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Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937-2016.

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Abstract

Objective

Late diagnosis of Alzheimer's disease (AD) may be due to missed early signs and symptoms or those that are mistaken as signs of old age or symptoms of other conditions. We aimed to determine the sequence and timing of the appearance of early signs and symptoms in people who are subsequently diagnosed with AD.

Methods

We used systematic review methodology to investigate the existing literature. Articles were reviewed in May 2016, using the following databases: MEDLINE, PsycINFO, CINAHL, British Nursing Index, PubMed central and the Cochrane library, with no language restriction. Data from the included articles were extracted independently by two authors and quality assessment was undertaken with the quality assessment and diagnostic accuracy tool-2 (QUADAS tool-2 quality assessment tool).

Results

We found that depression and cognitive impairment were the first symptoms to appear in some individuals with late-onset AD (LOAD). Memory loss also presented early and was experienced 12 years before the clinically defined AD dementia. However, the rapidly progressive late onset AD (RPLOAD), presented predominantly with 35 non-established focal symptoms including myoclonus (75%), disturbed gait (66%) and rigidity. These were misdiagnosed as symptoms of Creutzfeldt-Jacob disease (CJD) in all the cases. The participant with the lowest mini-mental state examination (MMSE) score of 25 remained stable for 2 years, which is consistent with the score of the healthy family members.

Conclusions

The findings of this review suggest that neurological and depressive behaviours are an early occurrence in early-onset AD (EOAD). Misdiagnosis of RPAD as CJD and the familial memory score can be confounding factors while establishing a diagnosis. However, the study was limited by the fact that each one of the findings was based on a single study.

SUMMARY

Alzheimer's disease (AD) is a devastating disease with multiple presentations. A systematic scoping review was carried out to identify the timing and sequence of the early presentation of the disease ; to understand how far back from diagnosis the first symptoms that will justify a diagnosis was reported. Studies selected included, those on the timing and sequence of the early signs and symptoms of AD with participants 30-85 years, within the developed countries.

Strengths

- The review indicates a paucity of data on the study objectives and heterogeneity in the timing of symptoms presentation in published studies.
- Comprehensive search strategy was used to identify articles for this review.
- This is the first review to identify the sequence and timing of the signs and symptoms in the early stage of AD.

Limitations

- Dearth of data, heterogeneity in methodology and findings, made it impossible to draw a definite conclusion.
- Several other potential sources of heterogeneity like age, gender and education could not be investigated with the dearth of data.

Author's conclusions

There is limited evidence of the early signs and symptoms associated with the diagnosis of AD. Further studies are required.

Keywords: Alzheimer's disease (AD), systematic scoping review, early signs and symptoms, mild cognitive impairment (MCI), early stage of AD.

Introduction

Alzheimer's disease (AD) is a devastating disease with multiple presentations. In the UK, a prevalence of 520,000 has been reported in 2014 (1- 3) with high individual, health care and financial burden.(4-5) There are challenges in diagnosing the disease early, which can result in severe cognitive and functional decline.(6-8) Among the reasons for the late diagnosis is that the signs and symptoms, at the early stages of AD, are sometimes not recognised and/or mistaken for signs of old age or symptoms of other conditions.(2, 9-11) The above may be partly due to the fact that the timing and sequence of the early presentation of signs and symptoms are not reported by current studies.(12-15) This review attempts to answer the following research question: how far back from diagnosis and in what sequence do the first symptoms that warrant an AD diagnosis appear? Further understanding of the timing and the sequence of the presentation of signs and symptoms may enable practitioners to offer timely intervention.

Methods

Types of studies

All types of empirical studies were considered, excluding those of qualitative design.

Participants

Included participants were aged between 30-85 years and diagnosed with AD.

Settings

Primary care, memory clinics or secondary care settings.

Target condition

AD, and any subtypes, were diagnosed with the following tools: (a) National Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders Association (NINCDS-ADRDA, UK), a commonly used criteria for AD dementia; (b) National

Institute on Aging-Alzheimer's Association (NIA-AA, US), more recent criteria that use biomarkers to support the diagnosis; (c) Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV);(16) and (d) DSM-5.(17)

Outcomes

The outcomes of this review included (I) the sequence of presentation of the signs and symptoms that are indicative of AD prior to diagnosis;(13) (II) the timing from the first reported symptom to diagnosis;(13) (III) the timing from MCI to diagnosed dementia stage; (30) (IV) the timing of assessments leading up to a diagnosis of AD (31) and (V) the timing from clinical presentations to case fatality or death.(32)

Index symptoms

We used an index of early symptoms as a reference to ascertain the timing and sequence of events prior to disease presentation. The index is based on previous studies,(18-22) which include apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, depression, irritability, hallucination and olfactory disturbances and weight loss.(18-22)

Exclusion criteria

- Participants with other dementia or other neurological conditions;
- Inaccurate diagnostic criteria;
- Single index symptom;

Search criteria for identification of studies

We searched the literature via OvidSP MEDLINE (1950), PsycINFO (1887), British Nursing Index (1994), CINAHL (1937), PubMed central (2000) and the Cochrane register for diagnostic and intervention studies. We also used "snowballing" and searched the references of relevant articles. Searches covered the period from 1937 until May 2016. No language or publication restrictions were applied. We used medical subject headings (MeSH) terms to standardise and improve the search; AD was the main term followed by the basic terms timing, onset and country, and the combination of terms. Details of the database search strategies are presented in Appendix **1.**

Data collection and analysis

Assessment of methodological quality

The qualities of included studies were assessed using the QUADAS-2 tool, a methodological quality assessment tool used to assess diagnostic accuracy studies (24) (**Table 1**).

Results

Results of the search

The process by which articles were identified, screened and selected for the review is described in **Figure 1**. A total of 3,528 articles were identified in the databases including 318 duplicates. Nine others were identified through hand searching and 3,179 were excluded based on the review of titles and abstract alone. The full-text versions of 40 were assessed for eligibility, 13 were initially included but nine later excluded (reasons stated below). Four articles were finally included in the review.

Reasons for exclusion

Although thirteen studies were reviewed in full, nine were excluded. The reasons for exclusion were; four studies were on unspecified dementia;(20, 25-27) one study was undertaken in a developing country;(28) another on caregiver's distress;(21) one study was on a single case;(15) one study had incomplete data;(29) while another did not have a reference point for the diagnosis of AD.(12)

Summary of findings:

Methodological quality of included studies

The methodological quality in each domain was assessed individually.

The QUADAS-2 scores for each domain **(Table 1)** of the studies included in the review are shown in **Figures 2 and 3.** The reviewer included a nested case-control with random sampling,(30) longitudinal follow-up of mild cognitive impairment (MCI) (red-flag or easier to diagnose) patients,(13) longitudinal prospective study of individuals at risk of autosomal

dominant familial AD(31) and a retrospective case study (post-mortem).(32) For the case studies,(13, 31-32) the exclusion criteria were appropriate and sample selection was consecutive, which reduced the risk of selection bias (**Table 2, Figure 2)**.

The index test was not influenced by the reference standard in three studies.(13, 30, 31) However, the index test domain was judged as having a high risk of bias in a study (32) due to the fact that the index tests were interpreted based on the knowledge of the disease (post-mortem). In the applicability concerns, the conduct and interpretation of the index symptoms were different from the review question in Fox et al (31) and Schmidt et al.(32) The Fox et al(31) study focused on the mean time from first assessment to the appearance of symptoms at reporting, while the study published by Schmidt et al (32) focused on identifying the median time span from clinical presentation of the disease to case fatality or death.

In the reference standard domain, all studies were undertaken using the diagnostic criteria for AD, recognised internationally that could correctly classify the condition with masking in all. The Schmidt et al study (32) on rapidly progressive AD was undertaken post-mortem, the gold standard for the diagnosis of AD. However, none of the studies reported how the reference standard was operationalised or applied. They were assessed as being a low risk of concern about applicability.

In the flow and timing domain, there was an appropriate interval between the appearance of symptoms and signs and the reference standard. There was no mention of treatment in between the timings and all of the participants were diagnosed using the same reference standard. All participants were included in the analysis.

