., 2013; Li et al., 2014) and could be due to the small sample size. A bigger sample with these signs and symptoms in combination could help predict accurately the onset of AD.

The symptoms and signs associated with AD were more striking in the white population than other ethnic group, supporting findings from previous study that AD is highly prevalence in the Caucasians than other ethnic groups (Farrer et al., 1997) and contrary to more recent research indicating a higher prevalence in the African Americans and the Asian groups (Whitmer et al., 2014). However, the prevalence in this research could be due to the high population of whites in the areas and chance, as it might be difficult for an ethnic minority to go for check-up regarding memory issues than their white counterparts, especially as the interviews indicate issues of language barriers and translation issues, which could confound the diagnosis.

Furthermore, the study indicates that the female gender had a higher prevalence of the signs and symptoms in AD than their male counterpart with increased odds of having episodic memory and auditory disturbance respectively. The female gender has been associated with the risk factor gene for AD A POE-E4 allele (Payami et al., 1996) with two of the most prominent non-modifiable risk

factors for AD identified as the female gender. However, episodic memory has only been associated with the female gender in measures and type, not the prevalence, even though the symptom correlates with high levels of amyloid deposition (Mortamais et al., 2016).

Excessive sweating, dehydration, poor appetite, abdominal pains, weight loss and constipation were all identified with AD. However, even though weight loss has been identified as an early sign and significant in this research (p-value <0.0001), the gastrointestinal symptoms have been associated with adverse effects of AD medications (Matsunaga et al., 2015; Wischik et al., 2015; Zhao et al., 2016) only, especially the clinical effects of memantine monotherapy. Dehydration and excessive sweating could be risk factors rather than signs; this is because AD is associated with dietary deficiency including water even at the mild to moderate stage of the disease (Buffa et al., 2010).

Depression was also associated with AD, which is consistent with Rosenberg et al. (2015) study, indicating the symptom as an AD mechanism. However, depression could be a reverse causality, as individuals reported the symptom as early as 60 years before diagnosis in this study, which could indicate the presence of depression with AD as a resulting factor.

Irritability was not identified with the cases in this study, which also supports other findings (Zhao et al., 2016) indicating that it is a less prevalence mechanism in AD. This is because the sign is related to functional connectivity alterations in the salience network (Balthazar et al., 2014); without the connectivity alterations, the sign could be a rare mechanism in AD.

Among the comorbidities associated with AD in this study, hypertension had the highest prevalence and supports other studies indicating that the symptom is one of the predominant comorbid condition associated with AD (Poblador-Plou et al., 2014). In a Spanish study of 72,815 patients over 64, hypertension had the highest prevalence of a comorbid condition with 38.6 for men and 44.9 for women (Poblador-plou et al., 2014). However, literature (Kruyer et al., 2015) suggests that it could be a modifiable risk factor rather than a comorbid factor, as hypertension accelerated cognitive deficits, microvascular deposits of β amyloid, vascular inflammation, and blood-brain barrier leakage and pericycle loss in mice and humans (Snyder et al., 2015).

High cholesterolemia was also identified as comorbidity. Even though the Framingham study (Tan et al., 2003) showed that the condition is not a risk factor for developing AD, others have identified it as a causative factor (Papolla et al., 2003). However, this is still debatable (Wood et al., 2014) due to

the blood-brain barrier mechanism that restricts the entry of blood-derived products into the brain including cholesterol.

The limitation of this study includes a sample size that will not allow the generalisation of the signs and symptoms preceding the clinical diagnosis of AD, even though sufficient data was obtained for a statistical analysis. The small sample size is not sufficiently representative of adults followed-up in primary care nor the overall adult population of Luton and Milton Keynes. Conversely, the controls were specifically selected and comorbidities and symptoms presented are similar to what is known of this population.

5.8 Conclusion

The research demonstrates that auditory disturbance, which was more striking in the Caucasian female gender, could predict the diagnosis of AD. While further research is advocated in a large scale, as the sample in this research is insufficient to initiate subgroup analysis, the result supports future plans to improve the early diagnosis of AD. The symptom could support the specific prediction of AD. There was no recall bias, as data collected was written at the point of collection.

Other symptoms identified with cases including headache and backache and depression, had higher odds of identifying individuals with AD, but with insignificant p-values in discriminating these individuals. While depression has previously been associated with AD, headache and backache were associated only as side effects of medications and a baseline that may vary with comorbidities and geographical location. Similar studies in large scale could indicate if the symptoms are associated with the disease. The success of the study could not be assessed as confusion remains around whether a symptom arises from another condition and can still present in the same manner, as there was no data to indicate previous patterns of the signs and symptoms preceding the clinical diagnosis of AD.

The study acknowledges that GPs have the potential to improve the diagnosis. Thus, such potential was considered in the context of available evidence through a semi-structured interview carried out in the next chapter; even though the GPs are not determinative of the cause of the delayed diagnosis, they will help guide the outcome of the studies.

CHAPTER SIX: General practitioners' perspectives of the early signs and symptoms of AD: A Qualitative interview

6.1 Introduction

Chapter 5 described the quantitative phase of my research. It is an innovative work as it identifies a symptom that could potentially help discriminate individuals with AD early. However, the low prevalence of AD led to a small sample population in these areas and will thus not allow for generalisation.

This chapter presents the findings from the qualitative interviews of GPs in Milton Keynes and Luton CCGs; to achieve objective 3 of this thesis, which is to explore the perspectives of the GPs regarding the early signs and symptoms of AD, issues of late diagnosis and recommendation to circumvent factors that delay an early diagnosis of the disease. These findings are part of a mixed method research with the data obtained from the systematic scoping review and RMRRS described in **chapters 4 & 5 respectively**, for the identification of patterns in signs and symptoms preceding the clinical diagnosis of AD.

Participants in this qualitative phase of the study included GPs (n=4) from Milton Keynes (three males and one female) and Luton (three females) general practices. Eligibility was based on their professional duties as GPs, including (predominantly) experience in the diagnosis and management of AD patients in primary care within the last ten years. There was no distinction between the ages of male or female participants, as the experience of managing AD individuals was the main inclusion criterion (**Figures 6.1 & 6.2**). The sampling technique was purposeful sampling, which was undertaken in light of the GPs experience and consent to be involved with the research. An extensive process of recruitment was followed painstakingly, which included emails to all the GPs and practice managers, personal recruitment, i.e. personally going to the GP practices to speak with individual GPs or their managers and recruitment through colleagues or medical pair recruitment that yielded few responses. The emails to the 27 GP surgeries yielded only one response, personal recruitment yielded four responses, while the medical pair yielded an additional two responses; this is further explained below. Had there been a substantial number of positive responses, I would have used the quota sampling to include some subgroups like gender and locality.

Favourable research ethics opinion was received from the Office of the Research Ethics Committee, North of Scotland and the Institute for Health Research Ethics Committee in the University of Bedfordshire. The protocol for the study, study materials and interview guide were all approved by

both the aforementioned ethics committees (Appendix I, II, III, IV and **Table 6.1).** Informed consent was sought from all participants before commencing the interviews.

The interviews, which were performed face-to-face, were semi-structured and conducted using the interview guide (Appendix VI) as an overarching framework that explored the commonalities of experience to allow the flexible exploration of the GPs perspectives on AD. The interview guide and questions were developed after reviewing the relevant literature (HSCIS, 2014; NHS, 2014; Jones et al., 2015) and after consulting with my academic supervisors. The questions were based on the need to identify patterns in the signs and symptoms preceding the clinical diagnosis of AD, issues surrounding the late diagnosis and recommendations to early detection of the disease; this was undertaken to allow the flexible exploration of GPs perspectives regarding the early diagnosis of the disease. The interview guide was piloted with three GPs prior to data collection to assess its practicability, comprehensiveness and acceptability. The questionnaires were returned with positive comments without the request for alteration (**Appendix XX)** and identified the same themes that were identified in the general interviews; hence, I proceeded for the general interviews.

The questionnaire covered the early signs and symptoms (Q3), issues with the late diagnosis of AD (Q4), benefits of early intervention (Q5) and recommendations against factors that delay early detection of the disease **(Table 6.1).** Interviews were undertaken in the GPs workplace and began with a brief introduction of the study, a description of its aim and objectives, ethics approval and the process of the interview (Appendix VIII). Participants signed the informed consent form (Appendix V) and recruitment continued until a point of thematic saturation was reached, which could be achieved with as little as six interviews (Guest et al., 2006), depending on the individual study topic and the depth of collected data. I initially planned to interview 16 GPS. I sent emails to 24 general practices introducing the research and requesting for their participation, visited 18 practices once (two practices kept making promises and were visited four times, five practices three times) and made frequent calls to the GP practices in MK. My supervisors and I then visited the CCG contact to solicit her support for the recruitment as a gatekeeper. The CCG contact sent emails to all the GPs in MK which did not result in further recruitment. However, after a series of personal visits, the researcher was able to recruit five GPs through the consent of the surgeries managers' and only one could not be interviewed as his manager declined his participation. For Luton CCG, the research was advertised in the GP bulletin. However, none of these yielded any engagement, except for the medical pair recruitment (recruitment through colleagues) that yielded three more interviews.
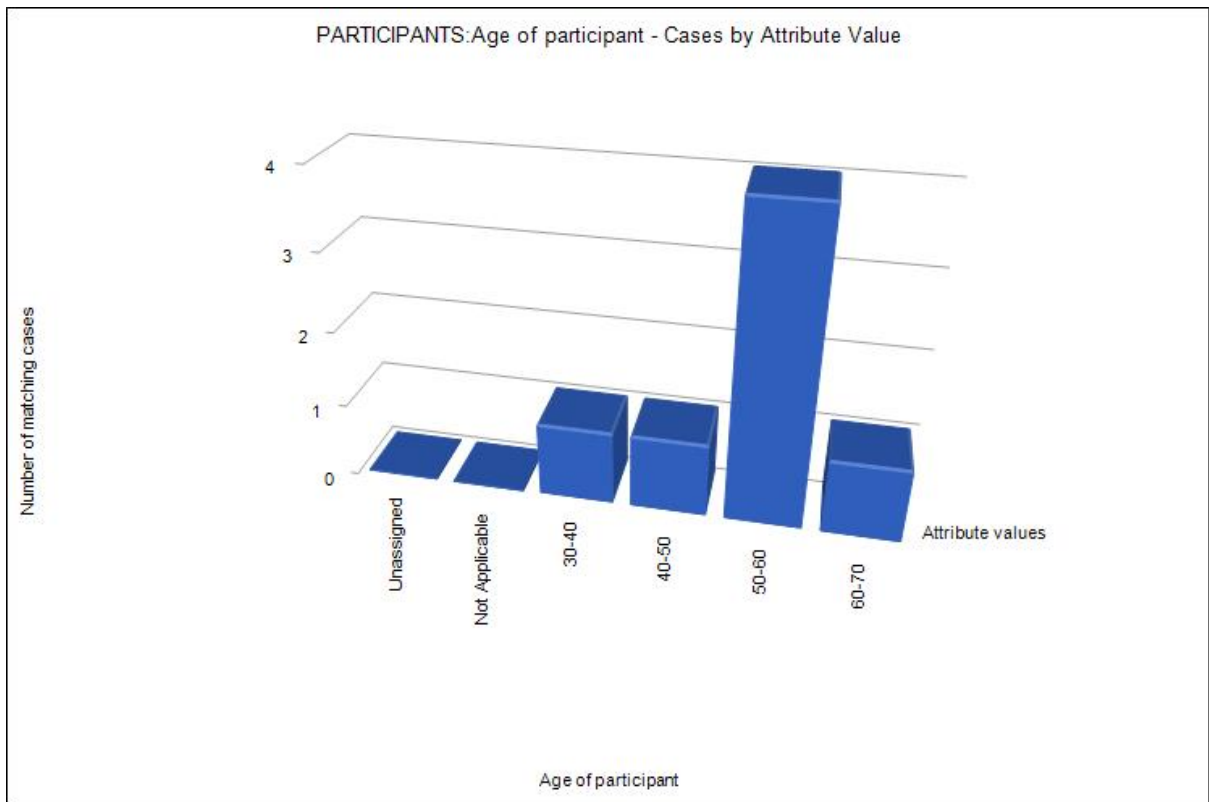
Figure 6.1: Participant age: Indicating the highest number of GPs within the 50-60 age groups.

Table 6.1: Interview guide: Questions structured around six themes.

University of Bedfordshire

LATE DIAGNOSIS OF ALZHEIMER'S DISEASE: RECOMMENDATION TO OVERCOME BARRIERS IN THE UK.
SEMI-STRUCTURED INTERVIEW GUIDE, FOR GENERAL PRACTITIONERS (GP) IN MILTON KEYNES.

Previous research indicates that the late diagnosis of Alzheimer's disease (AD) is a major challenge to public health. One in four individuals in the U.K. has received an official AD diagnosis. It sometimes takes two to three years from the symptoms presentation of the disease before a diagnosis is confirmed (HSCIS, 2014). Late diagnosis can result in accelerating the progression of the disease to a state of cognitive and functional decline, leading to extended hospital stays, an increase in health care costs and subsequent mortality. There is also a burden on the caregivers and a financial impact on health and social care institutions.

This interview guide was developed after the review of the relevant literature and consultations with my supervisors. This is a semi-structured interview guide, structured around six themes namely:

1. INTRODUCTION/ DEMOGRAPHIC QUESTIONS

How long have you been practicing as a medical practitioner?
How long have you been a partner/associate in this practice?
Can I ask how old you are? (A) 28-38, (B) 38-48 (C) 48-58 (D) 58+

Specific Questions
2. EARLY SIGNS AND SYMPTOMS OF AD
What are the signs and symptoms you notice in patients before their official diagnosis with AD?
How long before the diagnosis do you start to notice these signs?
Which sign or symptom appears first among those you have mentioned?
Have these signs and symptoms subsequently aided with the diagnosis?

3. DIAGNOSTIC CRITERIA
What are your GP surgery diagnostic criteria for AD?

4. LATE DIAGNOSIS OF AD
Are there issues that delay an earlier diagnosis of AD?
What are the issues you have observed with the late diagnosis?
Follow –up
You mentioned _____do you mean?
Could you expand on that, please?
5. BENEFITS OF EARLY DIAGNOSIS OF AD
Let's talk about the early diagnosis, how do you feel about early detection and diagnosis of AD?
Could you please explain that further?

Are there benefits or challenges with the early diagnosis?
Can you elaborate more on the challenges of the early diagnosis?
How has this impacted on your practice?
You mentioned the benefits to the patient, carers, and society; can you elaborate and be specific on this, please?

6. DIAGNOSING AD IN GP PRACTICES

How easy is it to diagnose an individual with AD in practice?
Are there specific challenges to diagnosing AD in your practice?
Are there specific challenges for you as a GP?
On a scale of 1-10, how would you assess the diagnosis of AD in terms of the early signs and symptoms in your practice?

Indirect Questions
Have you discussed this issue of late diagnosis of AD with your colleagues? How do they feel about it?
Probes
Do you mean that?
 Is it correct to say that you_____?
Follow up questions
Could you expand on that, please?
Do you have a further explanation or examples of this?
Is there anything you'd like to say that you haven't had the chance to say? If you think of anything else, please do email or call me.
Thank you for taking part in this study; as mentioned in the information sheet, the result of this interview will be anonymised and the data made available to you on request. You will be offered a chance to be an author in the form of Milton Keynes and Luton GP consortium, on any paper which emanates from the study. Thank you once more

6.2 Data analysis

The audio recorded interviews were analysed using framework analysis. My data included cases and codes and as framework analysis is flexible and a form of a content analysis that can be used to analyse data with numbers in qualitative studies (Ritchie & Lewis, 2013), it was identified as the ideal choice. Furthermore, its flexibility nature enabled me to summarise the output in a matrix of rows and columns as its methodical processes and 'spreadsheet' approach, aligned more closely to quantitative paradigm (Pope & Mays, 2009). The analysis involved familiarisation with data, identification of themes (nodes and codes) and interpretation of findings (Silverman, 2006; Bazeley & Jackson, 2013).

The first part of the analysis involved familiarisation with the data that had been collected, a process of immersing oneself in the data to get an understanding of the data as a whole. This process involved listening to the tape, transcribing and reading the transcripts (Appendix III). The transcripts were further checked for accuracy against the recording and reread several times line by line before sorting and transferring the data into Nvivo 11 for analysis.

Nvivo 11 software (QSR International (UK) Ltd, Cheshire, UK) facilitates the analysis of qualitative data with features such as characters-based coding, rich text capabilities and multimedia functions crucial for qualitative data management (Zamawe et al., 2015). In this research, I had the opportunity to learn and experience the use of the software for future use. The disadvantages of using Nvivo include the fact that the software does not accept all data files except with a converter; an individual could also force the package to fit the design in the proposal stage; and using synonyms to isolate themes could lead to partial retrieval of information, which forms part of Nvivo program (Zamawe et al., 2015). This study was devoid of using synonyms as I went through the transcripts in details more than once to create the themes from the data itself, hence my confidence in the value of the software. Nvivo is software that hastens the process of qualitative analysis as the process of converting printed data to softcopy as well as identifying themes and codes depends on the individual undertaking the process.

Emerging themes and patterns that constantly occurred in the data were defined and labeled with codes, which were refined as themes/nodes and redefined to produce themes and sub-themes while gaining an overview of the depth, richness and diversity of the data. An illustration of key themes was drawn from quotations of interview transcripts and themes were compared with the systematic scoping review and RMRRS to identify patterns in signs and symptoms preceding the clinical diagnosis of AD and extracts are presented below.

Eight main themes were identified from the transcripts following the interviews with GPs which included the early presentation of AD prior to a clinical diagnosis; diagnostic criteria used in GP practices; early diagnosis in terms of the early signs and symptoms of AD; ease of diagnosis with the S/S; discussion with other colleagues; issues with memory clinics; issues with the NHS and treatment of the ageing population. Further sub-themes from the analysis are presented solely on participants' narratives. These narratives are reproduced verbatim to explore the GPs perspectives on the early diagnosis of AD.   Interviews were transcribed with software (transcribe.wreally). A discussion section follows the presentation of extracts of interviews in line with some policies in

health service delivery and empirical evidence. Also, the demography of the participants, especially the age and age of services are coded to further enlighten the reader on another theme emerging in the discussion section, which is the aging professional.

6.2.1 Findings

The primary themes in these interviews were the interplay of the early signs and symptoms, early diagnosis and factors surrounding the late diagnosis. However, the emphasis was mainly on issues surrounding the late diagnosis with most explanations on consultations and individual patients; "where is the time" was a phrase reflected across the interviews. In this regard, the concepts portray the challenge faced with the ten minutes appointment time.