Findings

Outcome I

Of the 148 participants in the Devier et al study, (13)39 (26%) converted to AD and all of the converters were 55 years at baseline indicating an early onset AD (EOAD). There were differences in the first symptom at presentation with memory decline reported as the first in 118 (80%) of the cases, depressed mood in 13 (9%), declined language in six (4%), change in performance of higher order/cognitive activities in four (3%), disorientation in three (2%),

personality changes and behavioural changes in two (1%), with no group difference in symptoms reporting. Sequentially, memory decline was the first followed by performance changes, changes in language, disorientation, personality changes, depressed mood, behavioural changes and psychosis consecutively.

Outcome II

Memory decline was experienced in 38.5 months before diagnosis,(13) 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 the diagnosis.

Outcome III

Amieva et al (30) study reported cognitive decline 12 years before dementia in a measure of semantic memory and conceptual formation. Depressive symptoms appeared concomitantly with the cognitive decline and followed two years later with verbal memory decline. Two years later, visual disturbances were recorded and worsened until the dementia stage.

Outcome IV

Of the 63 subjects in the Fox et al (31) study, ten converted to probably AD and the mean time (±standard deviation (SD)) from first assessment to the appearance of symptoms was 2.6 ± 1.4 years. Episodic memory loss was the most common and noticed on average 6 months before symptomatic assessment. The study suggests that cognitive decline is present 2-3 years before symptoms and 4-5 years before individuals fulfill the criteria for probably AD. There was no distinction in presentations with regards to age, gender and handedness. Verbal memory was superior to semantic memory in differentiating AD from normal ageing, with the lowest score in MMSE of 25 in a subject remaining stable for two years consistent with family members with the same score that remained healthy.

Outcome V

Thirty-five distinct neurological, psychiatric and autonomic symptoms and signs were identified in the Schmidt et al (32) study. The sequence and timing in months (averagely 26.4) of the presentation of the signs and symptoms were as follows:- disinhibition 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 thereafter. A third of RPAD experienced rapid weight loss and sleep disorder indicating their significance in discriminating the disease from other dementias.

Signs and symptoms

A pooled estimate was not possible to be reported due to the differences in participants, symptoms and types of AD, as well the scarcity of research that had reported on the sequence and timing of the early signs and symptoms. MCI was required at baseline in the Devier et al study, (13) with memory complaints six months to ten years prior to enrolment. The study began long before the Petersen et al (33) MCI criteria definition. Prior to enrolment, memory loss was observed on average 38.5; depressed mood 37.4; performance 36.8; personality 32.1; behaviour deficits 31.1; language deficits 29.2; disorientation 29.1 and psychosis 14.0 months before diagnosis.

For the ten converters in the Fox et al study,(31) 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 deficit in 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 higher early sensitivity than the semantic memory and cognitive changes 2-3 years before the symptomatic phase. There was no difference observed between cases and non-converters in terms of age, gender, handedness or MMSE at initial assessment and symptomatic assessment.

In the Schmidt et al (32) study, the median disease duration was 26.4 months and the median age at clinical onset was 73 years. The authors were unable to obtain a summary of the data from the onset of the symptoms to disease diagnosis.

All the studies were diagnosed with the standardised diagnostic criteria and symptoms measured with the diagnostic accuracy measures.

Discussion

Four studies met the inclusion criteria which had heterogeneous objectives, diagnosis, and participants. The four studies had a total of 593 people who were followed for conversion to AD. All the studies assessed the timing of the signs and symptoms of AD prior to a formal diagnosis and/or case fatality, but with different participants and type of AD.

Studies were assessed methodologically with the QUADAS-2 tool. Three of the included studies (13,30,31) validated their results via the NINCDS-ADRDA and one study(32) via post-mortem examination.

Even though there were differences in timing, objectives, participants and type of AD, the Fox et al(31) study on FAD identified a participant with MMSE score of 25/30, the lowest in the converters group that remained the same for two years and was similar to family members that remained well in this group. This supports the evidence that the MMSE offers a reasonably good diagnosis and classification of AD,(34) especially the accuracy of the MMSE baseline score. However, critics advised that the measurement should be interpreted with caution.(35,36) Furthermore, Schmidt et al(32) discovered additional focal neurological symptoms consistent with CJD; AD was misdiagnosed as CJD until the post-mortem study proved AD as the cause of the presentations. This finding is in line with Mega et al (19) and Zahodne et al,(37) who reported that there are measurable behavioural changes in AD, and suggested that focal neurological symptoms are associated with poor prognosis.(37)

Memory disturbances remain the predominant differentiating factor between early AD and normal ageing in all of the studies. Verbal memory was more vulnerable than non-verbal in the EOFAD.(31) The memory test for words indicated significant differences in scores, 1-5 years before becoming symptomatic, against the notion of 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. However, memory loss presented early and frequently in this group too.(13,30) The rapidly progressive LOAD (32) presented predominantly with myoclonus (75%), disturbed gait (66%) and rigidity (50%). These symptoms were also early in the presentation process occurring before apathy. Neurological and depressive behavioural presentations are an early occurrence in EOAD.(13) This calls for further studies 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.

The main limitation of this systematic review was the dearth of data and heterogeneity in methodology and findings in the included studies. Moreover, pooled estimate or statistical analysis for the signs and symptoms was not possible to be calculated and several other potential sources of heterogeneity like the age of onset, gender and education could not be investigated given the paucity of relevant data.

We excluded studies on individual symptoms and signs, as well as other types of dementia, where it was not possible to isolate AD. Further and rigorous research is needed to understand the timing and sequence of the appearance of the signs and symptoms that elude to AD prior to diagnosis, with the aim of supporting as early an AD diagnosis as possible.

Conclusions

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 to diagnose AD early, by recognising the signs and symptoms as reliable predictive markers of the disease.(38-39)

There are currently insufficient published data on the sequence and timing of the early signs and symptoms of AD. We advocate that more research should be undertaken in this area.

This review is important to general practitioners, researchers, health policymakers the pharmaceutical industry and the public.

Abbreviations

AD: Alzheimer's disease; CJD: Creutzfeldt-Jacob disease; DSM-5: Diagnostic and Statistical Manual-5; EOAD: Early Onset Alzheimer's disease; FAD: Familial Alzheimer's disease; LOAD: Late Onset Alzheimer's disease; MCI: mild cognitive impairment; MeSH: Medical Subject Headings; MMSE: Mini Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communication Disorders and Stroke- Alzheimer's Disease and Related Disorders Association; QUADAS: Quality Assessment and Diagnostic Accuracy Studies; RPAD: Rapidly Progressive AD ; SD: Standard Deviation.

Declarations:

Authors' contributions

FB and BG conceived the study and participated in the design and drafting of the manuscript. DP participated in the analysis and helped to draft the manuscript. YP suggested the design, participated in the selection of studies, design and drafting of the manuscript. FB developed the protocol of the study, conducted the analysis and drafted the manuscript. FB, DP, BG and YP read and approved the final manuscript for this publication.

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FIGURE TITLE AND LEGEND SECTION:

Figure 1: Flowchart indicating the process for the selection of studies. The flow chart indicates the articles identified through the search; those reviewed as title and abstract, those reviewed fully and the ones that met the inclusion criteria.

Figure 2: Graph representing the risk of bias and applicability concerns. Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

Figure 3: The summary of the risk of bias and applicability concerns. The reviewer's judgment on each domain for the included studies is shown with a high risk of bias and applicability concerns on index test for.(32)

Appendix 1

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.

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.

Grey Literatures:

Dates for search: 9th May 2016. Included terms were AD, terms for cognitive impairment and limit same as databases limits.

Table 1. Quality assessment using the QUADAS tool.

DOMAIN	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING OF SIGNS AND SYMPTOMS
Description	Describe methods of participant selection: Describe 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 (diagnostic criteria): Describe the time interval and any interventions between index test(s) and reference standard; that is, any intervention/ medication given prior to diagnosis.
Signalling questions (Yes/no/unclear)	Was 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?	

TABLES **Table 2.** Summary of study methodology and key findings.

AUTHOR(S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	STUDY 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 decline and depressive symptoms, verbal decline in the 4th year and visual disturbance in the last 5-6 years into the study.	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.
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 in 9%, 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 was present 2-3 years before symptoms manifestation and 4-5 years before fulfilling the criteria for probable AD.	The study demonstrates that cognitive deficits predict 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 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.
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.

Figure 1: Flowchart of selection of studies

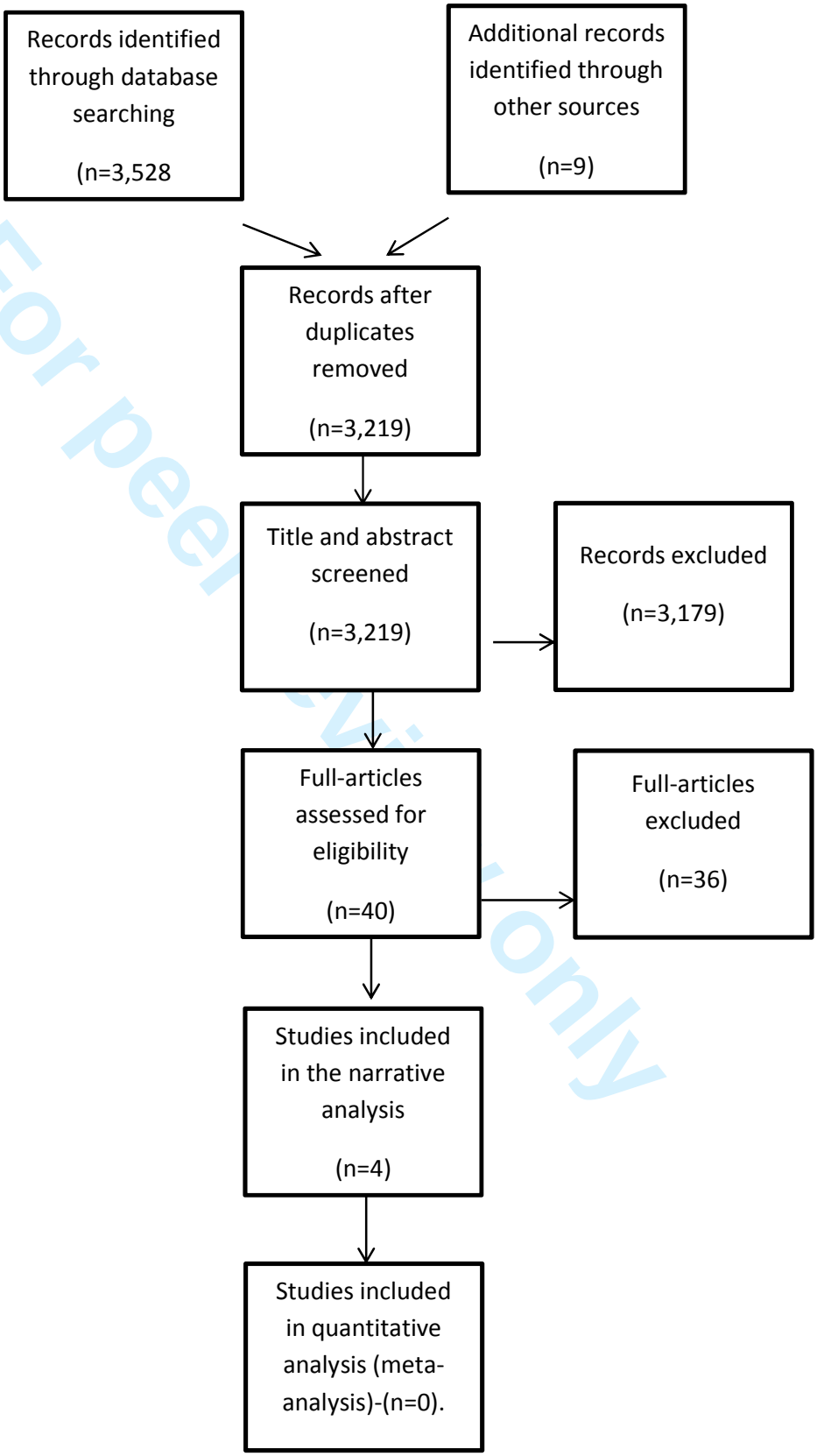

Figure 1: The flow chart indicates the articles identified through the search; those reviewed as title and abstract, those reviewed fully and the ones that met the inclusion criteria.

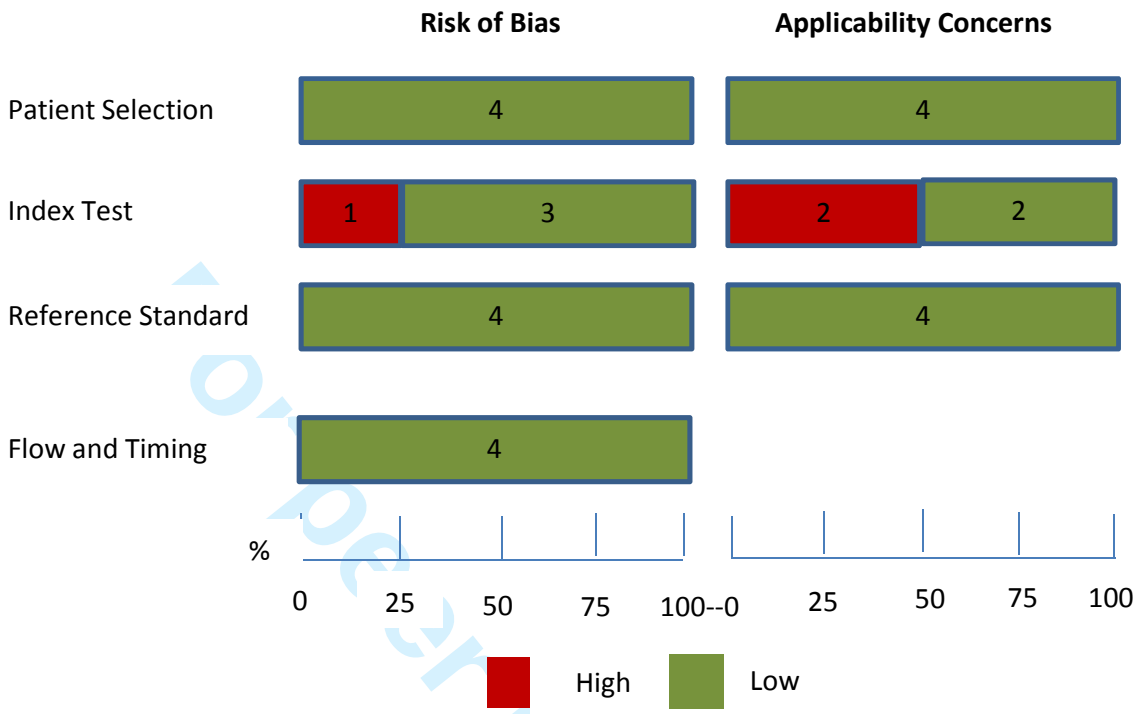

Figure 2. Graph representing the risk of bias and applicability concerns: Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