The findings of this study echo the literature that describes the diagnosis of AD as challenging. The notable difference with the literature was the lack of emphasis on biomarkers which were never discussed. Echoing a similar research in Amsterdam where the GPs indicated that they would only pursue a diagnosis (biomarkers examinations) when patients' cognition began causing problems in their overall functioning (Prins et al., 2016) the GPs felt that a diagnosis was necessary only if it had consequences for treatment and care.
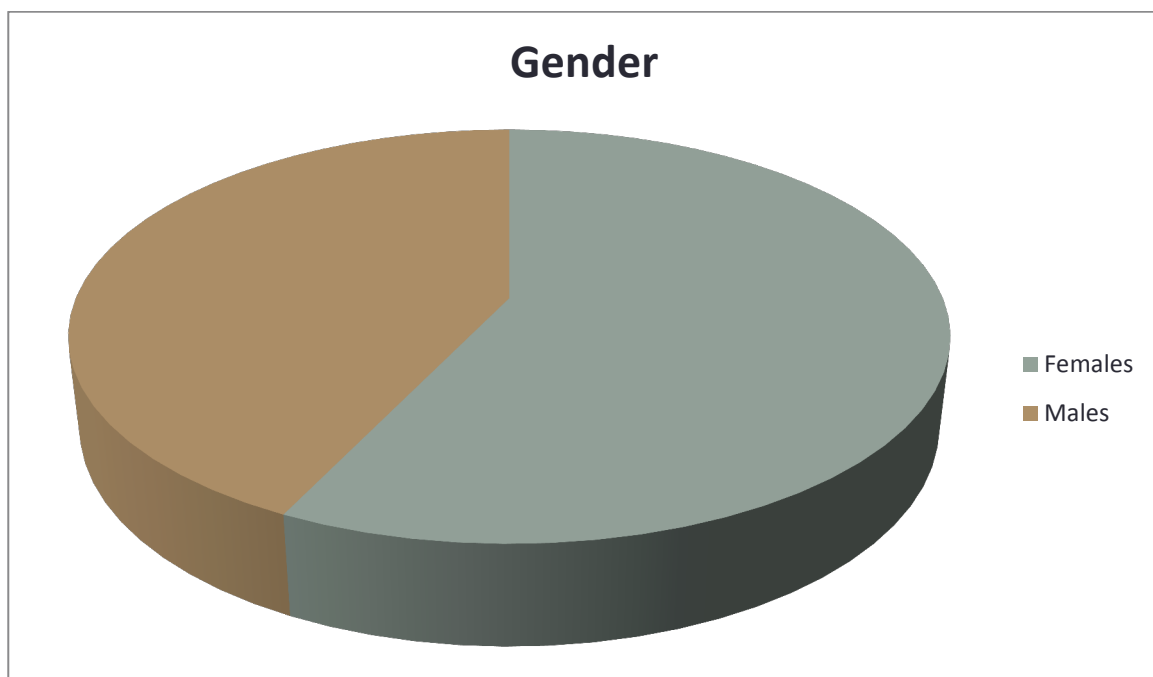
Figure 6.2: The participants' gender: Four females and three males.

Demographically, the participants' ages ranged from 32-66 years with a mean age of 51.7 years. The length of experience that the GPs had as post-qualification practitioners ranged from 8-41 years with a mean age of 23.2 years. Participants were associates in their various practices over a range of periods from 6 months to 31 years with a mean period of 13.6 years (n=7). The framework analysis afforded the researcher the flexibility to analyse codes and cases simultaneously, while assuming a content analysis. The eight themes are presented as follows:

- ❖ The presentation
- ❖ Diagnostic criteria
- ❖ Early diagnosis
- ❖ Ease of diagnosis with the early signs and symptoms
- ❖ Discussion with other colleagues
- ❖ Issues with the memory clinic
- ❖ Issues with the National Health Service (NHS)
- ❖ Treatment of the aging population

6.2.1 Presentations

In relation to the presentations, three sub-themes emerged (**Figure 6.3**) including early presentation; the timing of presentations and signs and symptoms aiding with the diagnosis.
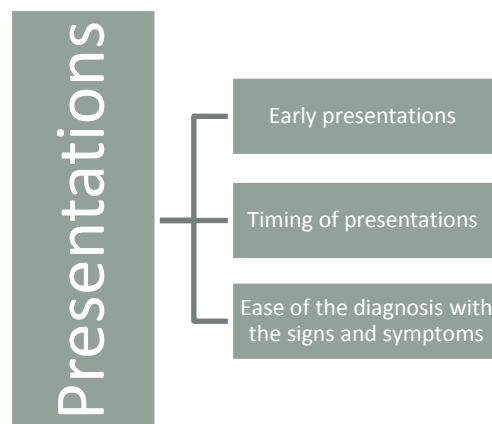
Figure 6.3: Sub-themes of presentation. The theme includes the signs and symptoms aiding with the diagnosis.

These sub-themes will be discussed individually.

The early signs noticed by the GPs and the symptoms reported by the patients included: memory loss; lack of understanding; depressive symptoms and psychiatric symptoms. Interestingly, 75% of the participants (**Figure 6.4)** indicated that memory loss was the first symptom to be noticed and reported, as the ten-minute appointment made it impossible to notice other signs; therefore, it became so much of concern about their memory loss than looking for other signs.

'But often these days in general practice where continuity of care practices is not the way many GPs would like it; it becomes so much of concern about their memory; it will exacerbate any anxiety (GP2).'

One of the GPs s opined that it is either the memory loss or depressive symptoms with subsequent psychiatric symptoms.

'So either they are forgetting things or their mood has changed, so for no reason, they have started to become aggressive (GP1).' However, the depressive symptoms were uncommon, which could probably be a reverse causality for AD.

'They are usually noticing changes in their memory, so the memory changes are mentioned first, they are more common, the changes in mood change is not common but noticed by them (GP2).'

The analysis further indicated that some patients, however, presented with arthritis and high blood pressure. This is because AD is a multi-faceted disease and could assume the nature of other illnesses, while other chronic illnesses of the blood and endocrine system could lead to memory loss, which further complicates and confuse the diagnosis.

'A lot of patients don't present with memory loss, but with at least arthritis, high blood pressure, mood changes, heart attack, diabetes, there are a lot of other chronic diseases, but then you think, is AD also a consideration? (GP3).'
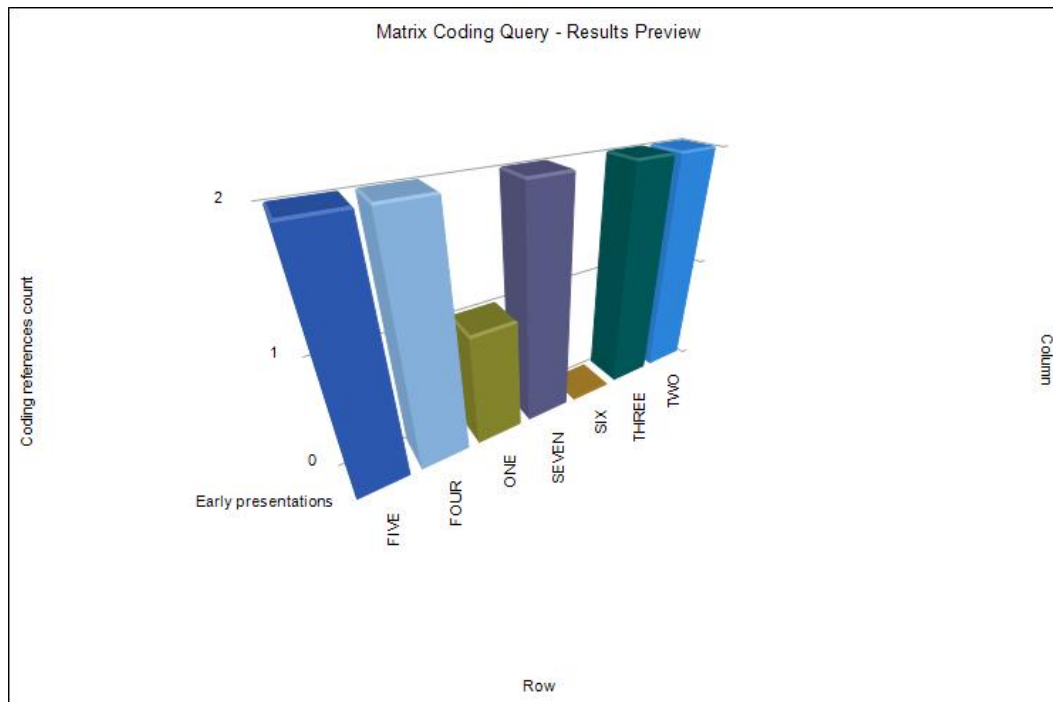
Figure 6.4: Participants matrix. Each colour of the matrix represents a participant and the numbers in the row represent the comments made by each participant regarding the early signs and symptoms.

6.2.1.2 Timing of presentations

As indicated by the participants (**Figure 6.5**), the timing between the manifestation of the signs and symptoms to the clinical diagnosis of the disease ranged from four months to one to two years. The lack of continuity of care was seen by the GPs as a hindrance to isolating the signs and symptoms early due to the fact that the individual was seen by different GPs, which hinder the ability to detect subtle changes in the individual. They further stated that the signs may not be noticeable because the patients may seem alright. However, if the patient has caring relatives or family, symptoms reporting might be early and presentation time could be short, say three months.

'But often these days in general practice where continuity of care practices is not the way many GPs would like it; it becomes so much of concern about their memory; recently I had a patient who had early dementia, but she waited nearly four months for the clinic appointment (GP4).'

'It could be months or even year or two (GP6)'

I think we are talking months, probably maybe between 6 and 12 months, but are very variable. You got somebody who's got very caring relatives or very close friends or

spouse, it may be the short amount it could be 3 months but I think in most cases of people I see, is over a period of somewhere between maybe 4 to 12 months, it's quite variable (GP4).'

When explaining about the difficulties of ascertaining the timing in presentation and isolating the signs and symptoms early, participants stressed the fact that the high turnover of staff and the ten-minute appointment delayed the ability to engage fully with the patient and likely impacted their ability to detect the early signs and symptoms of AD. The ten-minute appointment was by far the most raised issue among the GPs. It was a real concern due to the inability to strike a balance between meeting the current needs of the patient and trying to detect subtle changes of AD. Some of the GPs described the stake in taking a decision as follows:

'You have ten-minute appointments, you're looking at other physical diseases, multiple pathologies, morbidities and other things, so diagnosis is not an instance but is something that develops because of its family doctor. There are other things in general practice now; because there's a high turnover of staff (GP2).'

'General Practice has ten-minute appointment like it convey about, remember because we look after seven thousand patients; two doctors at the moment, we are short of doctors, so I am not proactive, most GP are not proactive in making the diagnosis, unless it's so obvious, then is not an issue (GP3).'

'Yeah, yeah, remember how the NHS works, a GP practitioner works ten minute appointments so I have ten minutes to see one patient for one problem, now so the way you diagnose is within the resources you have and a time limit you have; you might see the patient probably 6 or 7 times, before you start thinking that this is a firm diagnosis of AD (GP 6).'

The high turnover of staff contributed to the recruitment of locum, which in turn prevented an extended relationship that will foster the ability to detect changes in the Dr/patient relationship.
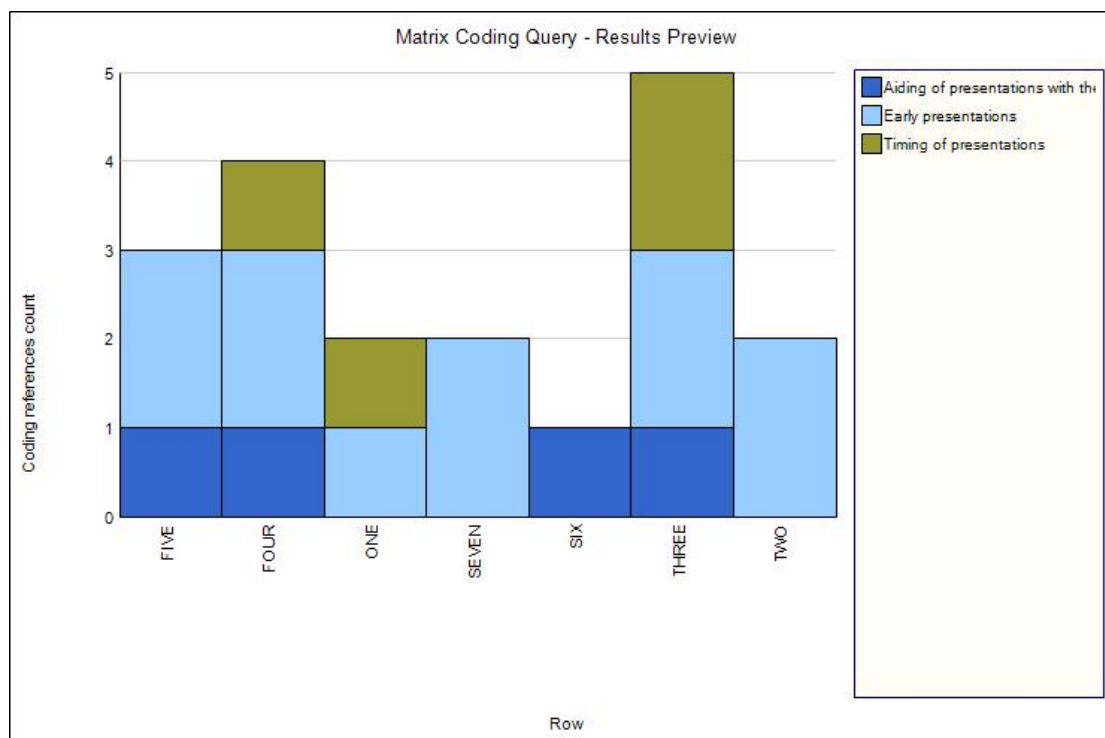
Figure 6.5: Matrix of presentation. The colours in this matrix represent the topic of discussion; 85% of participants that spoke more about the early presentations, 57% about aiding of the presentations with the diagnosis, while only 42% commented on the timing of signs and symptoms.

Another defining issue was the lack of continuity of care; this was caused by inconsistency in the same patient seeing different GPs at each visit, which made it impossible to know which signs and symptoms were presenting first and therefore, the focus was often based on a concern about the memory loss rather than a progressive decline in other presentations. In view of the lack of continuity of care, one of the GPs summed it up as 'continuity of care brings a diagnosis (GP2).'

Yeah if it is a patient known to you and you have multiple contacts with a patient you will pick things up, and then you will introduce that as something you need to be screened for that condition; there are other things in general practice now; you never see the same doctor you must see a locum company that diagnoses there and then because there is not a lot I can do at the moment (GP3).

Still, on the timing of presentations, GPs recognised that lack of cooperation was a challenge faced by patients as this impacted on the ability to detect the early signs. The lack of cooperation was seen to be brought about by the fear of stigma. Even though stigmatisation is not an extensive issue with AD, it still elicits fear among individuals and family, as the mechanism of coping with the diagnosis is challenging in the midst of trying to deal with the demands of the diagnosis and

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emotional turmoil it brings. The extracts further illustrate that the patient will sometimes use the excuse that forgetfulness is normal, which can confound a diagnosis. Perhaps, if other signs were considered, this might not be the case. GP2 reveals that in this GPs experience it is often the patient who is reluctant to seek a diagnosis of AD, as it is seen as a label that carries social connotations and possible stigmatisation. Some patients may not realise that there are benefits to having an earlier diagnosis. So more patient information should be available, that indicates the signs and symptoms patients and their family members/carers should look for and the options available to them.

Definitely, like the challenges are it's a big diagnosis; and say for instance the patient is relatively young or even if the patient is old but they have had a couple of or the patients themselves have had good quality of life, then, although they have noticed the memory problem, they were still coping, once they have got the label of AD, a lot of things changed. It happens suddenly because of the diagnosis (GP5).

I think that the delay is not on our side; sometimes patients themselves try and normalise the concerns. I have patients who have frequently come to me and say well everyone gets forgetful a bit as they get older and also relatives. I think less so, you know, when I am thinking about fifteen years ago when I was a GP, there was a huge stigma about being diagnosed with AD or dementia and a real reluctance to consult a consultant psychiatrist to discuss treatment options; but even the diagnosis was considered a shame and I have had many spouses/patients who really refuse to accept that their wives/husbands its becoming more and more muddled (GP2).

On the professionals' side, the lack of proactive investigations that would facilitate an early diagnosis by the GPs and inadequate training specifically with regards to the early signs and symptoms of AD, was another driver of the late diagnosis of the disease. The lack of sufficient knowledge of the disease pathology made it impossible to notice the timing of the first notable presentation as one of the GPs noted and attributed the diagnosis of the disease to the psychiatric team. Perhaps, with a suitable tool in the primary care, the diagnosis will not be the sole derogation of the secondary care.

GPs are not really trained adequately to assess people for AD, that's really the job of a psychiatrist and the psychiatric team. So what we tend to do is send people for memory test in various instances and then if the memory test is suggestive of Alzheimer's or

dementia, at that end, it is the secondary care who make the diagnosis rather than GPs
(GP1).

None of the participants mentioned finances as a hindrance to the early detection only the lack of resources in the NHS. However, they were optimistic that the development of a suitable tool for the early diagnosis could be beneficial.

6.2.1.3 Ease of diagnosis with the signs and symptoms

The role of the signs and symptoms in aiding with the diagnosis was emphasised as a factor in the early diagnosis of the disease. Although most of the GPs were not keen to isolate other early signs and symptoms apart from the memory loss, participants all stated that the signs and symptoms mentioned, aided with the diagnosis of the disease especially when the disease was at the advanced stage of dementia. The notion is that the family members would have noticed these presentations months or years before the diagnosis and waited to be sure that the symptoms were consistent and the changes pronounced, before seeking the attention of the physician; hence the ease of diagnosis.

So again it's like, obviously when they come to us with these specific presentations, the assumptions is that these symptoms would have started months or years prior to their coming to us, because they would have noticed the change probably for about a good six months, so the changes would be that they would lose keys in the house and not find them, they would probably be watching a soap probably on a regular basis and then when they ask them what it meant, probably they would not remember what happened previously. So these are the sort of signs and symptoms of their daily living, which the spouse notices because they are changes that are quite noticeable, because they were not there before and they are quite obvious and they do give it like I said, a fairly long time to see if there is consistency in their symptoms. So once they are convinced that there is something wrong, they come to us (GP1).

6.2.2 Diagnostic criteria used

In terms of the diagnostic criteria used, the majority of the participants indicated the preference for memory clinic as a way of making a diagnosis as there were no specific criteria for the primary care except the MMSE. While GPs used "GP code" (with six questions), "six sets test" and MMSE with full physical examinations, where possible, the GPs relied on the secondary care to make the final diagnosis. The GPs initiated the diagnosis after a full physical examination has been conducted to

exclude other diseases or conditions, with series of blood tests and electrocardiograph (ECG) to rule out other causes and establish a healthy heart before finally sending the patient to the memory clinic to establish the diagnosis; GP group echoed the series of test done before the diagnosis was established.

I don't think there are any specific diagnostic criteria to be followed, but it is the mini-mental test (MMSE) that we do on these patients. So once we are told that definitely there is a certain change they have noticed, then we bring the patient back for a 20-minute appointment and then we do the mini-mental test. I think that is a real gold standard for diagnosing memory problem (GP5).

We would use the six sets test, but obviously, we would do a full physical examination to ensure that, because physical problems can mimic this, like hyperthyroidism, interaction with other medications. So we do a full physical examination first and take a full history, hopefully from somebody who knew the patient well and then with the patient themselves, we would do the six set test (GP4).

We have quite strict criteria because we would always insist on referring to the memory clinic, so we have a certain number of routine blood tests that we need to organise first, for us to exclude certain conditions. We also do an ECG more because thinking about….if they are going to need treatment… lots of medications can have an effect on the way the electro-conducting mechanism of the heart works. So it's important to know they have a normal ECG before you start, then refer them to the memory service and nearly always, they would actually get a CT diagnosis as well….although, that is not absolutely mandatory to make the diagnosis. We don't ourselves just make the diagnosis without referring to the memory service (GP7).

6.2.3 Early diagnosis

I have split the issues that impact early diagnosis into four sub-themes including (1) the issues that delay early diagnosis; (2) the burden of late diagnosis; (3) the benefits of early diagnosis and (4) the challenges associated with early diagnosis, and these are considered below:-

6.2.3.1 Issues that delay early diagnosis

When asked about the issues that lead to delays in early diagnosis, participants indicated the lack of patients' insight into their early signs of dementia; they worried that the fear of losing their

independence prevented them seeking help at the early stage as well as the fear of being labeled with the disease. A GP sums it up as follows:

I suspect, there is a lot some of our patients who for… they won't want to have a diagnosis because they would have their fear; if it is working-age patients, they would fear loss of ability to drive, loss of ability to work and then I suspect probably a small proportion of patients don't want to be diagnosed with dementia, perhaps they are not presenting and perhaps they are having a hard time at home and well they are; yes I remember one of my patient, I think she did have dementia, but she was …and she did have a certain degree of insight but she was refusing……; she was so…….she didn't want that diagnosis. She was doing everything possible not be….. Laughed at …… labels by family or by professionals and she was so angry that we are talking in those terms, but then, unfortunately, she did decline over the years (GP3).

'Well, often the Patients have no insight, if they live alone, they might not appreciate that they are slowly dementing (memory loss) (GP4).'