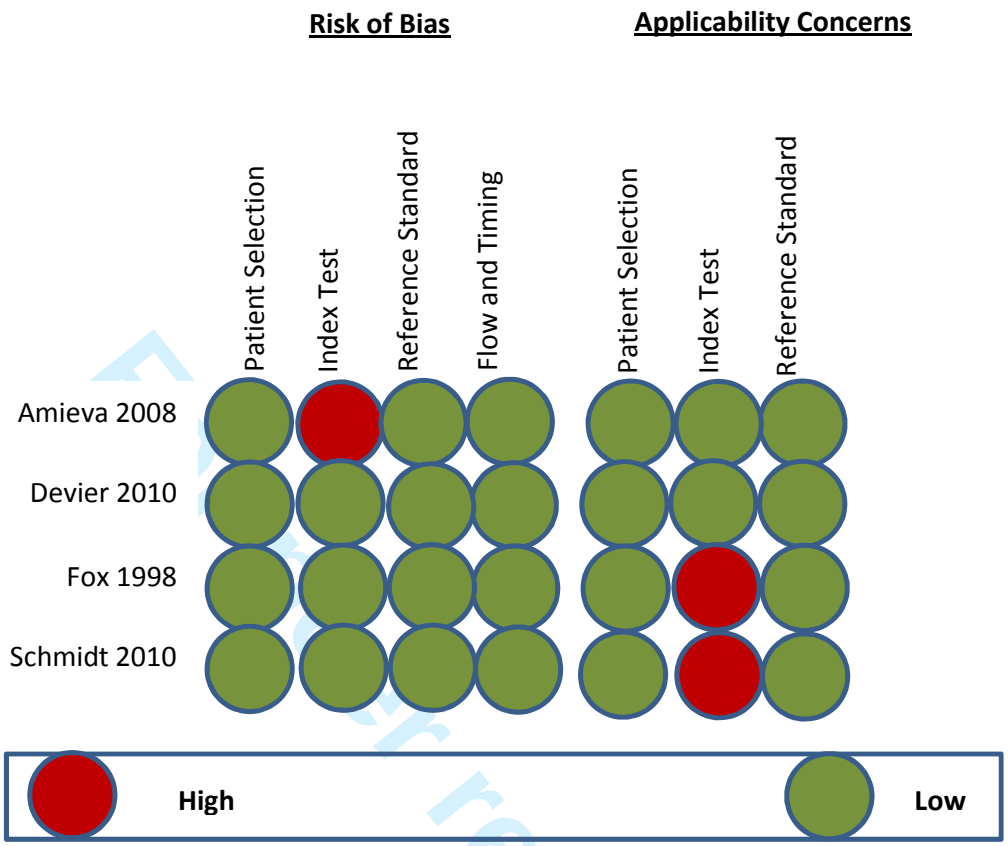

Figure 3. The summary of the risk of bias and applicability concerns: reviewer's judgement on each domain for the included studies is shown with high risk of bias and applicability concerns on index test for. [32]

SUPPORTING STATEMENT

We conducted according to and based the report of this systematic review on the preferred reporting items for systematic review and meta-analysis (PRISMA). We used a protocol, which we followed to avoid introducing bias to the review.

One author screened all titles. Two authors reviewed all abstracts and full texts with disagreement for inclusion resolved by a third author. We used the Quality Assessment Diagnostic Accuracy Studies (QUADAS-2) to appraise quality. The risk of bias was also 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 has been summarised in the summary tables and figures, with the PRISMA flow chart in the appendix.

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Systematic scoping review- 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and Implications of key findings; systematic review registration number.	2&3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5&6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Supplementary list
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5&6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6 & 25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21-26
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5&6
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and	7

Section/topic	#	Checklist item	Reported on page #
		any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5&6
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7&8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not undertaken due to dearth of data and heterogeneity in studies.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11&12
Additional analysis	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not done; same as response 13.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7&8 ;table 1; figure 2&3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
Synthesis of	21	Present results of each meta-analysis done,	Same as

Section/topic	#	Checklist item	Reported on page #
results		including confidence intervals and measures of consistency.	response 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11&12
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Same as response 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	11&12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N.A

From: Moher et al (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

Highlights

- The outcomes of this review suggest that neurological and depressive behaviours are indicators of early-onset Alzheimer's disease (EOAD).
- Misdiagnosis of Rapidly Progressing AD (RPAD) as CJD and the memory score of 25 in familial AD are confounding factors.
- There is paucity of data on the sequence and timing of presentation of the early signs and symptoms in AD.

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SYSTEMATIC 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. It is to be noted that though the scoping review is based on a systematic review protocol, it is neither an intervention nor a testing a diagnostic tool, but a review undertaken using a set procedure within a large and diverse literature. This is to understand the whole of the literature by systematically searching and synthesising so as not to miss any relevant literature.

BACKGROUND

Alzheimer's disease 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 2011, Dubois 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.

Alzheimer's disease 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 Society, 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.

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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.

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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, Brendan et al 2008, 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%;and47%&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 Alzheimer's disease 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 Alzheimer's disease 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

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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 (Freedman et al, 2013) 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), PsychINFO (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. Also, the disease theatre will be the main theatre, followed by the timing theatre, then the basic theatre including country, onset and combination theatres, before duplicate is removed. This is to systematically capture the desire 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 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:

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 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.

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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.

The quantitative data will be plotted with (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). 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.

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Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937-2016.

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Abstract

Objective

Late diagnosis of Alzheimer's disease (AD) may be due diagnostic uncertainties. We aimed to determine the sequence and timing of the appearance of established early signs and symptoms in people who are subsequently diagnosed with AD.

Methods

We used systematic review methodology to investigate the existing literature. Articles were reviewed in May 2016, using the following databases: MEDLINE, PsycINFO, CINAHL, British Nursing Index, PubMed central and the Cochrane library, with no language restriction. Data from the included articles were extracted independently by two authors and quality assessment was undertaken with the quality assessment and diagnostic accuracy tool-2 (QUADAS tool-2 quality assessment tool).

Results

We found that depression and cognitive impairment were the first symptoms to appear in 98.5% and 99.1% of individuals in a study with late-onset AD (LOAD) and 9% and 80% respectively in EOAD. Memory loss presented early and was experienced 12 years before the clinically defined AD dementia in the LOAD. However, the rapidly progressive late onset AD (RPLOAD), presented predominantly with 35 non-established focal symptoms and signs including myoclonus (75%), disturbed gait (66%) and rigidity. These were misdiagnosed as symptoms of Creutzfeldt-Jacob disease (CJD) in all the cases. The participant with the lowest mini-mental state examination (MMSE) score of 25 remained stable for 2 years, which is consistent with the score of the healthy family members.

Conclusions

The findings of this review suggest that neurological and depressive behaviours are an early occurrence in early-onset AD (EOAD) with depressive and cognitive symptoms in the measure of semantic memory and conceptual formation in LOAD. Misdiagnosis of RPAD as CJD and the familial memory score can be confounding factors while establishing a

diagnosis. However, the study was limited by the fact that each one of the findings was based on a single study.

Strengths

- The review indicates a paucity of data on the study objectives and heterogeneity in the timing of symptoms presentation in published studies.
- Comprehensive search strategy was used to identify articles for this review.
- This is the first review to identify the sequence and timing of the signs and symptoms in the early stage of AD.

Limitations

- Dearth of data, heterogeneity in methodology and findings, made it impossible to draw a definite conclusion.
- Several other potential sources of heterogeneity like age, gender and education could not be investigated with the dearth of data.

Keywords: Alzheimer's disease (AD), systematic scoping review, early signs and symptoms, mild cognitive impairment (MCI), early stage of AD.

Introduction

Alzheimer's disease (AD), the most common type of dementia is a devastating disease with multiple presentations. While the disease is associated with old age, scientists (1-2) have discovered that disease can develop at any age and the reason for this is unclear. The disease could develop before the age of 65 years, known as early onset AD (EOAD), which might be inherited or sporadic, or after the age of 65 years, known as late onset AD (LOAD), that accounts for 90% of all AD cases (3). In the UK, a prevalence of 520,000 has been reported in 2014 (4-6) with high individual, health care and financial burden.(7,8) There are challenges in diagnosing the disease early,(9-11) which can result to non-reversible symptoms progression, that lead to institutionalisationa and high mortality rate among this group.(12)There is also the emotional and physical burden to the care givers(13,14) as well as emotional, physical and financial burden to the health care system(15). Even though there is discourse in the meaning of the early diagnosis, here, it refers to the diagnosis at the lowest threshold of the disease or at the stage of mild cognitive impairment (MCI), with cluster of early signs and symptoms and the diagnosis of the pathology of the disease before dementia. This is because the disease has a preclinical stage with the clinical symptoms yet evident but with changes in the brain and the risk of progression unknown; intermediate stage with mild cognitive and functional changes and dementia due to AD stage with severe cognitive and functional decline.

Among the reasons for the late diagnosis is that the signs and symptoms, at the early stages of AD, are sometimes not recognised and/or mistaken for signs of old age or symptoms of other conditions. (5, 16-18) The above may be partly due to the fact that the timing and sequence of the early presentation of signs and symptoms are not reported by current studies. (19-21). Delaying onset of the disease by five years through early diagnosis and intervention could reduce the mortality rate of dementia (advanced stage of AD) by 30,000 yearly (22).

This review attempts to answer the following research question: how far back from diagnosis and in what sequence do the first symptoms that warrant an AD diagnosis appear? Further understanding of the timing and the sequence of the presentation of signs and symptoms may enable practitioners to offer timely intervention.