Social isolation was also an issue that was attributed to the late diagnosis of the disease. Individuals staying alone were often forgotten and their being isolated prevented others from noticing the early changes in their wellbeing. As one of the GPs put it *'I think people who are more socially isolated… maybe don't have family around or a lot of friends…they might not come to anybody else's attention because they manage somehow to function even though they have quite a level of disability in terms of committing public functions (GP7).'* Another supported this view by indicating that the delay is usually from the patients' side, especially when the individual is without relatives and friends.

The delay is usually either the patient is on his own. That's one of the areas probably where the diagnosis can be delayed because the patient either is been independent, they have not needed any carers, or the family probably is not around. They are in s situation perfectly where they were managing before and then their memory goes off… Because they are on their own and nobody else notices it, it does then get delayed because nobody is picking that up and bringing that patient to us about their concerns (GP3).

Additionally, logistical problems alongside delays in getting an appointment with the memory clinic contributed immensely to the delay in diagnosis.

The GPs are aware of the benefits of early detection; however, they were skeptical about the support to the patient after diagnosis. They were worried that the patient would not have the desired support or therapy needed especially with the limited resources and time as well as high turnover of staff in the NHS. Therefore, making a diagnosis would be difficult for the patient without therapy. Some of the GPs sum it up as:

That's the issue, in the NHS, where is the support? What do I do when I make this diagnosis? Is there a consultant out there who, is there enough of them to say I can see them or support them, or to introduce any therapy, psychological therapies, physical therapies, anything that can get this diagnosis well supported, finding it is extremely difficult...pause.... very difficult, because the NHS resources are limited (GP1).

If I had thirty minutes with a patient, it's easier, but I cannot afford thirty minutes per patient because we are looking after 7000 patients; one doctor looking after well over three thousand patients, plus there is a high turnover of medical staff, so yeah, if we had more time and more resources, it gets easier and easier to diagnose some of these our patients and say, we've got time, let's do some a longer chat, a longer discussion your problem and then it makes it easier to put that diagnosis into perspectives (GP3).

6.2.3.2 Burden of late diagnosis

Conversely, all the participants indicated that the burden to the individual is high, including cognitive and functional decline, resistance to treatment and poor support from family, friends, health and social care. The main burden to the family highlighted by the participants was stress and anxiety around obtaining a formal diagnosis as well as poor support from the NHS on how to cope. However, there was no mentioned of the burden on the healthcare system or healthcare personnel, which could be due to the fact that the GPs were more concerned about the issues facing the PC and how they contribute to the diagnosis of AD.

'S*o if the diagnosis is delayed considerably, then I think there is more resistance to treatment (GP5).'*

'*I think is the patient and the partner or the family that is struggling, I think that is the major issue and not only the other thing the late diagnosis a sort of traumatises them. Hmmm, it's a sort of it is Idolism. Is there anything else that can be done to make life easy? (GP1).'*

Well I think if you get a late diagnosis, it is inevitable that your patient probably gonna deteriorate and any intervention probably gonna be unsuccessful; so there is no point in given patients with a late diagnosis, well I won't say there is no point but, I would expect that there would be relatively little gain, because if they have a late diagnosis, they would probably have quite a severe degree of dementia and I suspect they are probably gonna have considerable cerebral atrophy and may well not respond to treatment which is available (GP2).

6.2.3.3 Benefits of early diagnosis

In terms of the benefits of early diagnosis, one of the participants stated that there was no negative aspect to an early diagnosis. Others (**Figure 6.6**) supported this view by stating that the early diagnosis was beneficial in terms of planning ahead, power of attorney and anticipatory care. Furthermore, it was beneficial to employers as they could support the patients and place them in suitable positions within the workplace.

I think it is really… really good; if we've got the resources and a good system available to us which can diagnose AD early, obviously the triaging area is us, so once we have identified and signpost and they are seen promptly, then it's very… very beneficial for the patient and for the family, because then, they can adjust to that real diagnosis and then manage it better. So I think all around, it's much more beneficial for the diagnosis to be made as early as possible (GP5).

There are undoubtedly benefits; I can't think of any negative aspect of early diagnosis, to be honest. I think for example if a person is at work and is struggling, I think it would be worthwhile for both for the patient and the employer, patients 'employer to know, so it will be helpful and whether they are able to accommodate the person you know, in position in which they could still work. I am not sure how much for the patient and the employer to have; yes I think it will be possible (GP4).

'There are lots of positives…because simple things like forward planning, anticipatory care and power of attorney over financial and health needs…obviously all those things are really important (GP7).'

6.2.3.4 Challenges associated with early diagnosis

The challenges reported by the participants that were associated with the early diagnosis included: denial by the patients as they were afraid to be associated with the disease due to the fear of losing their independence. Not only were they afraid of losing their independence, they were afraid of stigmatisation from the society, even though AD is not associated with much stigmatisation.

I suspect that some of our patients..... they won't want to have a diagnosis because they would have their fear; if it is working-age patients, they would fear about loss of ability to drive, loss of ability to work and then the stigma, being label dementia probably is going to be on themselves, I suspect probably a small proportion of patients don't want to be diagnosed with dementia, perhaps they are not presenting and perhaps they are having a hard time at home and well they are; yes I remember one of my patients ...I think she did have dementia, but she was or and she did have a certain degree of insight but she was refusing... she was so.......she didn't want that diagnosis. She was doing everything possible not be... Laughter ... labels by family or by professionals and she was so angry that we are talking in those terms, but then, unfortunately, she did decline over the years (GP2)
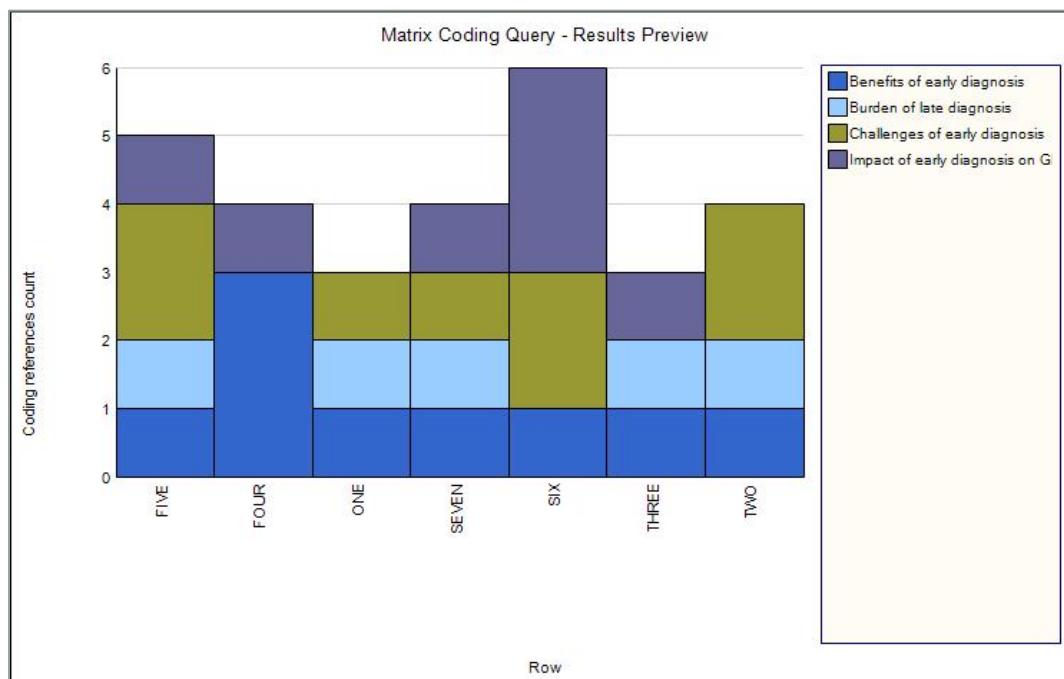
Figure 6.6: Benefit matrix. The participants in this matrix all spoke about the benefits of early diagnosis of the disease; 71% commented respectively on the challenges, burden and impact on the GPs.

The call for the early diagnosis was well supported by the GPs; raising the awareness of the disease especially through the media, has enabled individuals to seek help and the GPs were more sympathetic and considerate when treating the elderly. The GPs were far more able to have an open discussion of the disease with their patients and families on the diagnosis and interventions available. With consideration of the racial diversity of patients, the GPs were hopeful of a suitable tool for the diagnosis that could be used in a racially diverse population with language difficulties and comorbidities.

Oh certainly we are far more aware to consider it in an elderly person and there is more acceptable to discuss it early with patients and families and also as a GP, you get a query from relatives. So I think generally, which is good news, I think the media relations certainly raised lots of awareness for people on getting treatment early (GP6).

Also, issues of racial and cultural diversity proposed a challenge with early diagnosis of AD, especially the ethnic groups at risk of vascular dementia due to high vascular and metabolic disorders. The language barriers mean that there is the need to develop a tool that could be applicable to these ethnic groups.

We do have a very ethnically diverse population; we have a lot of southern Indians and people from Bangladesh, who are… certainly, have a higher risk of multi-infarct dementia, because they've got a higher incidence of hypertension, diabetes, metabolic syndrome already. But obviously, for some of those individuals again, the conventional testing isn't that friendly… I have to say I don't know whether there are tools that we could use with that population (GP7).

6.2.4 Ease of diagnosing with the signs and symptoms presented

The responses by the participants regarding the ease of diagnosing with the presence of the signs and symptoms are split into three sub-themes namely (1) ease of diagnosing the signs and symptoms in GP practices, (2) ease of diagnosing as individual GPs and (3) scale of diagnosis or points given with regards to how easy it is to diagnose the signs and symptoms presented (**Figure 6.7**).
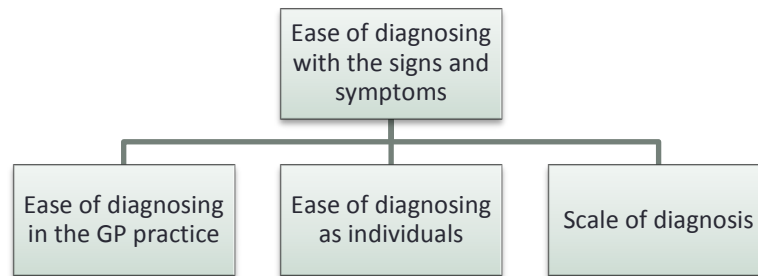
Figure 6.7: Sub-themes of ease of diagnosis.

6.2.4.1 Ease of diagnosing with signs and symptoms in the GP practice

The ease of diagnosing AD in the GP practice was regarded as challenging. Respondents all indicated that AD was difficult to diagnose except when the disease was at an advanced stage. Apart from the fact that some patients might insist on specialist confirmation, the GPs felt that further assessment was not required at an advanced stage of the disease.

'Practically it is difficult except that I think there are expectations I supposed, that the patients would want specialist confirmation, even though clinically it is feasible to diagnose them especially if they advanced, more of us can say they don't need to go through the assessment (GP1).'

The ease of diagnosing AD also depended on individual practitioner; the enthusiasm by the GP to examine the patient in-depth, especially if the patient had an inclination that something was wrong, all contributed to the ease of diagnosis. The evidence indicates that some of the GPs were sometimes less concerned about obtaining a diagnosis especially when there were no complaints from the patients. This is demonstrated best by the following quote (GP2).

I have worked with a number of different doctors and some doctors I worked with have very little interest in examining patients or doing anything for them, they just want them out of the door. So, it depends on your approach to life, I think it can be difficult diagnosis because it presents in very subtle ways, so if you have somebody who maybe doesn't think quite right but doesn't make a lot of fuss about it, you obviously won't say; or you will be fine, go away, goodbye and I am not bothered and that's what a lot of my

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colleagues do or have done and still do, I have seen lots of evidence of that. So you know,
it depends on your approach, but my approach has always been, what will I like a doctor
to do for me if I was that person, or that person was my relative (GP2).

Furthermore, it takes years before the signs and symptoms manifest while the degenerative processes continue. This could make the diagnosis challenging at the early stage when the signs and symptoms are subtle and could be mistaken for old age or other conditions. .

I think in itself, it can be difficult to recognise in the early stages... because, memory
changes and age happen together anyway...and to a certain degree, change of
personality...so it can be very challenging at the early stages, not so much towards the
end of the spectrum...it's a bit in the middle which is a kind of useful, but can be hard
(GP5).

Time and lack of resources were also mentioned as the contributors to the challenges faced in diagnosing the disease early. According to some of the GPs, there are no trained personnel or facilities that will make the process easy and a GP is torn between the choice of concentrating on current complaints or fully assessing the patient when it comes to the issue of time. One of the comments is as follows:

Yeah, exactly, it is challenging, general practice is very challenging, so your part is
changing every day, your part is more towards your time limit, your works load, what
you can diagnose, what you can't, whether there are resources to do that and work
properly; there is tremendous challenge in the NHS. Those are the challenges, have you
got time with your patients? Have you got more resources? Have you got mental health
practitioners working in your practice? You have none of that, do have any other trained
staff to help you with a diagnosis like this, no we don't. Do you have time? Are you under
tremendous time constraining? Yes, absolutely challenging, very challenging; the time
constraints etc (GP3).

6.2.4.2 Ease of diagnosing AD as individual GPs

As individual GPs, the achievement of a diagnosis was not challenging as long as they could listen to the patients' complaints and refer them to specialist clinics; *'The challenge will be not listening; as long as we are listening to the spouse and referring them further on, I don't think there is a challenge there (GP2).'* However, most of the GPs indicated that AD is not a common disease; one in twenty of

those 65 years and below with the prevalence variable in localities. Without a disposition, the signs and symptoms were sometimes mistaken for other conditions as they are not frequently encountered in the PC.

'You don't use to seeing it and so you may miss it, so you have to have a higher end suspicion and I have to say that I may miss things, I think everybody does, but it depends also on your approach to life (GP3).'

Additionally, the disease presents as other conditions like normal aging or diseases like CJD, which can delay the diagnosis as other conditions have to be excluded to establish a diagnosis of AD.

Well, lots of people often complain of similar illnesses or similar symptoms and they don't have dementia, they could be a little bit forgetful sometimes, or they may be going through stress. So you can't just say everybody who says I keep forgetting things or my memory is not so great, you can't assume that they are all demented, there may be many reasons for that, if they are physically unwell, they could be stressed to reasons. So physical illness makes you unwell, it affects your mental function and stresses you to do that. So it's quite difficult to tease out who is physically ill, who are just suffering from the stresses of life and who is got dementia (GP1).

Also, practitioners felt that time constraints due to the ten minutes appointment system enforced by NHS did not allow them to investigate the symptoms more thoroughly as the GPs were more concerned about the present complaints than looking for hidden ones.

'Generally speaking, it is not easy, smiles... for the reasons of, we are so busy; going backward, ten-minute appointment, conveying about medicine, so you can say it's not easy (GP4).'

Finally, the lack of a suitable tool for an ethnically diverse population, which could enhance the communication between the GP and the patient, was limited in terms of the availability of interpreters:

' Well, yes…that's a challenge to me because I don't necessarily have the communication skills to pick out those things because if you are going through an interpreter, you really can't go do a memory state examination successfully with someone else interpreting for you…..(GP7).'

When asked to rate the ease of diagnosing the signs and symptoms of AD on a scale of one to ten; one being the least easy and ten being the easiest to diagnose the presentations, participants opined that the diagnosis was difficult, with a range from 2-5 for each sign and symptom.

'Well, I think it's difficult, well I will say it's probably well there 2, 3, and 4. It's a difficult diagnosis to make and get right (GP2).'

One of the GPs stated '*I will give it a five' (GP5).* Additionally, they indicated that the diagnosis would be easy with familiarity with individual patients over time, as continuity of care and follow-up were necessary to make a successful diagnosis, which was a challenge within the NHS.

It could be ten out of ten if you have the time and the resources, yes; but in certain situations, if you don't have that, it may delay the diagnosis and is follow-up, and its management, not just making a diagnosis; because follow-up and management is part of the diagnosis and then you can say, where can I send you? And it's becoming increasingly difficult within the NHS to support your diagnosis (GP1).

Moreover, the screening tool in the PC was MMSE, which was considered unsuitable for highly educated individuals as they could manipulate the procedure and to individuals with Down syndrome due to limited intelligence; therefore, it was entirely dependent on the GP's relationship and knowledge of the patient.

I think we have to be specific…… Again the screening tool which we used, that is slightly subjective to the patient, if the patient has the intelligence, they can manipulate it either way; depending on the persons or patients with moderate or severe dementia cannot be able to do that. So early, I think it depends on I suppose clinician who knows the patient very well to be able to say they are manipulating it or not, by experience and by the knowledge of the patient. But why would they do it? Probably I do not know. So I will say five. (GP3).

6.2.5 Discussing the early diagnosis of AD with other colleagues

Findings from the study indicate that the low prevalence makes it impossible to discuss the disease with other colleagues, as some of the GPs indicated that low prevalence and patients' unwillingness

to undergo further testing hinder a proper discussion. However, some participants discussed the disease with other colleagues and felt that the AD patients needed more assessment and support, which could point to the issue of limited consultation time and professionals. They were happy with the considerable benefits of early diagnosis even when the patients were seen less regularly.

'Yeah, we have certainly discussed it in meetings and we all hear considerable benefits of early diagnosis (GP4).'

'They are of the same opinion as me; I guess as a GP, there are the challenges to really ensure that you are assessing all your patients adequately, because often we, these days we don't see patients as regularly perhaps as we used to (GP2).'

We don't have a huge (number of) patients in that cohort of elderly aged patients and therefore we don't have that many patients actually and being here ten years, my load of assignment since 2003 and the patients also; I have two patients at the moment with dementia and I don't have many willing and the patients who are nurtured earlier are not keen on going into any medicine or even assessment etc (GP1).

6.2.6 Issues with memory clinics

The result of this study suggests that the main issues with the memory clinics are logistical, as AD is underdiagnosed by these services; hence there is a backlog of patients waiting to be diagnosed. Perhaps, if there was a standard tool to be used in the PC, the backlog would not exist and certainly not to the same extent, as other conditions are excluded and a firm conviction of AD made before referring the patient to these specialist clinics. The GPs further stated that the waiting lists of patients in these centres were occupied by those who did not need this service.

'I think is just a logistical problem …I think in the memory clinic, for example, the patient I referred that has the advanced disease or typical case of dementia, I don't think she has yet had an appointment (GP4).'

'So I think that is a deficiency and I suspect partly the problem is that the waiting list is occupied by patients who perhaps who don't need to be there (GP2).'

6.2.7 Issues with the National Health Service (NHS)

In terms of issues with the NHS, the ten-minute appointment was the dominant concern as participants all indicated that the consultation time was not enough for a GP to have a proper

conversation and assessment of the patient (**Figure 6.8**). It has meant that a proper history taking or mental assessment is not possible within the consultation time, especially with comorbidities, except if the patient comes in with memory issues or dementia. The GPs felt that trained professionals within the PC should be carrying out the assessment (ie nurse practitioners) to provide a subsequent diagnosis of individuals with the disease.
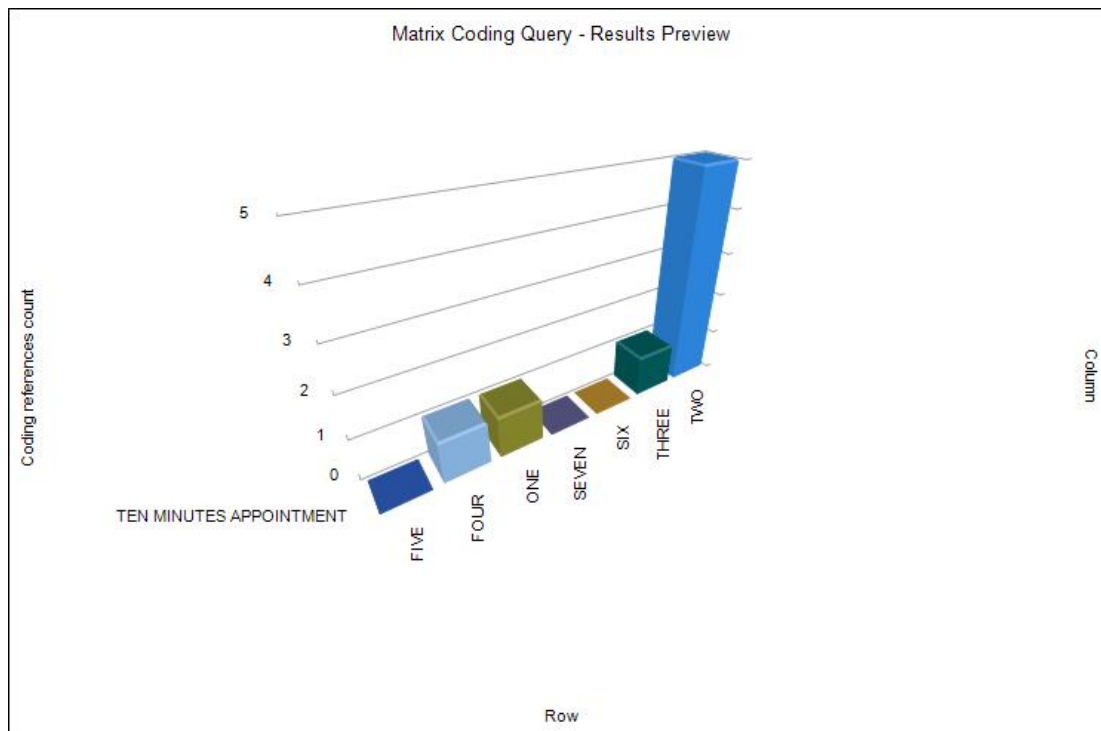
Figure 6.8: Ten-minute appointments. 57% of the participants spoke about the issues with the ten-minute appointment and one participant, in particular, spoke about this issue four times more than others. The issue was discussed due to its' impact on the time spent with the patient, to make a definite diagnosis.