Methods

Types of studies

All types of empirical studies were considered, excluding those of qualitative design.

Participants

Included participants were aged between 30-85 years and diagnosed with AD.

Settings

Primary care, memory clinics or secondary care settings.

Target condition

AD, and any subtypes, were diagnosed with the following tools: (a) National Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders Association (NINCDS-ADRDA, UK), a commonly used criteria for AD dementia; (b) National Institute on Aging-Alzheimer's Association (NIA-AA, US), more recent criteria that use biomarkers to support the diagnosis; (c) Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV);(23) and (d) DSM-5.(24)

Outcomes

The outcomes of this review included (I) the sequence of presentation of the signs and symptoms that are indicative of AD prior to diagnosis;(20) (II) the timing from the first reported symptom to diagnosis;(20) (III) the timing from MCI to diagnosed dementia stage; (25) (IV) the timing of assessments leading up to a diagnosis of AD (26) and (V) the timing from clinical presentations to case fatality or death.(27)

Index symptoms

We used an index of early symptoms as a reference to ascertain the timing and sequence of events prior to disease presentation. The index is based on previous studies,(28-32) which include apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, depression, irritability, hallucination and olfactory disturbances and weight loss.(28-32)

Exclusion criteria

- Participants with other dementia or other neurological conditions;
- Inaccurate diagnostic criteria;
- Single index symptom;
- Late stage AD (AD dementia); a set of symptoms including memory loss, difficulty in thinking, problem-solving or language difficulties.(33)

Search criteria for identification of studies

We searched the literature via OvidSP MEDLINE (1950), PsycINFO (1887), British Nursing Index (1994), CINAHL (1937), PubMed central (2000) and the Cochrane register for diagnostic and intervention studies. We also used "snowballing" and searched the references of relevant articles. Searches covered the period from 1937 until May 2016. No language or publication restrictions were applied. We used medical subject headings (MeSH) terms to standardise and improve the search; AD was the main term followed by the basic terms timing, onset and country, and the combination of terms. Details of the database search strategies are presented in **Appendix 1.**

Data collection and analysis

Assessment of methodological quality

The qualities of included studies were assessed using the QUADAS-2 tool, a methodological quality assessment tool used to assess diagnostic accuracy studies (34) (**Table 1**) and PRISMA checklist (**Supplementary file 6)**. The tool consist of fourteen items that rates the

Risk of bias, source of variations (Applicability and reporting of quality), with each item rated as ‘yes’ ‘no’ or ‘unclear’, tailored under four domains that includes: Participants Selection; Index Test (signs and symptoms interpretation) Reference Standard (diagnostic criteria that correctly classify the target condition) and Flow and Timing (time interval and intervention between Index Test and Reference Standard.

Table 1. Quality assessment using the QUADAS tool.

DOMAIN	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING OF SIGNS AND SYMPTOMS
Description	Describe methods of participant selection: Describe 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 (diagnostic criteria): Describe the time interval and any interventions between index test(s) and reference standard; that is, any intervention/ medication given prior to diagnosis.
Signalling questions (Yes/no/unclear)	Was 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?	

Results

Results of the search

The process by which articles were identified, screened and selected for the review is described in **Figure 1**. A total of 3,528 articles were identified in the databases including 318 duplicates. Nine others were identified through hand searching and 3,179 were excluded based on the review of titles and abstract alone. The full-text versions of 40 were assessed for eligibility, 13 were initially included but nine later excluded (reasons stated below). Four articles were finally included in the review.

Reasons for exclusion

Although thirteen studies were reviewed in full, nine were excluded. The reasons for exclusion were; four studies were on unspecified dementia;(30, 35-37) one study was undertaken in a developing country;(38) another on caregiver's distress;(31) one study was on a single case;(22) one study had incomplete data;(39) while another did not have a reference point for the diagnosis of AD.(19)

Summary of findings:

Methodological quality of included studies

The methodological quality in each domain was assessed individually.

The QUADAS-2 scores for each domain **(Table 1)** of the studies included in the review are shown in **Figures 2 and 3.** The reviewer included a nested case-control with random sampling,(25) longitudinal follow-up of mild cognitive impairment (MCI) patients,(20) longitudinal prospective study of individuals at risk of autosomal dominant familial AD(26) and a retrospective case study (post-mortem).(27) For the case studies,(20, 26,27) the exclusion criteria were appropriate and sample selection was consecutive, which reduced the risk of selection bias .(**Table 2, Figure 2)**

(**Table 2, Figure 2)**

TABLES **Table 2.** Summary of study methodology and key findings.

AUTHOR(S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	STUDY METHODS	KEY FINDINGS	STRENGTH	LIMITATION	STATEMENTS
Amieva et al, 2008.	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 decline and depressive symptoms, verbal decline in the 4th year and visual disturbance in the last 5-6 years into the study.	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.
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 in 9%, 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 was present 2-3 years before symptoms manifestation and 4-5 years before fulfilling the criteria for probable AD.	The study demonstrates that cognitive deficits predict 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 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.
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.

The index test was not influenced by the reference standard in three studies.(20, 25, 25) However, the index test domain was judged as having a high risk of bias in a study (27) due to the fact that the index tests were interpreted based on the knowledge of the disease (post-mortem). In the applicability concerns, the conduct and interpretation of the index symptoms were different from the review question in Fox et al (26) and Schmidt et al.(27) The Fox et al(26) study focused on the mean time from first assessment to the appearance of symptoms at reporting, while the study published by Schmidt et al (27) focused on identifying the median time span from clinical presentation of the disease to case fatality or death.

In the reference standard domain, all studies were undertaken using the diagnostic criteria for AD, recognised internationally that could correctly classify the condition with masking in all. The Schmidt et al study (27) on rapidly progressive AD was undertaken post-mortem, the gold standard for the diagnosis of AD. However, none of the studies reported how the reference standard was operationalised or applied. They were assessed as being a low risk of concern about applicability.

In the flow and timing domain, there was an appropriate interval between the appearance of symptoms and signs and the reference standard. There was no mention of treatment in between the timings and all of the participants were diagnosed using the same reference standard. All participants were included in the analysis.

Findings

Outcome I

Of the 148 participants in the Devier et al study, (20)39 (26%) converted to AD and all of the converters were 55 years at baseline indicating an early onset AD (EOAD). There were differences in the first symptom at presentation with memory decline reported as the first in 118 (80%) of the cases, depressed mood in 13 (9%), declined language in six (4%), change in performance of higher order/cognitive activities in four (3%), disorientation in three (2%), personality changes and behavioural changes in two (1%), with no group difference in symptoms reporting. Sequentially in the order of appearance of the signs and symptoms in

all the participants, memory decline was the first followed by performance changes, changes in language, disorientation, personality changes, depressed mood, behavioural changes and psychosis consecutively. However, for depression, 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 (40) and all cause dementia (41).

Outcome II

Memory decline was experienced in 38.5 months before diagnosis,(20) 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 the diagnosis.

Outcome III

Amieva et al (25) study reported cognitive decline 12 years before dementia in a measure of semantic memory and conceptual formation. Depressive symptoms appeared concomitantly with the cognitive decline and followed two years later with verbal memory decline. Two years later, visual disturbances were recorded and worsened until the dementia stage.

Outcome IV

Of the 63 subjects in the Fox et al (26) study of autosomal dominant FAD, ten converted to probably AD and the mean time (±standard deviation (SD)) from first assessment to the appearance of symptoms was 2.6 ± 1.4 years. Episodic memory loss was the most common and noticed on average 6 months before symptomatic assessment. The study suggests that cognitive decline is present 2-3 years before symptoms and 4-5 years before individuals fulfill the criteria for probably AD. There was no distinction in presentations with regards to age, gender and handedness. Verbal memory was superior to semantic memory in differentiating AD from normal ageing, with the lowest score in MMSE of 25 in a participant remaining stable for two years consistent with family members with the same score that remained healthy. This could help discriminate individuals at risk of conversion.