The extracts suggest that the NHS needs more human and material resources to help in the early diagnosis of AD, especially with a population that is racially diverse, as it is increasingly the case in the UK**.**

'I guess it's the time; most GPs have ten-minute consultations and I must admit I often

need longer than that (GP3).'

The reality is that we have a ten minute appointments to see patients, and that means

you see the patient, you take a history, you do an exam, you keep detail accurate records

and to do that for one problem, is very difficult, and to do it for more than one problem,

is impossible, you will not do it well; and to do a mental health assessment, we don't

have the time to do that, you need a lot of time to do that properly. And I cannot do it in a ten-minute consultation, so somebody else should be doing that, somebody who is trained adequately to assess somebody mentally should be doing that, and that's the only way you can figure out an early diagnosis in the majority of people that got dementia (GP2).

Not only is the NHS in need of more resources, participants felt that the service could organise itself and encourage individuals to go for an early assessment. Furthermore, the extract indicates the need to develop a system where those individuals who are 65 years and over are mentally assessed on an annual/regular basis possibly in their homes, as this was a strategy adopted in other developed countries to isolate the disease and other chronic diseases early. The GPs were also of the opinion that the public could be encouraged to contribute to their health care rather than believing that healthcare is meant to be free. The contributions could help ease the financial pressure or cut back faced in health care delivery.

Well, I think the main challenge is actually getting people to come to see us because a lot of people don't. So there isn't a mechanism in society at the moment to review people to get an assessment of their general health and their mental health. With the situation being as it is, where the NHS is in debts, that's highly unlikely, but if you go to France, France spends a lot more money in their NHS in France than they do here; well they don't have an NHS but they have an equivalence system and until public beliefs, stop believing that everything should be free, and start contributing, all successful governments double or triple or quadruple the amount of money going into NHS which is never gonna happen probably. The service that we get for everything, will not improve. So in an ideal world, you have somebody who is dedicated to go and see every single person age 65 and over, once a year to do a mental health assessment and I mean everybody, and that is never gonna happen, whether you go in to see somebody who is in their home or you have centres where people go to, if people don't turn up, then you go chasing them and go and see them. And you can have some of these systems whether they are in-depth, but this isn't in an ideal world (GP3).

Other challenges included the role and responsibilities of locum; the GPs related the high turnover of staff and the employment of the services of locums to the lack of continuity of care, as according to them, '*continuity of care gives a diagnosis (GP2)*'. Perhaps, recruiting more GPs or mental health

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nurses to undertake the screening of individuals and sustaining the continuity of care could be of benefit in the initiative for early diagnosis of the disease.

'in the general practice now; you never see the same doctor you must see a locum company and because there's a high turnover of staff, patients don't get continuity of care and continuity of care gives a diagnosis. We could have at least trained mental health nurses that would come and screened the population, because they know the GPs do not have the resources to it themselves, either too busy doing other things, but they came, I think when it was a government drive to make this diagnosis, there was a drive and all of a sudden it is falling apart because of the cuts back in the NHS. I believe there must have been a cut back to them, they disappeared (GP2).

6.2.8 Treatment of the aging population

With regards to the treatment of the aging population, participants noted that the aged were discriminated upon by the public and there was lack of enthusiasm from healthcare providers and the NHS in treating them as aggressively as younger generations. This discrimination and perhaps at best, unconscious bias, meant that the views of older patients were not addressed as thoroughly as those of the younger generation.

Well I think is very important, to me I think there is creeping ageism in our society and a lot of people now have very strong views about not treating people who get older with the same enthusiasm as you would treat young people; In fact, my wife had a hairdresser and she said the hairdresser and her friends have been talking and they thought that people over 65 years of age shouldn't be allowed to vote, because they didn't know what they were doing, and I mean that's a dreadful thought, dreadful opinion; I am 66, I am fully complimentist (work position), I am working full time, I work five days a week, I have five site commitment, I have a judicial appointee to the lord chancellor, so I have significant responsibilities, I have a heavy workload and I could pretty well do it and to suggest that somebody my age shouldn't vote is insulting and disreputable and I think the same approach goes in medicine (GP3).

The GPs lamented that aged individuals have not been treated fairly in the NHS and felt that these individuals should be treated equally whether they were newborn babies or aged. The GPs explain

that patient-centered care should be tailored to meet the needs of individuals in all circumstances. One of the GPs summarised it as follows:

The number of relatives who have been treated in the NHS, who are elderly, have not been treated well, have not been treated the same aggressive approach as you should approach any patient well. So I feel very strongly that you should treat everybody the same, irrespectful of their age and you should only not provide care if it is in the patient's best interest that that should happen. As far as making a diagnosis and treating a patient with AD or any other disease is concerned, I feel extremely strongly that you should get on and do it just as much as you will treat a baby who's got a head cold or an infected lung (GP6).

6.3 Discussion

This study is the first exploration of GPs' perceptions of the use of early signs and symptoms for the diagnosis of AD.   It also examined issues surrounding the late diagnosis as well as GP recommendations against the delays which may hinder an early diagnosis of AD. The GPs interviewed in this study, provided insights into the issues preventing the early diagnosis of AD. Individuals with AD diagnosed at an early stage have the potential to live longer, as the disease responds to treatment at this stage. The participants' mean age was 51.7 years and their length of practice ranged from 8-41 years indicating their experience and ability to comment on the issues at hand.

The gold standard for diagnosing AD is the advanced testing (Viola & Klein, 2015; Olsson et al., 2016) which is unavailable in the primary care setting and the MMSE available in the clinical practice is not sensitive enough due to communication barriers in autistic individuals and issues with literacy in highly intelligent people (Prins et al., 2016). Findings from this study indicate that the patients' concerns, physician observations and history from family, friends and other health professionals are essential to enable the early detection of the disease. However, it was widely acknowledged by the participants that these signs and symptoms are sometimes overlooked due to the current limitation on consultation times. This finding is supported by recent research that indicates the challenges with the current consultation time (Lewis et al., 2016; Mercer et al., 2016; Gove et al., 2016). Other challenges in healthcare mentioned include the ageing population, expectations from patients and shrinking budgets, which have interfered with the effective delivery of health care and the

subsequent late diagnosis of AD. Moreover, a valid instrument for early diagnosis in the PC might lead to fewer referrals to the memory clinic.

The NHS is the national body saddled with the responsibility of providing health care for its citizenry, which was borne in 1948. Recently, this body has been burdened with a rising tide of demand which conflicts with its lack of adequate financial and human resources (Filochowski, 2015). The situation has been tagged, the biggest crisis in NHS history (Alderwick & Ham, 2016), with deficits in hospital budgets, missed targets for patients 'care' and inadequate professionals resulting from, most recently, the Great Recession of 2008-9. All the participants reiterated that the NHS has deficits in finance, which made the resources unavailable, inadequate funding of enough professionals and huge demands of their time. All of these factors have contributed to the late diagnosis of AD individuals.

Supporting this is the crisis in general practice (Roland & Everington, 2016) which includes a breach of waiting time for consultations, increasing workload and overwhelming budget regulations. It is unsurprisingly common for a GP to have appointments and see 60 patients in a day (Roland & Everington, 2016) due to the increasing workload. GP participants confirmed that the current situation in the NHS afforded insufficient time compared to that required to engage fully and comprehensively with the patient. Some GPs however, are against the qualitative assessment and increased duration of the consultation, as they perceive this will increase workload (Croxson et al., 2017). The complexity of the ageing population, chronic or long-term conditions, as well as multi-morbidity, requires more complex and longer consultation to deliver quality care; this is a rising tide of workload that will require additional expertise (Thompson et al., 2016). A suitable tool might help reduce the workload and the need to increase the consultation time.

Furthermore, the funding crisis has seen the NHS employing the services of locums to sustain the services of doctors and plug the gaps created by a high turnover of staff. However, the use of locums in the NHS (Rimmer, 2016) has contributed to the lack of continuity of care, flouting the need for an integrated care approach for those in need of health care services, as patients are made to see different doctors on several consecutive occasions. This could affect the ability to establish a doctor-patient relationship that will enable patients to talk openly about their concerns and facilitate an early detection of AD. Additionally, the NHS spends nearly 25 times as much on locum agency fees as they spend on recruiting doctors for permanent positions (Lacobucci, 2016). If the

reverse was the case, it would be reasonable to believe that there would be less service gap, with adequate continuity of care for patients, and a subsequent early detection of AD.

Central to the study is the finding that memory loss is considered to be the primary indicator for further investigations to determine whether a diagnosis of AD is appropriate. The result is supportive of the literature (Cumming et al., 2013; Jahn, 2013; Tramutola et al., 2015; Viola et al., 2015) where memory loss was identified as the early sign of the disease. However, other symptoms including apathy and odour deficits have been identified, which are superior to memory loss in discriminating individuals at the early stage of the disease (Devanand et al., 2015; Ringman et al., 2015). The use of the PC data has also enabled us to identify other symptoms that presented earlier than memory loss, previously not investigated in AD (Bature et al., 2018). The knowledge of the early presentations and timing could help initiate patterns that could inform a predictive model for early detection to be used in PC, as the GPs acknowledged that they do not always recognise the disease in patients early.

Aside from the issues faced in the healthcare sectors, some of the reasons for the late diagnosis as opined by the GP participants, included a lack of insight of patients and their relatives into the early signs and symptoms of AD. The lack of insight (anosognosia) has been identified as one of the signs and symptoms of AD, as an early mechanism of the disease and part of a neuropsychological syndrome of AD (Migliorelli et al., 1995). The sign, which initially was not affiliated with the disease duration and severity (Reed et al., 1993), is however severe when patients are at the stage of severe cognitive decline (Conde-Sala et al., 2014) and it is associated with episodic memory loss (Senturk et al., 2016). Anosognosia predicts the progression of the disease (Munro et al., 2016) and could be an early mechanism and not a factor of delay, or vice visa.

My study also highlighted the role of the fear of stigmatisation which can delay an early diagnosis of the disease. This is in line with other studies (Gautier et al., 2013; Dubois et al., 2016) who have opined that AD diagnosis is associated with labeling or stigmatisation. Ironically, AD label is not associated with a significant level of stigmatisation in the society in general (Johnson et al., 2015; Gove et al., 2016).

One of the qualities of professionalism in the healthcare setting is the ability to seek and share advice on issues regarding health, including AD. When asked about discussing the issue of early diagnosis with professional colleagues, even though some GPs stated that they had fewer AD patients to initiate discussion, GPs that engaged with others felt strongly that the support on early

screening was inadequate in this regard. The GPs were of the opinion that mentoring, training and adequate resources were essential to empower the primary care medics to deliver effective diagnosis and management of AD. The findings of this study provide an insight into the needs of professionals to be trained in this area and corroborate the findings of other researchers (Simon et al., 2014; Blom et al., 2016; Curran & Wattis, 2016; Maresova et al., 2016) indicating the need for specialist training of healthcare professionals in the primary care setting. This is to ensure that GPs can manage multiple comorbidities simultaneously and provide high-quality health care to meet the public expectations and the standards set by the Care Quality Commission (CQC). Moreover, the fewer prevalence of the disease could be a yardstick to trigger a debate as to how the services could attract individuals with the disease.

Information sharing stretched beyond the professionals in the healthcare settings to as far as the patients' families and friends. Arguably, the majority of the participants spoke about the fact that reliable information about the signs and symptoms of AD were often collected from trusted families and friends and sometimes the healthcare receptionist. The result of this study supports the findings of other studies (El Haj, 2016) that indicate the challenges of retrieving information from AD individuals and echo those that reports that trusted information can reliably be received from informants (Rueda et al., 2015; Amariglio et al., 2015). The result further emphasises the need for effective communication and collaboration between professionals and patient's families and friends for effective healthcare delivery. On the contrary, genuine report of symptoms by AD individuals has closely been linked to social, cognitive and functional symptoms of AD (Jacova et al., 2013), indicating that information derived from the patients themselves is beneficial (Morris et al., 2014). Hence, there is a need for early diagnosis before the stage of AD dementia with irreversible memory loss.

AD is a disease that was initially associated with ageism due to the high prevalence in the elderly population; however, it is a known that the disease also affects the young, in a less frequent but often more dramatic way (Klimkowilz et al., 2014). Due to the fact that the prevalence increases with age, findings in this study indicate that the elderly population is not treated with the same enthusiasm as the younger generation. The findings further imply that the mistreatment of the aged is applicable to health care professionals and the society at large. A recent report by Tullo et al. (2015) on medical professionals indicates there is a lack of sympathy by this group towards the aged. Concern around this finding has led experts and policymakers to call for more training for the

medical students on geriatric medicine (Gordon et al., 2013; Masud et al., 2014; Cullinan et al., 2015). The call by the GPs for an annual check-up for those 65 years and above could also help diagnose AD earlier in this group.

6.4 Conclusion

The study highlights important changes that would facilitate the earlier diagnosis of AD, which would enable the effective use of healthcare professionals' time and financial resources available to the NHS. The identification of early signs and symptoms of AD may be beneficial to GPs and PC patients - providing a timely therapeutic intervention and support to all involved.

6.4.1 Implication for research, policy and practice

The interviews were held with a relatively small group of GP participants and cannot necessarily be generalised. Although the responses from most of the participants were broadly similar, the restriction of participants to only two CCGs may reflect perspectives within a narrow geography rather than at national level. While other researchers (Iacobucci et al., 2016; Lewis et al., 2016) have identified challenges faced in the primary care including the timing of consultation, the need for training of GPs, memory loss as a determinant to initiate an AD diagnosis and issues of stigmatisation in dementia awareness, this study goes further. The research highlights the views of the GPs regarding the early signs and symptoms of the disease, issues surrounding the late diagnosis and their recommendations to early detection of AD. Additionally, issues including isolation and lack of continuity of care as a hindrance to early detection of AD are discussed. Research is advocated in this regard to know if these views can be generalised with regards to the early diagnosis of the disease.

The limitation of the sample size means that conclusion cannot be drawn from the results of the interviews; policy implementation cannot be solicited at the moment until a wider audience within a wider geographical area that is a representation of all GPs is interviewed. However, the result has implications for practice, as GPs could consider issues of training and more awareness of the early signs and symptoms that could limit the emphasis on memory loss as a determinant to initiate a diagnosis in concerned areas. This could be beneficial even before the issues in the primary care are considered for policy implementation.

6.4.2 Study strength and Limitations

This study provides a summary of the perceptions of a representative/number of GPs regarding the constraints of ten minute consultation times, and the inability to provide continuity of care as the main contributors to late diagnosis of AD. Furthermore, they acknowledged that they do not always recognise the early signs and symptoms of AD in patients, hence the need to develop a predictive model which can be used within the PC setting. To the best of our knowledge, this is the first interview of GPs perspective on the early signs and symptoms of AD, issues surrounding the late diagnosis and their recommendations to factors against the delay in early diagnosis.

A limitation of the study is that the interviews were held with a relatively small group of GP participants and cannot necessarily be generalised. Although the responses from most of the participants were broadly similar, the restriction of participants to only two CCGs prevents its generalisation.

CHAPTER SEVEN: Final discussion and conclusion

7.1 Overview

This chapter describes and discusses the findings of the mixed method approach used in this thesis. The methods used were: a systematic scoping review of literature undertaken to map, synthesise and appraise the quality of existing evidence on the timing and sequence of signs and symptoms that justify the clinical diagnosis of AD; a retrospective medical record review using a case-control design to identify patterns in signs and symptoms preceding the clinical diagnosis of AD in general practice notes and patients' records, as these were presented by the AD patients before their clinical diagnosis; and semi-structured qualitative interviews that explored the perspectives of GPs regarding factors that may contribute to a late diagnosis and recommendations for overcoming barriers to timely diagnose AD.

7.2 Summary of results and broad implications

The early signs and symptoms of typical AD include memory loss with or without cognitive and behavioural changes, while the atypical presents without memory loss. Of the already known signs and symptoms, there are no patterns to distinguish the timing and sequence of these presentations from other diseases, as previous research has focused on identifying the symptoms without emphasising patterns, which is paramount to early diagnosis. Other researchers (Chen et al., 2001; Craig et al., 2005; Vos et al., 2013) have identified the advanced symptoms of the disease at the stage of dementia or after the disease establishment. So far, the diagnosis of AD according to the current diagnostic criteria (Dubois et al., 2014), is weighted on biomarkers without specificity of the pattern in signs and symptoms (Molin et al., 2016).

This study sought to investigate and offer the opportunity to establish patterns in signs and symptoms of the disease ten years' pre-diagnosis to suggest the development of a predictive model for early diagnosis of the disease, as the degenerative process takes between 10–30 years before the symptoms are reported. Furthermore, issues surrounding the late diagnosis of AD and recommendation to early diagnosis are presented from the GPs' point of view.

In relation to the identification of signs and symptoms, of the established fourteen signs and symptoms of AD, only anxiety, episodic memory loss, weight loss, depression, hallucination, irritability and appetite disorders were significantly associated with AD, with sleeplessness being

present in only one case. These could be due to the sample size, as there were few studies on the timing and sequence of AD and issues in the primary care. Other signs and symptoms that emerged from the RMRRS and interviews indicated headache, backache, dizziness, drowsiness, flatulence, loss of appetite and dehydration. However, gastrointestinal disturbances (flatulence, loss of appetite and constipation) were reported as side effects of medications (Matsunaga et al., 2015; Wischik et al., 2015).

The findings in this study, presented in chapters four, five and six, support previous studies indicating memory loss as an early mechanism and in the predementia stage (Arshavsky et al., 2010; Bateman et al., 2012; Mortamais et al., 2016). For example, memory loss was indicated as the first symptom in the EAOD and LOAD in the systematic scoping review and the interviews. The interview findings could be associated with the fact that AD is suspected if memory deficits are exhibited during the medical and physiological examinations. This was also noted in previous research (Santacruz & Swagerty, 2001), therefore could be considered as the first presenting symptom. Other signs and symptoms mentioned in the interviews as presenting first included anxiety and depression. Indeed, patients sometimes presented early with mood changes, supporting the hypothesis that depression is an early mechanism of AD (Rosenberg et al, 2015). However, depression could be a reverse causality, as it has been suggested as a risk factor for AD, with an overlap between the symptom and AD (Novais & Starkstein, 2015).

In the RMRRS, findings indicated that auditory disturbances in the form of tinnitus presented way beyond memory loss, especially in white females. This supports findings of other studies that memory loss is not the earliest presenting symptom (Oppenheim, 1994; Petersen et al, 2014), highlighting the fact that individuals with AD have higher odds of auditory disturbances in the early stage. Individuals presented with the disturbance 30 years before the diagnosis, indicating that it is an early symptom of the disease process. However, the symptom has not fully been investigated in AD, except auditory hallucinations and could also be a reverse causality or a confounder. To the best of my knowledge, there is no study that has investigated the relationship of auditory disturbances and the onset of AD, apart from studies looking into auditory hallucinations in psychosis in AD (Jeste et al., 2000) and psychiatric symptoms of AD (Arnold et al., 1998; Ballard et al., 1999; Murray et al., 2014; El Haj et al., 2017). Although we found that auditory disturbances may be associated with AD, this may be the case for other diseases too, so it will be interesting to look for associations with other dementia conditions.

Participants included in the study were diagnosed according to the NINCDS-ADRDA diagnostic criteria, with a MMSE score of 15 and above. Findings in the systematic scoping review indicate that the memory score of 25 in individuals at risk of the autosomal dominant AD could discriminate those at risk of conversion to AD. Even though there is no evidence supporting MMSE as a standalone test, the score could help identify individuals with autosomal AD for the more sophisticated diagnostic tool.

In addition, the systematic scoping review of the literature revealed 35 additional focal symptoms identified in individuals with RPAD. The focal symptoms and signs were consistent with a form of prion disease (CJD), including myoclonus and rigidity. A third of RPAD experienced rapid weight loss and had sleep disturbances, indicating their significance in discriminating the disease from other dementias. The rapid weight loss supports other findings indicating weight loss as an early sign. Ironically, other studies indicate that weight loss could be a sign of severe cognitive impairment, therefore not an early sign (Soto et al., 2012; Besser et al., 2014).

A longitudinal study (Tyas et al., 2001) and a case-control (Breteler et al., 1991) implicated headache/migraine as a risk factor for AD, with Matsunaga et al. (2015) suggesting it as a side effect of AD medications. In my RMRRS, AD individuals exhibited the symptoms with a mean age of 26.8 years before clinical diagnosis of the disease. The symptom was more common in the white males and mixed-race females as an early upstream mechanism. However, the symptom could be a risk factor, supporting previous literature indicating that the symptom is a risk factor for AD (Breteler et al., 1991; Tyas et al., 2001). There is a misconception that a chronic headache is not a serious problem and primary headache disorders are rarely professionally diagnosed (Olesen, 2013; Luna, 2016). Yet, it is estimated that a chronic headache for at least 15 days affects 2.4% and migraine 10% of individuals at some point in their lives. This is an indication that more research is required to establish the true relationship of this symptom to AD.

Lower backache was another symptom experienced by the AD groups and consistent with white females in the RMRRS. Individuals with the symptoms were 58% odds of being associated with AD. Lower backache has not been investigated in AD, except for lumbar puncture in AD (Peskind et al., 2009) and AD caregivers 'burden' (Shaji et al., 2003). This report calls for more research to understand whether backache is an early symptom in AD or not.

Additionally, the semi-structured interviews of GPs highlights and feeds into our understanding of GPs' perceptions on issues in general practice that contribute to the late diagnosis of the disease.

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The GPs reported the constraints of ten minute consultation times and the inability to provide continuity of care as the main contributors to late diagnosis of AD. Furthermore, they acknowledged that they do not always recognise the early signs and symptoms of AD in patients, hence the need to develop a predictive model which can be used within the PC setting. These perceptions are also consistent with recent literature (Dubois et al., 2016) indicating the constraints of the consultation time and lack of resources in the primary care and the NHS. These findings could be replicated by researchers and noted by policymakers to facilitate the provision of quality, evidence-based and person-centred care to individuals, especially the elderly, which will support an early diagnosis for better care outcomes.

The treatment of the ageing population was also a core theme in the semi-structured GP interviews, which was seen as unsatisfactory and bias. The interviews with GPs revealed that the elderly population is not treated with the same enthusiasm as younger generations by medical professionals. A recent report by Tullo, Khoo and Teodorczuk (2015) on medical professionals indicates there is a lack of sympathy of GPs towards the aged. Concern around this finding has led experts and policymakers to call for more training for medical students in geriatric medicine (Cullinan et al., 2015; Gordon et al., 2013; Masud et al., 2014). The call by the GPs for an annual check-up for those 65 years and above could also help diagnose AD earlier. AD is a disease that was initially associated with age due to the high prevalence in the elderly population, however, it is a known that the disease also affects the young, in a less frequent but often more dramatic way (Klimkowilz et al., 2014); it is pertinent to provide patient centred care irrespective of age. This will also reduce the burden of the disease on the health care system, as the burden arises more from disability than mortality (Prince et al., 2015).

The GPs' interviews also indicated that some individuals suspected of having AD and their families felt early diagnosis was irrelevant simply because they felt they were going to die anyway and there was no treatment to cure the disease. Such views are supportive of the critics of early diagnosis on the basis of identifying a disease without the options of treatment (Mattson et al., 2010; Gauthier et al., 2013). However, there are interventions that could slow the disease process, giving individuals more time with their families or the opportunity to make informed choices about their care and other issues. More information and awareness will help to educate patients on the importance of an early diagnosis and the interventions available.

7.3 Strengths and limitations of the study

The major strength of this study is the use of mixed methods to collect the information needed for this research, as the study had a robust and diverse collection of data to achieve the aim of the research. The study also benefitted from the use of general practice data, which is the primary data collected at the first point of contact with patients and gives first class/reliable information on the presentations at an early stage of AD. The general practice data used for the RMRRS afforded the researcher with the opportunity to ascertain the length of time from the presentation of the first symptom/sign to the clinical diagnosis of AD. This accorded the study the title of a retrospective longitudinal study.

Additionally, the research utilised a broad range of statistical analyses to identify the patterns in presentations; the systematic scoping review adopted the descriptive analysis, while the RMRRS utilised logistic regression and the semi-structured interviews used a framework analysis. An expert in the field of statistics, who is also one of my supervisors (Dr Pang), was involved to ensure that the process was reliable and valid. The researcher underwent a series of statistical training including STATA, MedCalc, SPSS and training on the Clinical Practice Research Database (CPRD) for technical expertise on statistical analysis, even though STATA and the CPRD data were not available for this analysis.

Furthermore, this study presents the first analysis of the sequence and timing of patterns of the signs and symptoms using primary care data and GP interviews, which adopted a sound methodological approach with varied samples and appropriate protocol for each study. The semi-structured interviews gave the GPs the freedom to explore wider issues and experiences in a conducive environment, thereby providing a broader understanding of the research topic in primary care that could confound the identification of the early signs.

Unlike other studies that derive information of the presentations of AD from informants, this study is free of confounding effects of misinformation, as these signs and symptoms were presented by the patients personally and timely. Hence, appropriate for identifying the sequence and timing of the disease. A longitudinal study would have been better to collect the early signs and symptoms of a disease with a long latency period as this, but impracticable in PhD research. However, the research involved a systematic scoping of studies that included a longitudinal study, while the RMRRS took the place of a longitudinal retrospective study, as primary care data is considered an

excellent choice in assessing conditions with a long latency period and rare occurrence of diseases including AD (Wu & Aston, 1997; Ickowicz, 2006).

The research also gathered information from the perceptions of professionals (GPs) dealing with individuals with AD as the first point of contact, thereby making the data reliable and valid. This is because GPs are in a unique position to assess the signs and symptoms as well as issues surrounding the late diagnosis of the disease. Even though each diagnostic criterion has its own merits and demerits, the RMRRS samples were diagnosed by the NINCDS-ADRDA, successful and reliable diagnostic criteria for the diagnosis of probable late onset AD with a sensitivity of 81% and specificity of 70% (McKhann et al., 1984; Knopman et al., 2001), and widely used in clinical trials and research. Although there has been a refinement of the criteria, it is still widely used and acceptable in research.

There are limitations that need to be acknowledged, as the data collected was insufficient to generalise the results in the RMRRS. A random sampling was not possible, which might have introduced a sampling bias. Nonetheless, the next best available sampling method, consecutive sampling that includes all prevalence available, was used. Moreover, the patterns could only be drawn for LOAD for the RMRRS, as cases of the disease diagnosed in the GP surgeries, which were included in the RMRRS, were above 65 years and typical indicating late onset typical AD. Consequently, there is the need for future studies to ascertain the patterns in subgroups of AD.

7.4 Implications for future research

At this stage, it is imperative to address implications for future research, policy and practice.

7.4.1 Research implications

The RMRRS findings indicate that individuals with AD have higher odds of auditory disturbances at the early stage of the disease, which could potentially help identify individual with the disease early. Headache and backache were reported in some individuals in the RMRRS, even though headache has only been reported as a risk factor and backache as a side effect of medication. Future research could explore more precisely the relationship between AD and these symptoms, especially at the early stage of the disease, as these findings highlight the need for further research in this area and the early detection of AD. Further research is advocated with sufficient data that is diversified and can be generalised, to draw explicit patterns on the different types and stages of AD regarding their

sequence and timing for the development of a predictive model for early detection. Researchers are encouraged to utilise the CPRD database that is diversified, reliable and valid for this purpose as patient-level data collected by professionals in general practice is up to standard with additional resources for a variety of purposes, including one such as this (William et al., 2012). Moreover, a new model for early diagnosis will be criteria that incorporate a topographic pattern of trajectory while supporting the pathology of the disease, as new validated criteria are essential to detect changes at the earliest stage of the disease.

7.4.2 Policy implications

This research highlights the issues in the primary care regarding the early signs and symptoms, early diagnosis and recommendations to timely diagnosis of the disease. The NHS and policymakers should consider these and aim to reduce the inequalities in health care, especially with the care of the elderly, as the prevalence of AD is high in this group. Policy should be reviewed by allocating more time for consultations and adequate material and manpower resources, as this will provide an opportunity to detect signs and symptoms at the earliest possible time, not just for AD, but for other diseases with a long latency period. This would allow the timely intervention to reduce the progression and burden of the disease. Late diagnosis of AD is not only detrimental to the individual's life but impacts on the health, emotions and economy of family members and healthcare institutions in general (Albers et al., 2014; Takizawa et al., 2015). Positive outcomes in patients will reduce the resources spent in health care, especially the institutionalisation of AD dementia patients. This is because the results presented in this study align with other studies indicating the issues in primary care and the NHS in general and the effect this has on the diagnosis of AD in the early stages. Early diagnosis is considerably beneficial (Sperling et al., 2011; Dubois et al., 2015; Dubois et al., 2016) not just to the patient, but to the general populace and health care.

7.4.3 Public health implications

The findings in this study also indicate issues of isolation in the elderly and not treating them with the same enthusiasm as the younger generations, which delays the ability to notice the signs early. These findings have significant public health implications as they could be barriers to early detection of the disease. Therefore, there is the need for greater awareness of issues surrounding the elderly. Public health should aim to distinguish barriers for easy access to health care, by providing adequate information to the general public and taking steps to improve the welfare of the elderly, which will,

in turn, reduce the cases of self-isolation and late diagnosis of the disease by identifying cases at the early stage.

7.5 Contributions to knowledge

Findings from previous studies on the AD have isolated and highlighted the early signs and symptoms of AD, especially at the MCI level to dementia, however, little is known about the sequence and timing of these presentations before the clinical diagnosis of the disease. This study contributes to three main areas in AD. Firstly, it extends the existing knowledge on the signs and symptoms, presenting the sequence and timing of the early signs and symptoms previously identified as well as new, as these were presented by patients before the clinical diagnosis in the primary care, that is, even before the MCI stage. These symptoms included headache with a mean time of 26.8 years before diagnosis, depression at 16.4 years, auditory disturbance at 14.5 years, backache at 9.2 years, episodic memory at 3.4 years and hallucination at 3.8 years. Furthermore, the study adds knowledge to the field of diagnosis by providing information to help identify patterns in early signs and symptoms in a large cohort, which could be used to develop a model in primary care as the only non-invasive cost-effective tool for early detection of AD. Secondly, the research adds knowledge as it is the first to collect clinical data to identify patterns in signs and symptoms of AD before diagnosis. Thirdly, the research provides useful information regarding the views of experts in primary care on early signs and symptoms, issues surrounding late diagnosis and recommendations to early detection of the disease. In general, the study provides evidence for the early presentation of AD to be investigated further with a large sample in primary care.

7.6 Future research

There is the need to replicate the findings of this study, which identified patterns in the sequence and timing of early presentations of AD and isolated new ones, using a larger scale sample. This is to further validate and confirm if the result is the same in other groups or cohorts. In particular, it would be beneficial to establish the relationship between auditory disturbances and AD in a large cohort as well as subgroups, which may provide the information needed to isolate the different subgroups of AD and other dementias, discriminating individuals at risk of conversion to the AD in general.

7.7 Conclusions

The heterogeneity concerning the three main determinants of preclinical AD, including normal cognition, cognitive decline and pathophysiological syndrome, due to the dearth of data (Epelbaum et al., 2017) has contributed to the late diagnosis of the disease, so this study sought to identify patterns in the signs and symptoms preceding the clinical diagnosis of AD. Even though the data was insufficient for generalisation, a statistical analysis was undertaken, which reported the sequence and timing of signs and symptoms preceding the clinical diagnosis of AD from primary care data. In particular, auditory symptoms were identified in individuals with AD and headache was reported as an early sign, but whether headache is a risk factor or a symptom remains to be established. The researcher is advocating for further research, using a large diverse sample that is sufficient to detect changes for generalisation of the results.

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APPENDICE

APPENDIX I: North of Scotland Research Ethics approval.

North of Scotland Research Ethics Committee
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

NHS
Grampian

05 May 2016

Ms Fidelia Bature
University of Bedfordshire
Park Square
LUTON
LU1 3JU

Dear Ms Bature

Study title:	**PATTERN OF SIGNS AND SYMPTOMS PRECEDING THE DIAGNOSIS OF ALZHEIMER'S DISEASE. A QUALITATIVE INTERVIEW**
REC reference:	16/NS/0034
IRAS project ID:	195174

Thank you for your letter of 4 May 2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Lead Reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Sarah Lorck, nosres@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Covering letter on headed paper: Cover letter - response	v3	04 May 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	20/07/2015	20 July 2015
Interview schedules or topic guides for participants: Interview Guide	v2	25 April 2016
IRAS Checklist XML		04 May 2016
Information on Qualitative Training	v2	25 April 2016
Participant consent form	v3	04 May 2016
Participant information sheet (PIS)	v3	04 May 2016
REC Application Form	195174/942883/1/92	15 March 2016
Referee's report or other scientific critique report: Supervisor's Comments	1	14 March 2016
Referee's report or other scientific critique report: Evidence that Supervisor's Comments have been taken on board	v2	25 April 2016
Referee's report or other scientific critique report: Dr Pang's Letter	v2	23 April 2016
Research protocol or project proposal	v2	25 April 2016
Summary CV for Chief Investigator (CI): Fidelia Bature	1	14 March 2016
Summary CV for supervisor (student research): Dong Pang	1	14 March 2016
Summary, synopsis or diagram (flowchart) of protocol in non technical language: A6-1 Revised Summary	v3	04 May 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

<u>Reporting requirements</u>

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

<u>Feedback</u>

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <u>http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance</u>

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <u>http://www.hra.nhs.uk/hra-training/</u>

16/NS/0034	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

**pp'd on behalf of
Professor Nigel Webster
Chair**

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Dr Dong Pang
                       Professor Gurch Randhawa, University of Bedfordshire

Appendix II: London-Central Ethics approval.

NHS

Health Research Authority

London - Central Research Ethics Committee

3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 1048 007

> Please note: This is the favourable opinion
> of the REC only and does not allow you to
> start your study at NHS sites in England until
> you receive HRA Approval

27 September 2016

Ms Fidelia Bature, PhD student
Institute of Health Research
Putteridgebury Campus
University of Bedfordshire
Luton
LU2 8LE

Dear Ms Bature

Study title:	Identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's Disease.
REC reference:	16/LO/1521
IRAS project ID:	212908

Thank you for your letter of 22 September 2016 responding to the Proportionate Review Sub-Committee's request for clarification on the above study.

The revised documentation has been reviewed and approved by the Sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Elaine Hutchings, NRESCommittee.London-Central@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Copies of advertisement materials for research participants [SURGERIES INVITATION]	Version 2, 25/08/2016	25 August 2016
Covering letter on headed paper [COVER LETTER]	VERSION ONE, 28/07/2016	28 July 2016
Covering letter on headed paper		17 August 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [INSURANCE INDEMNITY CERTIFICATE.]	VERSION ONE, 28/07/2016	28 July 2016
IRAS Application Form [IRAS_Form_01082016]		01 August 2016
IRAS Checklist XML [Checklist_01082016]		01 August 2016
IRAS Checklist XML [Checklist_26082016]		26 August 2016
IRAS Checklist XML [Checklist_22092016]		22 September 2016
Letters of invitation to participant [Invitation to surgeries]	2	25 August 2016
Other [Data abstraction form]	VERSION ONE, 28/07/2016	28 July 2016
Participant consent form [INFORMED CONSENT]	VERSION ONE, 28/07/2016	28 July 2016
Participant information sheet (PIS)	Version 2, 25/08/2016	25 August 2016
Research protocol or project proposal [RESEARCH PROTOCOL]	VERSION ONE, 28/07/2016	28 July 2016
Response to Request for Further Information		22 September 2016
Summary CV for Chief Investigator (CI) [BATURE CV]	VERSION ONE, 28/07/2016	28 July 2016
Summary CV for supervisor (student research) [SUPERVISOR CV]	VERSION ONE, 28/07/2016	28 July 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

<u>Reporting requirements</u>

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

<u>Feedback</u>

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/LO/1521	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Elaine Hutchings

pp
Dr Andrew Hilson
Chair

Email: NRESCommittee.London-Central@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *PROFESSOR GURCH RANDHAWA, University of Bedfordshire*

AppendixIII: Health Research Ethics approval.

NHS

Health Research Authority

Ms Fidelia Bature
PhD student
University of Bedfordshire
Institute of Health Research
Putteridgebury Campus
University of Bedfordshire
Luton
LU2 8LE

Email: hra.approval@nhs.net

21 December 2016

Dear Ms Bature

Letter of HRA Approval

Study title:	Identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's Disease.
IRAS project ID:	212908
REC reference:	16/LO/1521
Sponsor	University of Bedfordshire

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

1. Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **212908**. Please quote this on all correspondence.

Yours sincerely

Beverley Mashegede
Assessor

Email: hra.approval@nhs.net

Copy to: Professor Gurch Randhawa (University of Bedfordshire), Sponsor Contact
             Lead NHS R&D Contact

             Dr Dong Pang, Academic Supervisor

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Contract/Study Agreement [Statement of Activities]		21 December 2016
Copies of advertisement materials for research participants [SURGERIES INVITATION]	Version 2, 25/08/2016	25 August 2016
Covering letter on headed paper [COVER LETTER]	VERSION ONE, 28/07/2016	28 July 2016
Covering letter on headed paper		17 August 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [INSURANCE INDEMNITY CERTIFICATE.]	VERSION ONE, 28/07/2016	28 July 2016
IRAS Application Form [IRAS_Form_01082016]		01 August 2016
IRAS Application Form XML file [IRAS_Form_01082016]		01 August 2016
IRAS Checklist XML [Checklist_22092016]		22 September 2016
Letters of invitation to participant [Invitation to surgeries]	2	25 August 2016
Other [Schedule of Events]		21 December 2016
Other [INVALIATED APPLICATION]	VERSION ONE, 28/07/2016	22 March 2016
Other [Data abstraction form]	VERSION ONE, 28/07/2016	28 July 2016
Participant consent form [INFORMED CONSENT]	VERSION ONE, 28/07/2016	28 July 2016
Participant information sheet (PIS)	3	15 December 2016
Research protocol or project proposal [RESEARCH PROTOCOL]	VERSION ONE, 28/07/2016	28 July 2016
Response to Request for Further Information		22 September 2016
Summary CV for Chief Investigator (CI) [BATURE CV]	VERSION ONE, 28/07/2016	28 July 2016
Summary CV for supervisor (student research) [SUPERVISOR CV]	VERSION ONE, 28/07/2016	28 July 2016

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Gurch Randhawa
Tel: 01582743797
Email: gurch.randhawa@beds.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	The participant information sheet has been updated to bring it in line with HRA Approval standards via a minor amendment.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor intends to use a Statement of Activities as the form of agreement with participating NHS organisations.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study.
4.3	Financial arrangements assessed	Yes	No application for external funding has been made. No funds will be provided to the participating organisation to support this study.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	Provisional Opinion was issued on 12 August 2016. Favourable Opinion was issued on 27 September 2016.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Yes	No comments
6.3	Devices – MHRA notice of no objection received	Yes	No comments
6.4	Other regulatory approvals and authorisations received	Yes	No comments

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Participating NHS Organisations in England

This is a non-commercial student (PhD) and there is one site type

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**.