Outcome V

Thirty-five distinct neurological, psychiatric and autonomic symptoms and signs were identified in the Schmidt et al (27) study. The sequence and timing in months (averagely 26.4) of the presentation of the signs and symptoms were as follows:- disinhibition 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 thereafter. A third of RPAD experienced rapid weight loss and sleep disorder indicating their significance in discriminating the disease from other dementias.

Signs and symptoms

A pooled estimate was not possible to be reported due to the differences in participants, symptoms and types of AD, as well the scarcity of research that had reported on the sequence and timing of the early signs and symptoms. MCI was required at baseline in the Devier et al study, (20) with memory complaints six months to ten years prior to enrolment. The study began long before the Petersen et al (42) MCI criteria definition. Prior to enrolment, memory loss was observed on average 38.5; depressed mood 37.4; performance 36.8; personality 32.1; behaviour deficits 31.1; language deficits 29.2; disorientation 29.1 and psychosis 14.0 months before diagnosis.

For the ten converters in the Fox et al study,(26) 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 deficit in 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 higher early sensitivity than the semantic memory and cognitive changes 2-3 years before the symptomatic phase. There was no difference observed between cases and non-converters in terms of age, gender, handedness or MMSE at initial assessment and symptomatic assessment.

In the Schmidt et al (27) study, the median disease duration was 26.4 months and the median age at clinical onset was 73 years. The authors were unable to obtain a summary of the data from the onset of the symptoms to disease diagnosis.

All the studies were diagnosed with the NINCDS-ADRDA diagnostic criteria and symptoms measured with the neuropsychiatry inventory score.

Discussion

Four studies met the inclusion criteria which had heterogeneous objectives, diagnosis, and participants. The four studies had a total of 593 people who were followed for conversion to AD. All the studies assessed the timing of the signs and symptoms of AD prior to a formal diagnosis and/or case fatality, but with different participants and type of AD.

Studies were assessed methodologically with the QUADAS-2 tool. Three of the included studies (20, 26, 27) validated their results via the NINCDS-ADRDA and one study(27) via post-mortem examination.

Even though there were differences in timing, objectives, participants and type of AD, the Fox et al(26) study on FAD identified a participant with MMSE score of 25/30, the lowest in the group, that remained the same for two years, similar to family members that remained well throughout. This supports the evidence that the MMSE offers a reasonably good diagnosis and classification of AD,(43) especially the accuracy of the MMSE baseline score. However, critics advised that the measurement should be interpreted with caution.(44,45) Furthermore, Schmidt et al(27) discovered additional focal neurological symptoms consistent with CJD; AD was misdiagnosed as CJD until the post-mortem study proved AD as the cause of the presentations. This finding is in line with Mega et al (29) and Zahodne et al,(43) who reported that there are measurable behavioural changes in AD, and suggested that focal neurological symptoms are associated with poor prognosis.(46)

Memory disturbances remain the predominant differentiating factor between early AD and normal ageing in all of the studies. Verbal memory was more vulnerable than non-verbal in

the EOFAD.(26) The memory test for words indicated significant differences in scores, 1-5 years before becoming symptomatic, against the notion of 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. However, memory loss presented early and frequently in this group too.(20,40) The rapidly progressive LOAD (42) presented predominantly with myoclonus (75%), disturbed gait (66%) and rigidity (50%). These symptoms were also early in the presentation process occurring before apathy. Neurological and depressive behavioural presentations are an early occurrence in EOAD.(20) This calls for further studies 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.

The main limitation of this systematic review was the dearth of data and heterogeneity in methodology and findings in the included studies. Moreover, pooled estimate or statistical analysis for the signs and symptoms was not possible to be calculated and several other potential sources of heterogeneity like the age of onset, gender and education could not be investigated given the paucity of relevant data.

We excluded studies on individual symptoms and signs, as well as other types of dementia, where it was not possible to isolate AD. Further and rigorous research is needed to understand the timing and sequence of the appearance of the signs and symptoms that elude to AD prior to diagnosis, with the aim of supporting as early an AD diagnosis as possible.

Conclusions

There is a proposition of multiple definitions including MCI and subjective cognitive decline (SCD) to capture the intermediate stage between ageing and mild cognitive changes, which is in line with the effort to diagnose AD early, by recognising the signs and symptoms as reliable predictive markers of the disease.(47,48)

There are currently insufficient published data on the sequence and timing of the early signs and symptoms of AD. We advocate that more research should be undertaken in this area.

This review is important to general practitioners, researchers, health policymakers the pharmaceutical industry and the public. The review is also of importance to neurologists and other practitioners dealing with dementing disorders.

Abbreviations

AD: Alzheimer's disease; CJD: Creutzfeldt-Jacob disease; DSM-5: Diagnostic and Statistical Manual-5; EOAD: Early Onset Alzheimer's disease; FAD: Familial Alzheimer's disease; LOAD: Late Onset Alzheimer's disease; MCI: mild cognitive impairment; MeSH: Medical Subject Headings; MMSE: Mini Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communication Disorders and Stroke- Alzheimer's Disease and Related Disorders Association; QUADAS: Quality Assessment and Diagnostic Accuracy Studies; RPAD: Rapidly Progressive AD ; SCD: Subjective Cognitive Decline ; SD: Standard Deviation.

Declarations:

Authors' contributions

FB and BG conceived the study and participated in the design and drafting of the manuscript. DP participated in the analysis and helped to draft the manuscript. YP suggested the design, participated in the selection of studies, design and drafting of the manuscript. FB developed the protocol (**Supplementary file 7)** of the study, conducted the analysis and drafted the manuscript. FB, DP, BG and YP read and approved the final manuscript for this publication.

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Consent for publication: Not applicable.

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FIGURE TITLE AND LEGEND SECTION:

Figure 1: Flowchart indicating the process for the selection of studies. The flow chart indicates the articles identified through the search; those reviewed as title and abstract, those reviewed fully and the ones that met the inclusion criteria.

Figure 2: Graph representing the risk of bias and applicability concerns. Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

Figure 3: The summary of the risk of bias and applicability concerns. The reviewer's judgment on each domain for the included studies is shown with a high risk of bias and applicability concerns on index test for.(32)

Figure 1: Flowchart of selection of studies

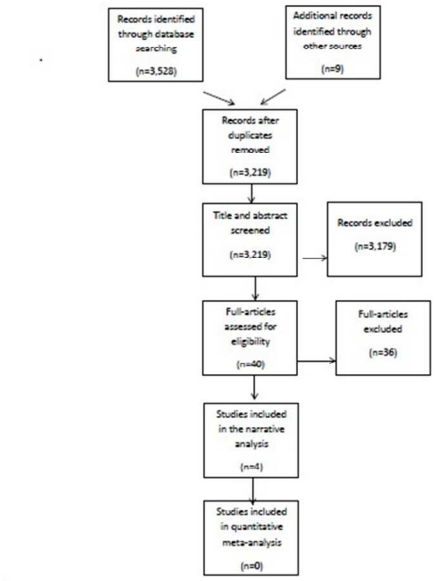

Figure 1: The flow chart indicates the articles identified through the search; those reviewed as title and abstract, those reviewed fully and the ones that met the inclusion criteria.

69x50mm (300 x 300 DPI)

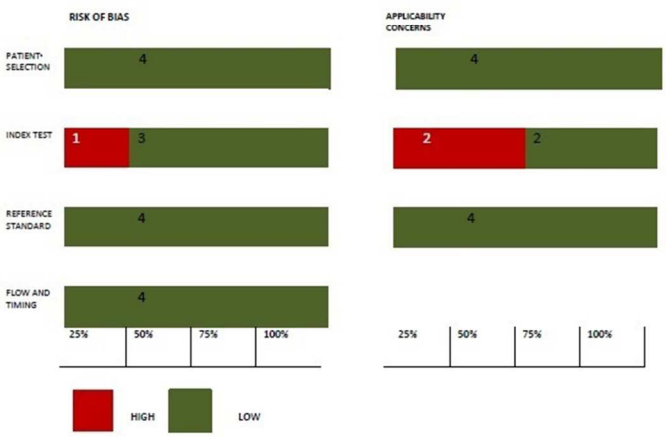

Figure 2: Proportion of studies with the risk of bias and applicability concerns: Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

69x50mm (300 x 300 DPI)

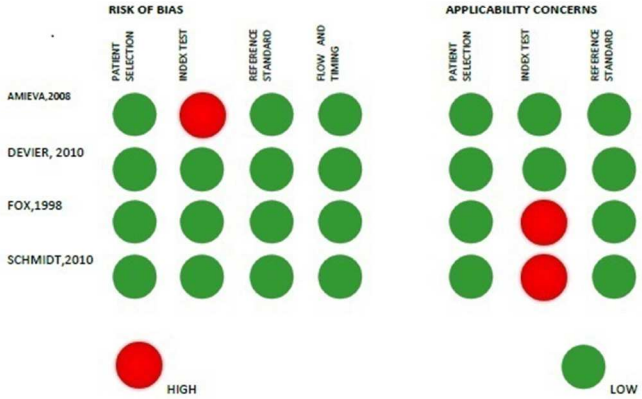

Figure 3: The summary of the risk of bias and applicability concerns; reviewer's judgement on each domain for the included studies is shown with high risk of bias on the index test for study 25 and applicability concerns on index test for study 26 and 27.