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

A Principal Investigator is expected at each participating organisation.

GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

No access arrangements are expected for this study as screening and anonymisation of data will be undertaken by local GP staff.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

The applicant has indicated that they <u>do not intend</u> to apply for inclusion on the NIHR CRN Portfolio.

Appendix IV: University of Bedfordshire Ethics approval.

University of
Bedfordshire
Institute for Health Research
Putteridge Bury
Hitchin Road
Luton
Beds LU2 8LE

18 May 2016

Fidelia Bature
Student number: 0913452

Dear Fidelia Bature
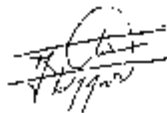
Re: IHREC Application No: IHREC630

Project Title: Identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's disease.

The Ethics Committee of the Institute for Health Research has considered your application and has decided that the proposed research project should be approved with no amendments.

Please note that if it becomes necessary to make any substantive change to the research design, the sampling approach or the data collection methods a further application will be required.

Yours sincerely

Dr Yannis Pappas
Head of PhD School, Institute for Health Research
Chair of Institute for Health Research Ethics Committee

APPENDIX V: Letter of request for support sent to GP surgeries.

My name is Fidelia Bature, a 2nd year Ph.D. student at the University of Bedfordshire. I am undertaking a research on signs and symptoms preceding the diagnosis of Alzheimer's disease, to identify patterns in presentations and develop a predictive model for early detection.

The rationale is that early detection of AD delays the progression and enables individuals to live independently and there is a need for a non-invasive, inexpensive and observable detective measures that can be used in the primary care settings, to complement the biomarkers examination.

I will be looking into the anonymous and coded patient data in the GP surgeries and interview GPs in Milton Keynes. The review will be carried out within a period of six months to a year while the GP interview takes between half to an hour. My supervisors and I are delighted to have the full support of the Clinical Commissioning Group (CCG) and on board already are some GPs and their surgeries. GPs who engage with the study will be offered Membership to the Milton Keynes General Practice consortium, which will be cited in any publications generated from this study.

I will be grateful to discuss the project proposal with you at your convenience and have you engage with the study, as it has the potential to improve outcomes for patients with Alzheimer's disease. I am currently applying for ethics approval for the review study through IRAS (NHS, REC), which is the health regulatory authority that is an exception to the ethical and legal requirement of an informed consent. My supervisors (Dr. Dong Pang, Dr. Barbara Guinn & Dr. Yannis Pappas) and I are keen to know who might be interested in engaging with the study to ensure the application is appropriately worded. The ethics for the interview was sought and approved by the Research Ethics Committee, which is available on request.

Kindest regards,

Fidelia Bature.

University of
Bedfordshire

LATE DIAGNOSIS OF ALZHEIMER'S DISEASE: RECOMMENDATION TO OVERCOME BARRIERS IN THE UK.
SEMI- STRUCTURED INTERVIEW GUIDE, FOR GENERAL PRACTITIONERS (GP) IN MILTON KEYNES.
Previous research indicates that late diagnosis of Alzheimer's disease (AD) is a major challenge to public health in general. One in four individuals with AD has been diagnosed in the UK; it sometimes takes two to three years before a diagnosis is confirmed (HSCIS, 2014). Late diagnosis can result in accelerating the progression of the disease to a state of cognitive and functional decline, leading to extended hospital stays, an increase in health care costs and subsequent mortality. There is also a burden on the caregivers and a financial impact on health and social care institutions.

This interview guide was developed after the review of the relevant literature and consultations with my supervisors. This is a semi-structured interview guide, structured around six themes namely:

1. INTRODUCTION/ DEMOGRAPHIC QUESTIONS
- How long have you been practicing as a medical practitioner?
- How long have you been a partner/associate in this practice?
- Can I ask how old you are? (A) 28-38, (B) 38-48 (C) 48-58 (D) 58+

Specific Questions
2. EARLY SIGNS AND SYMPTOMS OF AD
- What are the signs and symptoms you notice in patients before their official diagnosis with AD?
- How long before the diagnosis do you start to notice these signs?
- Which sign or symptom appears first among those you've mentioned?
- Have these signs and symptoms subsequently aided with the diagnosis?

3. DIAGNOSTIC CRITERIA
- What are your GP surgery diagnostic criteria for AD?

4. LATE DIAGNOSIS OF AD
- Are there issues that delay an earlier diagnosis of AD?
- What are the issues you have observed with the late diagnosis?

Follow –up
You mentioned _____do you mean?
Could you expand on that, please?

5. BENEFITS OF EARLY DIAGNOSIS OF AD
- Let's talk about the early diagnosis, how do you feel about early detection and diagnosis of AD?

- Could you please explain that further?
- Are there benefits or challenges with the early diagnosis?
- Can you elaborate more on the challenges with the early diagnosis?
- How has this impacted on your practice?
- You mentioned the benefits to the patient, carers, and society; can you elaborate and be specific on this, please?

6. DIAGNOSING AD IN GP PRACTICES

- How easy is it to diagnose an individual with AD in practice?
- Are there specific challenges to diagnosing AD in your practice?
- Are there specific challenges to you as a general practitioner?
- On a scale of 1-10, how would you assess the diagnosis of AD in terms of the early signs and symptoms in your practice?

Indirect Questions
- Have you discussed this issue of late diagnosis of AD with your colleagues? How do they feel about it?

Probes
- Do you mean that?
- Is it correct to say that you_____?

Follow up questions
- Could you expand on that please?
- Do you have further explanation or examples of this?
- Is there anything you'd like to say that you haven't had the chance to say? If you think of anything else, please do email or call me.

Thank you for taking part in this study ;as mentioned in the information sheet, the result of this interview will be anonymised and the data made available to you on request. You will be offered a chance to be an author in the form of Milton Keynes and Luton GP consortium, on any paper which emanates from the study. Thank you once more

Appendix VII: Participants information sheet (interviews).

PARTICIPANTS' INFORMATION SHEET.

This participants' information sheet is for the general practitioners in Milton Keynes and Luton who are invited to participate in research, titled "Identifying Pattern in Signs and Symptoms Preceding the Clinical Diagnosis of Alzheimer's Disease".

Fidelia Bature

University of Bedfordshire

Alzheimer's Research

Introduction

My name is Fidelia Bature, a student researcher with the Institute for Health Research, University of Bedfordshire. I am undertaking research on Alzheimer's disease (AD), the most prevalent type of dementia and the current leading cause of death in those 65 years and above in this country. I am informing and inviting you to be part of this research and you are under no obligation to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

What is the study about? Research indicates that there are cases of late diagnosis of patients with Alzheimer's disease. These patients have a greater cognitive impairment and faster progression that leads to an extended period of institutionalisation and increases mortality than those identified earlier in the disease process. We want to find ways of identifying the disease earlier for timely interventions. We want to know your perspective regarding the issue of late diagnosis of AD and your recommendations for improving early diagnosis rates. We also want to know your experience on the early symptoms of the disease because this knowledge might help us to learn how the disease presents itself at an early stage.

Why have I been invited? You are being invited to take part in the research because we feel that your experience as a general practitioner can contribute much to our understanding and knowledge of Alzheimer's disease and it's early detection.

Do I have to take part? Your participation in this research is entirely voluntary. The choice that you make will have no bearing on your job or any work-related evaluations or reports. You might change your mind later and stop participating even if you had agreed earlier.

What will happen if I take part? If you accept, you will be asked to participate in an interview with me. If you do not wish to answer a question during the interview, which will take place in your surgery, you may say so and I will move on to the next question. No one else but the interviewer will be present unless you would like someone else to be there. The information recorded is confidential, and no one else except my University supervisors will have access to the information documented during the interview. The entire interview will be audio-recorded and transcribed, but no-one will be identified by name. All transcripts will be anonymised, using a number instead of your name. Only the researcher will know what this number is and the information will be kept securely under lock and key. The information recorded is confidential, and no one else except my academic supervisors will have access to the transcripts of the interview. The audio-recordings will be destroyed one year after the interviews have been transcribed.

What will I have to do? The research takes place over a two year period. During this time, I will interview you once, which will take about half an hour.

Your participation is likely to help us find out more about how to enable the early diagnosis of AD.

Will my participation be kept confidential and what happens to the information? Nothing that you tell us will be shared with anybody outside the research team, and all information will be kept confidential as required by data protection law. Nothing will be attributed to you by name. Rather, pseudonyms or codes will be used for easy collection and analysis of data.

Quotes from this interview which might be published or used for presentations or training will be anonymised with pseudonyms or codes, without a personal identifier. A consent form is attached for this purpose.

How will the data be linked back to participants?

The data from this study will not be linked back to participants and if at any point clarification is needed, this will be undertaken by the researcher confidentially; otherwise, all data will be anonymised.

What will happen in the case of professional misconduct?

The aim of the study is to identify patterns in the presentation of early signs and symptoms of AD. The researcher will not be in a position to identify professional misconduct or make a judgement on whether professional misconduct occurred. This is because I do not possess the necessary specialist medical knowledge, that is required to make such judgement or observation, and secondly because the data that I will receive will be anonymised for the purposes of the study. For all other cases of professional misconduct, including unacceptable behaviour or poor communication by the health practitioner, I will follow the established protocol which is to inform the Preliminary Proceedings Committee, based in part 144, section B of the Health Practitioners Act 2009.

What will happen to the findings of this study? The knowledge that we will gain from this research will inform a thesis for the partial fulfilment of a postgraduate research degree. Findings can be shared with you on your request. The findings will become available to the public through national and international academic journals and conferences.

Contact for further information: Thank you for your interest in the study. If you would like further information or wish to ask questions later, you may contact any of the following:

Fidelia Bature

Institute for Health Research,

University of Bedfordshire

The United Kingdom.

Email-fidelia.bature@study.beds.ac.uk

OR

Dr. Dong Pang

Director of Study

Institute of Health Research,

University of Bedfordshire

United Kingdom

OR

Professor Gurch Randhawa,

Professor of Diversity in Public Health and Director, Institute for Health Research,

University of Bedfordshire.

Who has reviewed the study? This proposal has been reviewed and approved by the University of Bedfordshire Research Ethics Committee, which is a committee whose task it is to make sure that research

participants are protected from harm. Also, 'The North East-Newcastle & North Tyneside 2 Research Ethics Committee' has reviewed the study.

The study is being supervised by Dr. Dong Pang and Dr. Yannis Pappas, all of the University of Bedfordshire; Dr. Barbara Guinn of the School of Life Science, University of Hull.

Appendix VIII: Consent form for GPs.

Study Number: 195174.

GP SURGERIES CONSENT FORM

TITLE OF PROJECT: Identifying Pattern in Signs and Symptoms Preceding the Clinical Diagnosis of Alzheimer's Disease:

Name of Researcher: FIDELIA BATURE.

Please initial box

I confirm that I have read and understand the information sheet dated............................ (Version ....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my duties or legal rights being affected.

☐

I give permission to publish direct quotes from this interview

☐

I agree with Anonymised quotes from this interview to be used in this research for publication and training purpose.

☐

I agree to be audio/video recorded and I understand that the recordings will be kept secure and destroyed one year after the interviews have been transcribed.

☐

I agree to take part in the above study.

☐

_____   _____   _____
Name of Participant   Signature   Date

_____   _____   _____
Researcher   Signature   Date

Appendix IX: Information sheet for GP surgeries.

University of Bedfordshire

IRAS ID: 212908.

INFORMATION SHEET FOR GP SURGERIES

This information sheet is for the GP surgeries in Milton Keynes and Luton, who are invited to participate in research, titled "Identifying Patterns in Signs and Symptoms Preceding the Clinical Diagnosis of Alzheimer's Disease": A retrospective medical record review study.

Fidelia Bature

University of Bedfordshire

Alzheimer's Research

Information sheet

Introduction

My name is Fidelia Bature, a student researcher with the Institute for Health Research, University of Bedfordshire. I am undertaking a research on Alzheimer's disease (AD), the most prevalent type of dementia and the 5th leading cause of death in this country. I am informing and inviting you to be part of this research. You are under no obligation to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

What is the study about? Research indicates that there are cases of late diagnosis of Patients with Alzheimer's disease. These patients have greater cognitive impairment and faster progression that leads to an extended period of institutionalisation and increases mortality than those early identified. We want to find ways to identify the disease early and administer the right intervention at the right time. This will be undertaking by identifying the early signs and symptoms of the disease through the medical records of patients with AD and those without AD but with the signs and symptoms of the disease, because this knowledge might help us to learn how the disease presents itself at an early stage.

Why has the GP surgery been invited? You are being invited to take part in the research because we feel that as a primary care provider, you are the first point of contact with the patient and therefore, might have data about the patient that could be of importance and contribute to identifying the early signs and symptoms and develop a predictive model for early detection of Alzheimer's disease.

Does the GP surgery have to take part? Your participation in this research is entirely voluntary. The choice that you make will have no bearing on the GP surgery or any work-related evaluations or reports. You might change your mind later and stop participating even if you agreed earlier.

What will happen if the GP surgery takes part? We are asking you to help us learn more about Alzheimer's disease in Milton Keynes and if you accept, we would be delighted to have access to your patients' anonymous data. The information recorded is confidential, and no one else except my supervisors will have access to the information documented from the data. Any information about your patients will have a number on it instead of your patient's names. Only the researcher will have access to this information which will be kept privately under lock and key. The information recorded is confidential, and no one else except my supervisors will have access to the anonymous data. The data will be destroyed after the information has been coded.

What will the GP surgery have to do? Provide data that has been anonymised. The researcher has already developed a data abstraction form for this purpose.

HOW WILL THE PATIENTS SELECTION BE UNDERTAKING?

The design of this study is a case-control study, that is, case notes of individuals diagnosed with the disease and those without the disease, but within the same age group, sex and locality; the researcher will select case notes of those with the disease and the controls base on their age, sex and who have attended the same GP practice. The design has been chosen to help us discriminate the disease from other dementias or neurological conditions.

Will the patients' data be kept confidential and what happens to the information? All information will be anonymised by the GP surgery before receipt by the investigator. Anonymised data will be stored in a computer with a password only known by the researcher and the computer kept secured always.

What will happen to the findings of this study? The knowledge that we will gain from this research will inform thesis for the partial fulfilment of a research degree. Findings can be shared with you on your request. Findings will become available to the public through the national and international academic journals, and conferences.

How will the data be linked back to participants?

The data from this study will not be linked back to participants and if at any point clarification is needed, this will be undertaken anonymously.

What will happen in the case of professional misconduct?

The aim of the study is to identify patterns in the presentation of early signs and symptoms of AD. The researcher will not be in a position to identify professional misconduct or make a judgement on whether professional misconduct occurred. This is because I do not possess the necessary specialist medical knowledge, that is required to make such judgement or observation, and secondly because the data that I will receive will be anonymised for the purposes of the study. For all other cases of professional misconduct, including unacceptable behaviour or poor communication by the health practitioner, I will follow the established protocol which is to inform the Preliminary Proceedings Committee, based in part 144, section B of the Health Practitioners Act 2009.

What will happen to the findings of this study? The knowledge that we will gain from this research will inform a thesis for the partial fulfilment of a postgraduate research degree. Findings can be shared with you on your request. The findings will become available to the public through national and international academic journals and conferences.

Contact for further information: Thank you for your interest in the study. If you would like further information or wish to ask questions later, you may contact any of the following:

Fidelia Bature

Institute for Health Research,

University of Bedfordshire

The United Kingdom.

OR

Dr Dong Pang

Director of Study

Institute of Health Research,

University of Bedfordshire

United Kingdom

OR

Professor Gurch Randhawa,

Professor of Diversity in Public Health and Director, Institute for Health Research,

University of Bedfordshire.

Who has reviewed the study? This proposal has been reviewed and approved by the University of Bedfordshire Research Ethics Committee, which is a committee whose task it is to make sure that research participants are protected from harm. Also, 'The North East-Newcastle & North Tyneside 2 Research Ethics Committee' has reviewed the study.

The study is being supervised by Dr Dong Pang and Dr Yannis Pappas of the University of Bedfordshire; Dr Barbara Guinn of the University of Hull.

Appendix X: Informed consent for practice managers.

INFORMED CONSENT FORM.

I have been invited to participate in research about Alzheimer's disease.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily that the anonymous data from this study be used for the purpose of this study only.

Print Name participant _____

Signature participant_____

Date_____

    Day/Month/Year___/___/____/

Statement by the researcher / person taking the consent:

I have accurately read out the information sheet to the potential participant and to the best of my ability made sure that the participant understands that the following will be done.

1. Anonymous patients 'data will be extracted to identify the early signs and symptoms of AD disease.

2. Other factors related to the early presentation of the disease will also be collected.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participants.

Print Name of Researcher ___Fidelia Bature_____

Signature of Researcher_____

Date_____

    Date/Month/Year___/____/_____/

Appendix XI: Interview script for GPs (General).

Interviewer: It's a pleasure to have you today; as I explained in the participant's information sheet, the research is about identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's disease (AD). This is to develop a predictive model for early detection of the disease, and your being interviewed today is to get your personal experience regarding the early signs and symptoms, issues surrounding the late diagnosis of Alzheimer's disease, as well as your recommendation to barriers against early detection of the disease.

Participant: Ok

Interviewer: The interview should not last more than 30 minutes and I still need to check out some few things with you before we get started.

Participant: Laughter, make it 15, I got to go and see a patient.

Interviewer: Thank you so much

Participant: Well try and shorten it a little bit, alright? Smile

Interviewer: Well I still need to check out some few things with you before we get started.

Participant: Ok

Interviewer: I know you have agreed by signing to take part in this interview, is this still the same?

Participant-: Yea that is perfectly fine.

Interviewer- It is also important to let you know that at any point, if you want to stop or you want a pause, you just let me know and that will be fine. Again, if you do not want to answer any question that will be absolutely fine.

Participant: Interrupted and completed the sentence -say so, that is fine, general laughter

Interviewer: Thank you. Well, as we agree earlier, the interview is part of research and quotes from this interview might be used for teaching purpose; I hope this is still fine with you?

Participant: That is perfectly fine.

Interviewer: Do you have any question before we begin?

Participant: Interruption- No, not really.

Interviewer: That is fine; I will go to the first question…..

Appendix XII: Systematic scoping review protocol.

This is a protocol for systematic scoping review to collect and synthesise evidence on frequency and timing of the signs and symptoms to draw patterns for the detection of AD. The reviewer will investigate and identify how far back from diagnosis the first symptoms reporting that will warrant diagnosis. Gaps in the evidence will be identified for further research.

BACKGROUND

AD is the most common type of dementia and unlike other dementias, it is characterised by the deposition of intracellular amyloid and extracellular tau proteins in the nerve cells, which cause degeneration of the nerve cells. The disease is an insidious disease with a long latency period, which was initially thought to be the disease of old age, as the signs and symptoms are easily mistaken for old age.

In 2015, there was a prevalence of 520,000 in the UK (Alzheimer's Statistics, UK, 2015), with 60,000 mortality directly attributed to dementia yearly. AD is the fifth leading cause of death among the elderly in the UK (Alzheimer's Society, 2014). The high mortality rate is largely attributed to diagnosing the disease at the advanced stage in the majority of cases. Approximately 75% of AD is diagnosed in the advanced stage. Delaying onset of the disease by five years through early diagnosis nd intervention could reduce the mortality rate of dementia (advanced stage of AD) by 30,000 yearly (Dementia 2014 Report Statistics).The late diagnosis could be due to due to diagnostic uncertainties including limited awareness and recognition of symptoms by patients and physicians (Shim et al 2013) and lack of understanding of the transitional point of the asymptomatic and the symptomatic phase (Cassell et al, 2013; Lowe et al, 2014; Alz.Org, 2015). The variable presentation and non-specific signs and symptoms is a challenge to diagnosing the disease early.