69x50mm (300 x 300 DPI)

SUPPORTING STATEMENT

We conducted according to and based the report of this systematic review on the preferred reporting items for systematic review and meta-analysis (PRISMA). We used a protocol, which we followed to avoid introducing bias to the review.

One author screened all titles. Two authors reviewed all abstracts and full texts with disagreement for inclusion resolved by a third author. We used the Quality Assessment Diagnostic Accuracy Studies (QUADAS-2) to appraise quality. The risk of bias was also 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 has been summarised in the summary tables and figures, with the PRISMA flow chart in the appendix.

SYSTEMATIC 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. It is to be noted that though the scoping review is based on a systematic review protocol, it is neither an intervention nor a testing a diagnostic tool, but a review undertaken using a set procedure within a large and diverse literature. This is to understand the whole of the literature by systematically searching and synthesising so as not to miss any relevant literature.

BACKGROUND

Alzheimer's disease 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 and 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 2011, Dubois 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.

Alzheimer's disease 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 Society, 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, Brendan et al 2008, 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%;and47%&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 Alzheimer's disease 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 Alzheimer's disease 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 (Freedman et al, 2013) 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), PsychINFO (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. Also, the disease theatre will be the main theatre, followed by the timing theatre, then the basic theatre including country, onset and combination theatres, before duplicate is removed. This is to systematically capture the desire 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 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:

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 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.

The quantitative data will be plotted with (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). 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.

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Appendix 1

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.

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.

Grey Literatures:

Dates for search: 9th May 2016. Included terms were AD, terms for cognitive impairment and limit same as databases limits.

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Systematic scoping review- 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and Implications of key findings; systematic review registration number.	2&3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5&6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Supplementary list
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5&6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6 & 25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21-26
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5&6
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and	7

Section/topic	#	Checklist item	Reported on page #
		any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5&6
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7&8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not undertaken due to dearth of data and heterogeneity in studies.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11&12
Additional analysis	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not done; same as response 13.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7&8 ;table 1; figure 2&3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
Synthesis of	21	Present results of each meta-analysis done,	Same as

Section/topic	#	Checklist item	Reported on page #
results		including confidence intervals and measures of consistency.	response 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11&12
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Same as response 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	11&12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N.A

From: Moher et al (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

BMJ Open

Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937-2016.

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Manuscript ID	bmjopen-2016-015746.R2
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diagnostics, Neurology, Epidemiology, Public health, Pathology
Keywords:	Dementia < NEUROLOGY, NEUROLOGY, EPIDEMIOLOGY

Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937-2016.

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Abstract

Objective

Late diagnosis of Alzheimer's disease (AD) may be due diagnostic uncertainties. We aimed to determine the sequence and timing of the appearance of established early signs and symptoms in people who are subsequently diagnosed with AD.

Methods

We used systematic review methodology to investigate the existing literature. Articles were reviewed in May 2016, using the following databases: MEDLINE, PsycINFO, CINAHL, British Nursing Index, PubMed central and the Cochrane library, with no language restriction. Data from the included articles were extracted independently by two authors and quality assessment was undertaken with the quality assessment and diagnostic accuracy tool-2 (QUADAS tool-2 quality assessment tool).

Results

We found that depression and cognitive impairment were the first symptoms to appear in 98.5% and 99.1% of individuals in a study with late-onset AD (LOAD) and 9% and 80% respectively in EOAD. Memory loss presented early and was experienced 12 years before the clinically defined AD dementia in the LOAD. However, the rapidly progressive late onset AD (RPLOAD), presented predominantly with 35 non-established focal symptoms and signs including myoclonus (75%), disturbed gait (66%) and rigidity. These were misdiagnosed as symptoms of Creutzfeldt-Jacob disease (CJD) in all the cases. The participant with the lowest mini-mental state examination (MMSE) score of 25 remained stable for 2 years, which is consistent with the score of the healthy family members.

Conclusions

The findings of this review suggest that neurological and depressive behaviours are an early occurrence in early-onset AD (EOAD) with depressive and cognitive symptoms in the measure of semantic memory and conceptual formation in LOAD. Misdiagnosis of RPAD as CJD and the familial memory score can be confounding factors while establishing a

diagnosis. However, the study was limited by the fact that each one of the findings was based on a single study.

Strengths

- The review indicates a paucity of data on the study objectives and heterogeneity in the timing of symptoms presentation in published studies.
- Comprehensive search strategy was used to identify articles for this review.
- This is the first review to identify the sequence and timing of the signs and symptoms in the early stage of AD.

Limitations

- Dearth of data, heterogeneity in methodology and findings, made it impossible to draw a definite conclusion.
- Several other potential sources of heterogeneity like age, gender and education could not be investigated with the dearth of data.

Keywords: Alzheimer's disease (AD), systematic scoping review, early signs and symptoms, mild cognitive impairment (MCI), early stage of AD.

Introduction

Alzheimer's disease (AD), the most common type of dementia is a devastating disease with multiple presentations. While the disease is associated with old age, scientists (1-2) have discovered that disease can develop at any age and the reason for this is unclear. The disease could develop before the age of 65 years, known as early onset AD (EOAD), which might be inherited or sporadic, or after the age of 65 years, known as late onset AD (LOAD), that accounts for 90% of all AD cases (3). In the UK, a prevalence of 520,000 has been reported in 2014 (4-6) with high individual, health care and financial burden.(7,8) There are challenges in diagnosing the disease early,(9-11) which can result to non-reversible symptoms progression, that lead to institutionalisation and high mortality rate among this group.(12)There is also the emotional and physical burden to the care givers(13,14) as well as emotional, physical and financial burden to the health care system(15). Even though there is discourse in the meaning of the early diagnosis, here, it refers to the diagnosis at the lowest threshold of the disease or at the stage of mild cognitive impairment (MCI), with cluster of early signs and symptoms and the diagnosis of the pathology of the disease before dementia. This is because the disease has a preclinical stage with the clinical symptoms yet evident but with changes in the brain and the risk of progression unknown; intermediate stage with mild cognitive and functional changes and dementia due to AD stage with severe cognitive and functional decline.

Among the reasons for the late diagnosis is that the signs and symptoms, at the early stages of AD, are sometimes not recognised and/or mistaken for signs of old age or symptoms of other conditions. (5, 16-18) The above may be partly due to the fact that the timing and sequence of the early presentation of signs and symptoms are not reported by current studies. (19-21). Delaying onset of the disease by five years through early diagnosis and intervention could reduce the mortality rate of dementia (advanced stage of AD) by 30,000 yearly (22).

This review attempts to answer the following research question: how far back from diagnosis and in what sequence do the first symptoms that warrant an AD diagnosis appear? Further understanding of the timing and the sequence of the presentation of signs and symptoms may enable practitioners to offer timely intervention.

Methods

Types of studies

All types of empirical studies were considered, excluding those of qualitative design.

Participants

Included participants were aged between 30-85 years and diagnosed with AD.

Settings

Primary care, memory clinics or secondary care settings.