Advances in AD research have led to the identification of appropriate biomarkers including amyloid protein and phosphorylated tau that aid the diagnosis of the disease (McKhann et al, 2011, Dubois et al, 2007 & 2014). The diagnosis is supported with two clinical phenotypes. However, the most accurate pattern of the signs and symptoms is yet to be determined. Other markers including the signs and symptoms are not clearly specified in the clinical settings, as studies indicate heterogeneity in the early presentation of the disease. AD can have a significant impact on the cognitive and functional ability in individuals, especially if it is diagnosed late. This affects the quality of life leading to loss of dignity, independence and subsequent institutionalisation of individuals.

DESCRIPTION OF THE CONDITION

The diagnosis of AD is difficult and often late, largely because the disease shares similar symptoms with other conditions including other types of dementia and other neurological conditions like dementia with Lewy bodies, korsakoff syndrome and old age.

AD is a progressive and irreversible brain disease characterised by the depositions of amyloid protein plaques and tau protein tangles in the brain cells. More than 62% of cases of dementia are AD (Alzheimer's Association, 2015). The disease is most common in adults 65 years and above and the prevalence increases as the age progresses. The current understanding of AD suggests that the disease is heterogeneous in the presentation. Advances in AD research have greatly enhanced our understanding of the disease. The early-onset AD (EOAD)which begins at age 60 and below is attributed to rare genes which are inherited by the individual and present frequently with atypical presentations with fewer memory presentations (Klimkowilz et al ,2014). The late-onset AD (LOAD) is attributed to genetic and environmental factors with typical memory presentations, which begins at age 65 and above (Imitiaz et al 2014). The EOAD and LOAD display distinct genetic patterns and different presentations (Casseli et al 2013, Lowe et al 2014, Shoemark et al 2015).

Reviews existing are mostly on neuropsychological predictors of mild cognitive impairment (MCI), the accuracy of these predictors and individual symptoms (Drago et al 2011, Gainotti et al 2014). This review will include the sequence and timing of early presentations of all types of AD.

SYMPTOMS

The progression and the degenerative processes of AD sometimes take between ten to thirty years before the manifestation of the signs and symptoms. Literature (Bateman et al, 2012) indicates that significant changes are yet evidence in the pre-clinical stage which is often asymptomatic with changes in the brain and the risk of progression unknown. Sometimes, an individual might be aware that something is wrong but unable to know what that is unless if this is detected by biomarkers. The pre-clinical stage is closely followed by mild cognitive impairment (MCI) stage with mild symptoms and elevated level biomarkers (Albert et al, 2012). The symptoms frequently reported at this stage include apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, dysphoria, irritability, hallucination and olfactory disturbances and weight loss. The sequence and timing of these symptoms are, however, not clearly defined and sometimes mimic other neurological and psychological conditions making the early detection and diagnosis challenging.

CLINICAL PATHWAY

The first point of contact of symptomatic individuals is the primary care settings, where they undergo series of tests and investigations and memory test, before being referred to the secondary settings for the more advanced diagnostic procedure. The International Working Group (IWG) and the National Institute on Aging-Alzheimer's Association (NIA-AA) have suggested a diagnostic pathway where the disease is diagnosed using the combination of cerebrospinal fluid (CSF) examination for biomarkers and PET scan in combination with two clinical phenotypes for typical and atypical AD (Dubois et al 2015). Dumurgier et al (2013) and a recent multicentre study in the US opined that there is variability in CSF collection methods with intra-subject variability in CSF levels (Lucey et al 2015). The variability also in the signs and symptoms (Casseli et al 2013) and lack of patterns of the signs and symptoms preceding the clinical diagnosis of the disease are major concerns.

RATIONALE

The evidence is suggestive that AD pathology can accumulate decades before the onset of clinical manifestation of the signs and symptoms (Bateman et al 2002, Price et al 2009). Even with the advances in research and diagnostic criteria for AD, the disease continues to be diagnosed late.

In line with the current diagnostic criteria for AD (Dubois et al 2015), the combination of the biomarkers examinations and clear patterns of the signs and symptoms allow better diagnostic outcomes. Accurate and early diagnosis of AD is important to ensure timely therapeutic interventions that are effective mostly at the preclinical stage, to reduce the degenerative process and enable individuals to live independent lives. Therefore, knowing the sequence and timing in the presentation of the signs and symptoms at the early stage of AD is important.

AIM

To map, appraise and synthesise the quality of existing evidence on the signs and symptoms of AD.

OBJECTIVES

1. To identify the sequence and timing of the presentation of signs and symptoms at the early stage of AD, to inform a primary study.

2. To understand how far back from diagnosis the first symptoms that will justify a diagnosis was reported.

METHODS

Criteria for considering evidence for this review include:

INCLUSION CRITERIA

TYPES OF STUDIES

Qualitative and quantitative empirical evidence relating to the impact of the early signs and symptoms on the early detection and diagnosis of AD will be synthesised in the systematic review of studies in developed countries.

PARTICIPANTS

Individuals aged 30-85 years of age, diagnosed with AD, will be reviewed. The age restriction is because the pathophysiology takes between 10-30 years. The incidence of the disease among those 30-40 years is rising (12.7% in 2009) (Harvey et al 2003, Alzheimer's Association Europe 2009) hence the inclusion of these group. The early-onset begins at age 60 and below while the late onset begins at age 65 and above. Studies of individuals with the mixed diagnosis will be considered as long as the outcomes have been reported separately.

INDEX SYMPTOMS

The majority of individuals with AD present with multiple signs and symptoms that begins years before the diagnosis of the disease. Studies have been carried out on the early signs and symptoms but few undertaken on the sensitivity and specificity, as well as the sequence and timing of these presentations. At the early stage, the early symptoms recorded so far include apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, dysphoria, irritability, hallucination and olfactory disturbances and weight loss with a sensitivity and specificity of 14% & 19%; 30% & 99%; 15% & 99%; 16% & 100%;16% & 96% and 47% & 92% respectively (Igbal et al 2013).

The index symptoms as anticipated would be utilised as a tool to develop a predictive model for early detection of AD in the primary care centres to complement the biomarkers examinations.

The review will include combinations of signs and symptoms alone. Studies restricted on single signs and symptoms will be excluded.

TARGET CONDITIONS

All types and stages of AD will be included in the review.

REFERENCE STANDARDS

The potential reference standard for the diagnosis of AD is included which is the standard clinical diagnostic criteria commonly used for AD; the National Institute of Neurological and Communicative Disorders, Stroke and AD and Related Disorders Association (NINCDS-ADRDA) the criteria for probable or possible AD (McKhann et al 2011). Individuals followed-up for less than a year before diagnosis might incorrectly classify the early stage of AD. Judgement will depend on whether the disease can be separated into early stage and late stage of AD. The more recent clinical diagnostic criteria for AD that uses biomarkers to support diagnosis; the National Institute on Aging-Alzheimer's Association (NIA-AA)(Jack et al 2012) will also be considered for the more recent studies that might have used the new criteria. Diagnostic and statistical Manual of the American Psychiatric Association (DSM-IV (American Psychiatric Association, 1994), DSM-5 will also be considered.

Individuals followed-up for less than a year before diagnosis might incorrectly classify the early stage of AD. Judgement will depend on whether the disease can be separated into early stage and late stage of AD.

OUTCOMES

1. The sequence and timing of presentation.

2. The timing between diagnosis and first symptom reporting that justify a diagnosis.

LANGUAGE OF PUBLICATION

No language restriction will be applied to the search

EXCLUSION CRITERIA

Studies focusing on developing countries, other neurological conditions, and non-empirical studies will be excluded. Also, studies on other dementias and late stages of AD where it is not possible to separate data on early stage of AD will be excluded.

SEARCH STRATEGY

This implies the specific terms to use in searching the database and the global approach to searching including the specific database to search.

RESEARCH EVIDENCE

REFWORKS will be used as the referencing software.

The databases to use will include:

•	Specialist literature databases: Ovid MEDLINE (1946), PUBMED (1996), CINAHL (1937) (Ebsco), Psych INFO (1967), Web of Science, Scopus, Nursing Index (1994) and Health Technology Assessment Database (HTA). We would search each database from early inception in other to capture all evidence on the early signs

and symptoms of AD. Hand searching of the reference list of systematic review for signs and symptoms, conference proceedings from Alzheimer's Association and Dissertations Express.

- Specialist systematic review databases: Cochrane register of diagnostic test accuracy studies.

Other literature sources will include Google and Google scholar. Hopefully, this approach should uncover literature to use in the review. There will be a different search term for each database as their parameters could be different (Jefferson et al 2011).

PUBLICATION STATUS

Published articles from a bibliographic database, specialists journals and reference lists from articles will be considered. Unpublished (grey or fugitive literature) or informally reported studies as full papers, including theses, reports, book chapters and conference abstracts, will be included as long as the full study details are available (Song et al, 2000). The studies would have been conducted from primary care centres, memory clinics, hospitals and community populations to capture and established a diagnosis of AD.

COUNTRY OF FOCUS

Countries classified as developed countries due to a high human development index (HDI) by the World Bank, will be included. This is to ensure that the population from the review studies are the same as the study population in terms of economic status, standard of living, infrastructures availability, provision of amenities and locality.

KEYWORDS INCLUDE

In this research, AD includes the two types of AD (EOAD and LOAD). Early detection or diagnosis is different from early-onset AD. The definition is based on the timing of the disease process when the neurodegenerative process has not or slightly began. The early theatre is used rather than the late theatre to allow the reviewer to find studies undertaken at the early stage of AD and report signs and symptoms before the full manifestation of the disease or dementia (the final stage of AD). These studies should have been done retrospective or prospectively within a period of 2-10 years before diagnosis, as the neurodegenerative process takes between 10-30 years before the manifestation of signs and symptoms (Bateman et al 2012), while the early stage is approximated to be six years before diagnosis.

Search one:

AD AND Early detection OR early assessment OR early diagnosis OR early signs OR early symptoms OR early intervention OR dementia OR cognitive imbalance OR mild cognitive impairment OR subjective cognitive decline OR biomarkers OR biological markers OR brain pathology OR neuropsychological tests OR neuropsychological index OR tomography OR cerebrospinal fluid analysis OR mini-mental state examination OR screening OR magnetic resonance imaging OR MRI.

Search two:

AD AND (Early detection OR early assessment OR early diagnosis OR early signs OR early symptoms OR early intervention OR dementia OR cognitive imbalance OR mild cognitive impairment OR subjective cognitive decline OR behavioural symptoms OR psychiatric symptoms OR clinical presentations OR clinical features OR preclinical manifestations OR clinical presentations OR early manifestations OR early presentations OR early detection OR biomarkers OR biological markers OR brain pathology OR neuropsychological tests OR

neuropsychological index OR tomography OR cerebrospinal fluid analysis OR mini-mental state examination OR screening OR magnetic resonance imaging OR MRI) AND (Andorra OR Argentina OR Australia OR Austria OR Bahrain OR Belgium OR Bermuda OR Brunei OR Canada OR Chile OR Croatia OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Faroe Islands OR Finland OR France OR Germany OR Greece OR Holy See (Vatican)OR Hong Kong OR Iceland OR Ireland OR Israel OR Italy OR Japan OR Korea South OR Kuwait OR Latvia OR Liechtenstein OR Lithuania OR Luxembourg OR Malta OR Monaco OR Montenegro OR Netherlands OR New Zealand OR Norway OR Poland OR Portugal OR Qatar OR SanMarino OR Saudi Arabia OR Singapore OR Slovakia OR Slovenia OR South Africa OR Spain OR Sweden OR Switzerland OR Turkey OR United Arab Emirates OR United Kingdom OR United States).

DATA COLLECTION AND ANALYSIS

QUALITY ASSESSMENT

The criteria to assess the data quality includes the Quality Assessment Diagnostic Accuracy Studies (QUADAS-2), which contains assessment domain with signalling questions to select patients, index symptoms and timing (Whiting 2011). The risk of bias will be assessed with the QUADAS standard risk of bias template   that rates studies based on good quality paper, poor quality paper, or uncertain for bias (selection). The result will be summarised in the summary tables and graphs.

MISSING DATA

The researcher understands that missing data could be pervasive. Statistical analysis based only on complete case subsamples could introduce biased estimates and standard error while the impact of the missing value will reduce the sample size and concomitant loss of statistical power based on comparative datasets. However, there are conditions under which missing data can be ignored (Eff and Don 2009, Stekhoven et al 2012), which depend entirely on the relationship between the variable of interest missing and the available variable to help explain the missing value.

 Authors of empirical studies with missing data will be contacted for the full study reports while being clear as to the nature of data required (mean, median or standard deviation value). The data extraction forms might be sent to the authors to complete and authors will be re-contacted again if there is no answer the first time and all correspondents would be logged in as part of the review.

Before then, the researcher will make sure that there are no publications that have been missed from the search that contains the data missing; perhaps a study has been published after the search was completed, without limiting the language of publication, to avoid language bias. If the full data cannot be retrieved after all these, the papers will be excluded. Whatever approach taken will be stated as part of the challenges faced while undertaking the study.

STUDY SELECTION

The screening process will include title screening, abstract screening of primary studies on AD against the inclusion criteria to identify relevant articles and reduce waste of time and resources in reviewing articles that do not meet the necessary inclusion criteria. A title and abstract screening forms have been developed (see Appendix1) and will be pretested before the scoping review.

The second level of review will include the review of the full articles deemed relevant. Articles that are only available in an abstracts format and meet the inclusive criteria will be included at the second level of review while acknowledging their inclusion limitations, to avoid missing out on recently reported studies available only in abstract format (Boland, 2014). All other articles that do not meet the eligibility criteria will be excluded.

EXTRACTION OF DATA

The data extraction forms and tables have been devised and will be piloted from the first five to ten studies using the data-charting form, to know if the data extraction approach is consistent with purpose and questions. Data in a PDF format will be copied and pasted to avoid input errors

The researcher and her three supervisors would extract the data from each source (each supervisor will extract 20% of the data while the 40% will be extracted from the researcher) record and tabulate using Endnote (EN) as a standardised extraction template. Data will be extracted including copies of tables and figures and quality assessed to include objectives and statement, methods, participants, sample size, statistical methods of comparison, analysis and results including outcomes.

DATA SYNTHESIS

Although data synthesis (collating, summarising and reporting) is minimal in a scoping review, an attempt is made to include quality assessment, to apply meaning to the results (Armstrong et al 2011). Additionally, this is to consider the implications of the findings within the broader research, policy and practice, as the researcher intends to publish the result for use by a wider audience and reduction of duplication of effort to guide in future research.

For the quantitative data, estimates of sensitivity and specificity will be plotted in (i) forest plots and (ii) ROC plots with sufficient data. The synthesis will be undertaken using the weighted meta-analysis estimates where there are compatible designs and heterogeneity is considered reasonably (data quality as evidenced by CASP tools used across different designs including CASP cohort study checklist and CASP diagnostic checklist). Heterogeneity among the study results will be examined using the sub-group analysis (Pham et al, 2014). The analysis will be performed using Stata version 14 (StataCorp LP 2015).

Where meta-analysis is not possible due to insufficient quantitative data and incompatible studies, qualitative weighing of evidence through a narrative synthesis will be carried out with a summary of each study under the themes provided. Reporting the results of the study will assume a two dimension 1) descriptively on study characteristics and 2) analytical on outcomes of the study (Boland, 2014).

ASSESSMENT OF REPORTING BIAS

Formal assessment will be reported based on symptoms interpretation with or without biomarkers examinations and PET scans.

Appendix XIII: Titles and abstract form

TITLES AND ABSTRACT FORMS

NO	DATE	REFERENCE	INCLUDED AT SCREENING?	OBTAINED PAPER/ELECTRONIC VERSION	DOES THE ARTICLE MEETS THE INCLUSION CRITERIA	INCLUDED AT SELECTION?	REASONS FOR EXCLUSION
1	09/05/2016	Amieva et al 2014	Yes	Electronic	No	No	Excludes discussion on reliability in timing of presentation from diagnosis
2	08/05/2016	Beards et al, 2013	Yes	Electronic	No	No	This is an interview
3	13/05/2016	Benoit et al, 2003	Yes	Electronic	yes	No	Looking at the most common Symptoms
4	09/05/2016	Burke el al, 2016	Yes	Electronic	No	No	Establish diagnosis
5	10/05/2016	Chan et al, 2008	Yes	Electronic	No	No	Comparing VAS and AD
6	09/05/2016	Chiba et al, 2012	Yes	Electronic	No	No	Retrospective survey of symptoms between AD and dementia
7	09/05/2016	Chui et al, 1994	Yes	Electronic	No	No	Prediction of extra pyramidal signs
8	13/05/2016	Eustace et al, 2002	Yes	Electronic	Yes	No	No information on timing of symptoms and patients not confirmed pathologically as AD
9	10/05/2016	Fristoni et al, 1999	Yes	Paper	No	No	Behavioural syndrome study
10	13/05/2016	Gabelle et al,2016	Yes	Electronic	Yes	No	Looking at a single sign-palmomental reflex
11	09/05/2016	Hodgson et al, 2003	Yes	Electronic	No	No	Symptom seeking behaviour
12	13/05/2016	Igbal et al 2013	Yes	Electronic	No	No	Looking at sensitivity and specificity of symptoms
13	11/05/2016	Meyers et al, 2006	Yes	Electronic	No	No	Clinical clips
14	10/05/2016	Palmqvist et al 2012	Yes	Electronic	No	No	Association between sub cortical lesions and behavioural and psychological symptoms in patients with AD
15	13/05/2016	Park et al, 2015	Yes	Electronic	Yes	No	Looking at commonality of symptoms in cognitive profile
16	09/05/2016	Patterson et al, 1990	Yes	Electronic	No	No	Assessment of the present of signs and symptoms
17	10/05/2016	Perquine et al, 2012	Yes	Paper	No	No	A survey interview for the prospect of a prospective. cohort study
18	13/06/2016	Picco et al, 2011	Yes	Electronic	Yes	No	Based on a single symptom
19	13/06/2016	Pognet et al, 2013	Yes	Electronic	Yes	No	Changes in BPS
20	11/05/2016	Reeves et al, 2015	Yes	Electronic	Yes	No	The outcome is to establish whether the cognitive phenotype or psychological symptoms in AD could localise discrete pathology and target symptoms treatment
21	13/05/2016	Ringman et al, 2015	Yes	Electronic	No	No	Common symptoms in Familiar AD
22	09/05/2016	Seidl et al, 2009	Yes	Electronic	No	No	Association of neurological soft signs with cognitive deficits

23	11/05/2016	Shimizu et al, 2011	Yes	Electronic	Yes	No	Comparing the clinical profile of AD and Semantic dementia
24	13/05/2016	Suh et al, 2004	Yes	Electronic	Yes	No	Longitudinal association
25	13/05/2016	Toyota et al, 2007	Yes	Electronic	Yes	No	Difference in cognitive profile with sequence or timing
26	13/05/2016	Tsolaki et al, 2001	Yes	Electronic	Yes	No	Prevalence and correlate of extra pyramidal symptoms
27	11/05/2016	Urbanowitsch et al, 2015	Yes	Electronic	Yes	No	Establish the frequency of Neurological softs signs in AD
28	10/05/2016	Van der Mussele, 2016	Yes	Electronic	Yes	No	Data research dissertation
29	10/05/2016	Wilsosz et al, 2010	Yes	Paper	No	No	Trajectory of cognitive decline

Appendix XIV: Data extraction form.

DATA EXTRACTION FORM

AUTHOURS & YEAR OF PUBLICATION	Amieva et al,2008	Devier et al, 2010	Fox et al1998	Schmidt et al, 2010
TITLE OF STUDY	Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms.	Predictive utility of type and duration of symptoms at initial presentation in patients with MCI.	Pre-symptomatic cognitive deficits in individuals at risk of familiar Alzheimer's disease.	Clinical feature of rapidly progressive Alzheimer's disease.
TYPE OF STUDY	Case-control from the PAQUID study cohort	Longitudinal follow-up	Longitudinal prospective study	Retrospective case analysis
FULL STUDY OR ABSTRACT PAPER	Full study	Full study	Full study	Full
STUDY LOCATION	France	New York, USA	London, UK	Germany
STUDY POPULATION	Cohort subjects that experienced developing AD	MCI Participants	Asymptomatic individuals at risk of autosomal dominant familiar AD	Rapidly progressive AD
EXPOSURE	AD	MCI-AD	AD	AD
STUDY AIM/OBJECTIVES	To examine the emergence of the first clinical symptoms over a 14-year period of follow-up before dementia	To assess 1) the duration and symptoms 2) impact of the symptoms on predicting conversion to AD.	To assess the earliest clinical and neuropsychological features of the disease	To examine the clinical features in terms of symptoms frequency, time span until onset and time point of onset relative to disease.
OVERVIEW OF METHODS	A longitudinal nested case-control study	Longitudinal assessment interviewing reliable informants to collect data.	Case selection of asymptomatic at-risk members of early-onset familiar AD	Retrospective case analysis.
STATEMENTS	The first symptom to appear is memory loss, followed by cognitive decline, depression visual disturbance and verbal memory loss. ADL scores followed two years later. MMSE scores slightly declined (0.05%	Memory loss was reported as the first symptom in 80% of cases, depression in9%, language deficit 4%, cognitive changes 2%, behavioural and personality changes 1%.	Seven of the subjects were left handed, 55 right handed and one ambidextrous. Of the 63 subjects, 10 converted to AD with no difference in gender, age or left handedness.	35 neurological, psychiatric and autonomic symptoms were identified in a rapid progressive AD, with median time of survival being 26.4 months. Neurological symptoms

	point/year) from the 11 year.			reported in the study are not considered in the Mckhann (2014) diagnostic criteria. However, there is no control in the study
FOLLOW-UP	14 years	1-9 years	1-6 years	11 years
STUDY SPONSORSHIP	This research has been supported by ARMA (Bordeaux), Caisse Nationale d' Assurance Maladie des Travailleur salaries (CNAMTS),Conseil General de la Dordogne, Conseil General de la Gironde, Conseil Regional d'Aquitaine, Foundation de France	Supported in part by the National Institute on Aging.	This research has been supported by the Medical Research Council, the Alzheimer's Disease Society, the David and Frederick Barclay Foundation and the Charles Wolfson Charitable Trust.	Supported by grants from the Federal Ministry of Education and Research, Federal Ministry of Health and Robert Koch Institute.
PARTCIPANTS CHARACTERISTICS				
Number of participants	350	148	63	32
Age (Mean)	86.2 years	67.1 ±9.9 years	44.7±8.1	73 (median)
Gender	36.6 males	55% females	32 females	53% females
Signs and Symptoms	Memory (verbal) loss, depression, cognitive decline, visual disturbance and ADL.	Memory loss, language deficit, psychosis or depression, cognitive changes, disorientation and personality changes.	Memory loss-episodic and verbal, cognitive changes.	35 neurological symptoms and signs.
Diagnostic criteria	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA	Post-mortem examination of the brain
Level of education	42% had no diploma, 40.6% with primary diploma, 17.4% with higher education	15.1±4.3 years	Not stated	Not stated
MMSE Score	27.2 vs 27.2	27.5 ±2.2.	29.2 ± 1.2	Not stated
OUTCOME/ RESULT ONE (Sequence and timing of presentation	Activities of daily living scores were the least to appear at 13-14 year of the study, MMSE scores remained the same till the 12 year, memory decline 12 year	Heterogeneity in first symptom to appear with sequence and timing (average time in months) as follows:	Partly; initial first symptom only	The most common symptoms reported were myoclonus (75%), disturbed gait (66%) and rigidity (50%). The sequence in

	before diagnosis, closely followed by cognitive decline and depressive symptoms, visual disturbance in the last 5-6 years and Verbal 4 years into the study.	Memory loss 38.5, depressed mood 37.4, performance 36.8, personality 32.5, behaviour 31.1, language 29.2, disorientation 29.1 and psychosis 14.0. For the converters, the average time from the onset of first symptom to AD diagnosis was 62 months (a range from 19-176 months).		appearance of symptoms were disorientation, depression, impaired concentration, anxiety, disturbed gait, seizures, myoclonus and hallucination consecutively, rigidity, sleep disturbance, apathy, weight loss and disinhibition
OUTCOME TWO (period between diagnosis and first symptom reporting).	As above	Average time from first symptom presentation to AD diagnosis was 62 months.	Timing from initial assessment to first symptom presentation.	The symptoms median time span from clinical onset of the disease to the fatal end point was reported (in months); disinhibit ion 51.1, apathy 17.0, sleep disorder 16.0, delusions 15.0, myoclonus, hallucinations, seizures 13.0, impaired concentration 4.5, depression 4.0 and disorientation 2.0.
STRENGTH	Nested case control of 14 years period, contributing to evidence on the long duration of the predementia phase.	The provision of new information about the relationship of early symptoms in person presenting with cognitive decline.	The study demonstrate that cognitive deficits predate symptoms in familiar AD by several years	Reported the symptom frequency, time span until onset and time point of onset relative to disease end point.
LIMITATIONS	Absence of an accurate measure for episodic memory. The composition of the study sample was heterogeneous.	A small number of converters within a group of EOAD. No detailed reports on the timing from first symptoms report to AD diagnosis.	No comparison group. It was not possible to determine the exact point at which AD became clinically diagnosable within the three year follow-up.	Fast declining AD cases without control and few numbers of subjects, which could limit generalisation.

LIMITATIONS	The composition of the study sample which was heterogeneous	There was no detailed reports on the timing from first symptoms report to AD diagnosis	It was not possible to determine the exact point at which AD became clinically diagnosable within the three year follow-up.	Fast declining AD cases without control.

Appendix XV: Table of summary of studies.

AUTHOR (S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	OVERVIEW OF METHODS	KEY FINDINGS	STRENGTH	LIMITATION	STATEMENTS
Amieva et al, 20o8.	Prodromal Alzheimer's disease: the Successful emergence of clinical symptoms.	To examine the emergence of the first clinical symptoms over a 14-year period of follow-up before dementia.	350	A longitudinal nested case-control study.	Activities of daily living scores were the least to appear at 13-14 year of the study, MMSE scores remained the same till the 12 year, memory decline was reported 2years into the study, closely followed the same year by cognitive	Nested case control of 14 years period, contributing to evidence on the long duration of the pre-dementia phase.	The absence of an accurate measure of episodic memory. The composition of the study sample was heterogeneous.	The first symptom to appear was memory loss, followed by a cognitive decline, depression visual disturbance and verbal memory loss. (0.05% point/year) from the 11 years.

AUTHOR (S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	OVERVIEW OF METHODS	KEY FINDINGS	STRENGTH	LIMITATION	STATEMENTS
					decline and depressive symptoms, verbal decline in the 4th year and visual disturbance in the last 5-6 years into the study.			
Devier et al, 2010.	Predictive utility of type and duration of symptoms at initial presentation in patients with MCI.	To assess 1) the duration and symptoms; 2) the impact of the symptoms on predicting conversion to AD.	148	Longitudinal assessment, interviewing reliable informants to collect data.	Heterogeneity in the first symptom to appear with sequence and timing (average time in months) as follows: Memory loss 38.5, depressed mood 37.4, performance 36.8, personality 32.5, behaviour 31.1, language 29.2, disorientation 29.1 and psychosis 14.0. For the converters, the average time from the onset of the first symptom to AD diagnosis was 62 months (a range from 19-176 months). Average time in the presentation was 62months.	The provision of new information about the relationship of early symptoms in person presenting with cognitive decline.	A small number of converters within a group of EOAD. No detailed reports on the timing from first symptoms report to AD diagnosis.	Memory loss was reported as the first symptom in 80% of cases, depression in9%, language deficit 4%, cognitive changes 2%, behavioural and personality changes 1%.
Fox et al, 1998.	Presymptomatic cognitive deficits in individuals at risk of familial AD.	To assess the earliest clinical and neuropsychological features of familial AD.	63	Case selection of asymptomatic at-risk members of early-onset familial AD.	The study suggests that memory decline is one of the earliest measurable cognitive deficits in AD, with the verbal memory more discriminating than the non-verbal. Cognitive decline	The study demonstrates that cognitive deficits predate symptoms in familiar AD by several years.	No comparison group. It was not possible to determine the exact point at which AD became clinically diagnosable within the three-year follow-up.	Seven of the subjects were left handed, 55 right handed and one ambidextrous. Of the 63 subjects, 10 converted to AD with no difference in gender, age or left-handedness.

AUTHOR (S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	OVERVIEW OF METHODS	KEY FINDINGS	STRENGTH	LIMITATION	STATEMENTS
					was present 2-3 years before symptoms manifestation and 4-5 years before fulfilling the criteria for probably AD.			
Schmidt et al, 2010.	Clinical features of rapidly progressive AD.	To examine the clinical features in terms of symptoms frequency, time span until onset and time point of onset relative to disease.	32	Retrospective case analysis.	35 neurological, psychiatric and autonomic symptoms were identified in a rapid progressive AD, with a median time to survival being 26.4 months.	The study reported the symptom frequency, time span until onset and time point of onset relative to disease end point.	Fast declining AD cases without control and few numbers of subjects, which could limit generalisation.	The most common symptoms reported were myoclonus (75%), disturbed gait (66%) and rigidity (50%). The sequence in the appearance of symptoms was disorientation, depression, impaired concentration, anxiety, disturbed gait, seizures, myoclonus and hallucination consecutively, rigidity, sleep disturbance, apathy, weight loss and disinhibition.

Appendix XVI: Search terms for systematic scoping review.

A. MEDLINE search strategy

1. Alzheimer's/

2. Alzheimer's disease/

3. Cognitive disease/

4. Cognitive impairment*.tw.

5. Cognitive decline*. tw.

6. Cognitive changes*.tw.

7. Mild cognitive impairment*.tw.

8. Brain pathology *.tw.

9. Memory Imbalance *.tw.

10. Or /1-9

11. Early signs and symptoms/

12. Early symptoms *.tw.

13. Early signs *.tw.

14. Early presentations *.tw.

15. Early manifestations *.tw.

16. Early detection *.tw.

17. Clinical presentations/ preclinical *.tw.

18. Characteristics *.tw.

19. Clinical features*.tw.

20. Brain pathology/

21 .Behavioural symptoms and signs/

22. Psychological symptoms and signs/

23. Neuropsychological symptoms and signs/

24. Neuropsychiatric inventory/

25. Extrapyramidal symptoms/

26. Pyramidal symptoms/

27. Or /11-26

28. 25 or 27

29. Early onset Alzheimer's disease/

30. Early onset AD *.tw.

31. Early onset familial AD*.tw.

32. Early onset sporadic AD*.tw.

33. Early genetic AD*.tw.

34. Or /29-33

35. 28 or 34

35. Late onset Alzheimer's disease/

36. Late degenerative disease *.tw.

37. Late onset AD*.tw.

38. Late onset sporadic AD*.tw.

39. Late onset familial AD *.tw.

40. Or / 35-39

41. 34 or 40

42. Dementia*.tw.

42. Markers/

43. Computed tomography*.tw.

44. Cerebrospinal fluid analysis*.tw.

45. CSF*.tw.

46. Mini-mental state examination*.tw.

47. MMSE *.tw.

48. Screening *.tw.

49. Cognitive examination*.tw.

50. Magnetic resonance imaging *.tw.

51. MRI *.tw.

52. PET scan *.tw.

53. SPECT scan *.tw.

54. Or/42-53

55. 41 or 54

56. Developed countries/

57. Andorra *.tw.

58. Argentina *.tw.

59. Australia *.tw.

60. Austria *.tw.

61. Bahrain *.tw.

62. Belgium *.tw.

63. Bermuda *.tw.

64. Brunei *.tw.

65. Canada *.tw.

66. Chile *.tw.

67. Croatia *.tw.

68. Cyprus *.tw.

69. The Czech Republic *.tw.

70. Denmark *.tw.

71. Estonia *.tw.

72. Faroe Island *.tw.

73. Finland *.tw.

74. France*.tw.

75. Germany*.tw.

76. Greece*.tw.

77. Holy see (Vatican) *.tw.

78. Hong Kong *.tw.

79. Iceland *.tw

80. Ireland*.tw.

81. Israel *.tw.

82. Italy*.tw.

83. Japan*.tw.

84. Korea South*.tw.

85. Kuwait*.tw.

86. Latvia*.tw.

87. Liechtenstein *.tw.

88. Lithuania*.tw.

89. Luxembourg*.tw.

90. Malta*.tw.

91. Monaco*.tw.

92. Montenegro*.tw.

93. Netherlands*.tw.

94. New Zealand*.tw.

95. Norway*.tw.

96. Poland*.tw.

97. Portugal*.tw.

98. Qatar*.tw.

99. San Marino *.tw.

100. Saudi Arabia *.tw.

101. Singapore *.tw.

102. Slovakia*.tw.

103. Slovenia *.tw.

104. South Africa *.tw.

105. Spain*.tw.

106. Sweden*.tw.

107. Switzerland*.tw.

108. Turley*.tw.

109. United Arab Emirate*.tw.

110. United Kingdom*.tw.

111. United States*.tw.

112. OR/ 56-111.

B. Other databases

PSYCINFO (1806-9th May 2016) - Same MeSH, keywords, limits and study types used in MEDLINE search with appropriate syntax.

Cochrane Library (CMR last update 2012) - Same MeSH, keywords, and date limits used as per MEDLINE search. The adjusted syntax for Cochrane based search.

CINAHL (1937-7th May 2016)-Same MeSH, keywords, and study types as used in MEDLINE with appropriate syntax.

Nursing Index (1994-7th May 2016) - Same MeSH, keywords and study types as per MEDLINE search with suitable syntax.

C. Grey Literatures

Dates for search; 9th May 2016. Included terms were AD, terms for cognitive impairment and limit same as databases limits.

Appendix XVII: Logistic regression result; Syntaxes (Imputation and Original DATASET).

1. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=FSTEP(COND) EPISODIC_MEMORY_LOSS_YEARS

 /CLASSPLOT

 /PRINT=GOODFIT CI(95)

 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

2. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=ENTER EPISODIC_MEMORY_LOSS_YEARS GENDER

 /CONTRAST (EPISODIC_MEMORY_LOSS_YEARS)=Indicator

 /CLASSPLOT

 /PRINT=GOODFIT SUMMARY CI(95)

 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

3. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=ENTER EPISODIC_MEMORY_LOSS_YEARS GENDER ETHNICITY

 /CONTRAST (EPISODIC_MEMORY_LOSS_YEARS)=Indicator

 /CONTRAST (ETHNICITY)=Indicator

 /CLASSPLOT

 /PRINT=GOODFIT SUMMARY CI(95)

 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

4. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=ENTER AUDITORY_DISTURBANCE

 /CLASSPLOT

 /PRINT=GOODFIT SUMMARY CI(95)

 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

5. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=ENTER AUDITORY_DISTURBANCE GENDER

 /CLASSPLOT

 /PRINT=GOODFIT SUMMARY CI(95)

 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

6. LOGISTIC REGRESSION VARIABLES GROUP

 /METHOD=ENTER AUDITORY_DISTURBANCE GENDER ETHNICITY

/CONTRAST (ETHNICITY)=Indicator

/CLASSPLOT

/PRINT=GOODFIT SUMMARY CI(95)

/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

7. LOGISTIC REGRESSION VARIABLES GROUP

/METHOD=ENTER DEPRESSION

/CLASSPLOT

/PRINT=GOODFIT SUMMARY CI(95)

/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

8. LOGISTIC REGRESSION VARIABLES GROUP

/METHOD=ENTER DEPRESSION GENDER

/CLASSPLOT

/PRINT=GOODFIT SUMMARY CI(95)

/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

9. CORRELATIONS

/VARIABLES=GROUP GENDER EPISODIC_MEMORY_LOSS_YEARS AUDITORY_DISTURBANCE

/PRINT=TWOTAIL NOSIG

/MISSING=PAIRWISE.

ORIGINAL DATA:

10. LOGISTIC REGRESSION VARIABLES GROUP

/METHOD=ENTER EPISODIC_MEMORY_LOSS_YEARS GENDER

/CONTRAST (GENDER)=Indicator(1)

/CLASSPLOT

/PRINT=GOODFIT SUMMARY CI(95)

/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

11. METHOD=ENTER GENDER AUDITORY_DISTURBANCE

/CONTRAST (GENDER)=Indicator(1)

/CLASSPLOT

/PRINT=GOODFIT SUMMARY CI(95)

/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

Appendix XVIII: BMJ Open email regarding the reviewers' judgement.

More

BMJ Open - Decision on Manuscript ID bmjopen-2016-015746.R1

BMJ Open

24-May-2017

Dear BATURE:

Inbox

24 May

Manuscript ID bmjopen-2016-015746.R1 entitled "Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic

scoping review of literature from 1937-2016." which you submitted to BMJ Open, has been reviewed. The comments of the reviewer(s) arE

included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to

respond to the reviewer(s)' comments and revise your manuscript. Please note that reviewer Van Den Bossche comments on the paper not being clear enough, but we do not see a problem with the sequence of the paper and we do not believe that this needs addressing, unless

you would like to. Please just provide a sentence in your response explaining that you have not acted on this recommendation.

To revise your manuscript, log into https://mc.manuscriptcentral.com/bmjopen and enter your Author Center, where you will find your

manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has be

appended to denote a revision.

You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your

manuscript. If you use the below link you will not be required to login to Scholar One Manuscripts.

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmjopen?URL MASK=5d76625460d34faabd38fc2f2f0bc2ca

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a we

processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the

track changes mode in MS Word or by using bold or colored text.

1/1

Appendix XIX: BMJ Open decision to publish. BMJ Open

<onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.co

07-Jun-2017

Dear BATURE:

It is a pleasure to accept your manuscript entitled "Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic

scoping review of literature from 1937-2016." in its current form for publication in BMJ Open .

In order to support making all research published in BMJ Open fully open access, an article-processing charge is levied. This charge

supports the peer review process, production costs (typesetting, copy editing, etc.), and the costs of maintaining the content online and

marketing it to readers.

Therefore, your payment of £1350 (excluding VAT) for accepted manuscript bmjopen-2016-015746.R2 is now due.

A separate e-mail will follow shortly with a link to payment options and instructions. This Will be from BMJ's partner, Copyright Clearance

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University of
Bedfordshire

LATE DIAGNOSIS OF ALZHEIMER'S DISEASE: GPs PERSPECTIVES.

SURVEY QUESTIONS

Please answer the following questions with regards to the interview questions that you have answered:

1. Was the interview too long or short?   good fine

2. Were the questions clear and understandable? (If no, please state your reasons)………………yes….

3. Was the flow of questions clear or confusing? (Which one and why)…………………………No……flow was good

For further comments to improve the questionnaire, please state here in this box, or communicate with the researcher directly.

4. Did you object to any question? (If yes, which one and why)?……no…………

Thank you!

![University of Bedfordshire logo]

**University of
Bedfordshire**

LATE DIAGNOSIS OF ALZHEIMER'S DISEASE: GPs PERSPECTIVES.

SURVEY QUESTIONS

Please answer the following questions with regards to the interview questions that you have answered:

1. Was the interview too long or short?   *Moderate*

2. Were the questions clear and understandable? (If no, please state your reasons)...........*Yes*........

3. Was the flow of questions clear or confusing? (Which one and why)...............*Clean*...............

> *For further comments to improve the questionnaire, please state here in this box, or communicate with the researcher directly.*

4. Did you object to any question? (If yes, which one and why)?......*none !*

Thank you!

University of Bedfordshire

LATE DIAGNOSIS OF ALZHEIMER'S DISEASE: GPs PERSPECTIVES.

SURVEY QUESTIONS

Please answer the following questions with regards to the interview questions that you have answered:

1. Was the interview too long or short?   8   Short -

2. Were the questions clear and understandable? (If no, please state your reasons)...............Yes....

3. Was the flow of questions clear or confusing? (Which one and why)............Clear....:............

> *For further comments to improve the questionnaire, please state here in this box, or communicate with the researcher directly.*

4. Did you object to any question? (If yes, which one and why)?.......No......

Thank you!

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