Target condition

AD, and any subtypes, were diagnosed with the following tools: (a) National Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders Association (NINCDS-ADRDA, UK), a commonly used criteria for AD dementia; (b) National Institute on Aging-Alzheimer's Association (NIA-AA, US), more recent criteria that use biomarkers to support the diagnosis; (c) Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV);(23) and (d) DSM-5.(24)

Outcomes

The outcomes of this review included (I) the sequence of presentation of the signs and symptoms that are indicative of AD prior to diagnosis;(20) (II) the timing from the first reported symptom to diagnosis;(20) (III) the timing from MCI to diagnosed dementia stage; (25) (IV) the timing of assessments leading up to a diagnosis of AD (26) and (V) the timing from clinical presentations to case fatality or death.(27)

Index symptoms

We used an index of early symptoms as a reference to ascertain the timing and sequence of events prior to disease presentation. The index is based on previous studies,(28-32) which include apathy, agitation, anxiety, anosognosia, aberrant motor behaviour, acalculia, alexia, anomia, disinhibition, depression, irritability, hallucination and olfactory disturbances and weight loss.(28-32)

Exclusion criteria

- Participants with other dementia or other neurological conditions;
- Inaccurate diagnostic criteria;
- Single index symptom;
- Late stage AD (AD dementia); a set of symptoms including memory loss, difficulty in thinking, problem-solving or language difficulties.(33)

Search criteria for identification of studies

We searched the literature via OvidSP MEDLINE (1950), PsycINFO (1887), British Nursing Index (1994), CINAHL (1937), PubMed central (2000) and the Cochrane register for diagnostic and intervention studies. We also used "snowballing" and searched the references of relevant articles. Searches covered the period from 1937 until May 2016. No language or publication restrictions were applied. We used medical subject headings (MeSH) terms to standardise and improve the search; AD was the main term followed by the basic terms timing, onset and country, and the combination of terms. Details of the database search strategies are presented in **Appendix 1.**

Data collection and analysis

Assessment of methodological quality

The qualities of included studies were assessed using the QUADAS-2 tool, a methodological quality assessment tool used to assess diagnostic accuracy studies (34) (**Table 1**) and PRISMA checklist. The tool consist of fourteen items that rates the Risk of bias, source of

variations (Applicability and reporting of quality), with each item rated as 'yes' 'no' or 'unclear', tailored under four domains that includes: Participants Selection; Index Test (signs and symptoms interpretation) Reference Standard (diagnostic criteria that correctly classify the target condition) and Flow and Timing (time interval and intervention between Index Test and Reference Standard.

Table 1. Quality assessment using the QUADAS tool.

DOMAIN	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING OF SIGNS AND SYMPTOMS
Description	Describe methods of participant selection: Describe 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 (diagnostic criteria): Describe the time interval and any interventions between index test(s) and reference standard; that is, any intervention/ medication given prior to diagnosis.
Signalling questions (Yes/no/unclear)	Was 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?	

Results

Results of the search

The process by which articles were identified, screened and selected for the review is described in **Figure 1**. A total of 3,528 articles were identified in the databases including 318 duplicates. Nine others were identified through hand searching and 3,179 were excluded based on the review of titles and abstract alone. The full-text versions of 40 were assessed for eligibility, 13 were initially included but nine later excluded (reasons stated below). Four articles were finally included in the review.

Reasons for exclusion

Although thirteen studies were reviewed in full, nine were excluded. The reasons for exclusion were; four studies were on unspecified dementia;(30, 35-37) one study was undertaken in a developing country;(38) another on caregiver's distress;(31) one study was on a single case;(22) one study had incomplete data;(39) while another did not have a reference point for the diagnosis of AD.(19)

Summary of findings:

Methodological quality of included studies

The methodological quality in each domain was assessed individually.

The QUADAS-2 scores for each domain **(Table 1)** of the studies included in the review are shown in **Figures 2 and 3.** The reviewer included a nested case-control with random sampling,(25) longitudinal follow-up of mild cognitive impairment (MCI) patients,(20) longitudinal prospective study of individuals at risk of autosomal dominant familial AD(26) and a retrospective case study (post-mortem).(27) For the case studies,(20, 26,27) the exclusion criteria were appropriate and sample selection was consecutive, which reduced the risk of selection bias .(**Table 2, Figure 2)**

(**Table 2, Figure 2)**

TABLES **Table 2.** Summary of study methodology and key findings.

AUTHOR(S) & YEAR	TITLE OF STUDY	STUDY OBJECTIVE	SAMPLE SIZE	STUDY METHODS	KEY FINDINGS	STRENGTH	LIMITATION	STATEMENTS
Amieva et al, 2008.	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 decline and depressive symptoms, verbal decline in the 4th year and visual disturbance in the last 5-6 years into the study.	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.
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 in 9%, 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 was present 2-3 years before symptoms manifestation and 4-5 years before fulfilling the criteria for probable AD.	The study demonstrates that cognitive deficits predict 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 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.
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.

The index test was not influenced by the reference standard in three studies.(20, 25, 26) However, the index test domain was judged as having a high risk of bias in a study (27) due to the fact that the index tests were interpreted based on the knowledge of the disease (post-mortem). In the applicability concerns, the conduct and interpretation of the index symptoms were different from the review question in Fox et al (26) and Schmidt et al.(27) The Fox et al(26) study focused on the mean time from first assessment to the appearance of symptoms at reporting, while the study published by Schmidt et al (27) focused on identifying the median time span from clinical presentation of the disease to case fatality or death.

In the reference standard domain, all studies were undertaken using the diagnostic criteria for AD, recognised internationally that could correctly classify the condition with masking in all. The Schmidt et al study (27) on rapidly progressive AD was undertaken post-mortem, the gold standard for the diagnosis of AD. However, none of the studies reported how the reference standard was operationalised or applied. They were assessed as being a low risk of concern about applicability.

In the flow and timing domain, there was an appropriate interval between the appearance of symptoms and signs and the reference standard. There was no mention of treatment in between the timings and all of the participants were diagnosed using the same reference standard. All participants were included in the analysis.

Findings

Outcome I

Of the 148 participants in the Devier et al study, (20)39 (26%) converted to AD and all of the converters were 55 years at baseline indicating an early onset AD (EOAD). There were differences in the first symptom at presentation with memory decline reported as the first in 118 (80%) of the cases, depressed mood in 13 (9%), declined language in six (4%), change in performance of higher order/cognitive activities in four (3%), disorientation in three (2%), personality changes and behavioural changes in two (1%), with no group difference in symptoms reporting. Sequentially in the order of appearance of the signs and symptoms in

all the participants, memory decline was the first followed by performance changes, changes in language, disorientation, personality changes, depressed mood, behavioural changes and psychosis consecutively. However, for depression, 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 (40) and all cause dementia (41).

Outcome II

Memory decline was experienced in 38.5 months before diagnosis,(20) 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 the diagnosis.

Outcome III

Amieva et al (25) study reported cognitive decline 12 years before dementia in a measure of semantic memory and conceptual formation. Depressive symptoms appeared concomitantly with the cognitive decline and followed two years later with verbal memory decline. Two years later, visual disturbances were recorded and worsened until the dementia stage.

Outcome IV

Of the 63 subjects in the Fox et al (26) study of autosomal dominant FAD, ten converted to probably AD and the mean time (±standard deviation (SD)) from first assessment to the appearance of symptoms was 2.6 ± 1.4 years. Episodic memory loss was the most common and noticed on average 6 months before symptomatic assessment. The study suggests that cognitive decline is present 2-3 years before symptoms and 4-5 years before individuals fulfill the criteria for probably AD. There was no distinction in presentations with regards to age, gender and handedness. Verbal memory was superior to semantic memory in differentiating AD from normal ageing, with the lowest score in MMSE of 25 in a participant remaining stable for two years consistent with family members with the same score that remained healthy. This could help discriminate individuals at risk of conversion.

Outcome V

Thirty-five distinct neurological, psychiatric and autonomic symptoms and signs were identified in the Schmidt et al (27) study. The sequence and timing in months (averagely 26.4) of the presentation of the signs and symptoms were as follows:- disinhibition 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 thereafter. A third of RPAD experienced rapid weight loss and sleep disorder indicating their significance in discriminating the disease from other dementias.

Signs and symptoms

A pooled estimate was not possible to be reported due to the differences in participants, symptoms and types of AD, as well the scarcity of research that had reported on the sequence and timing of the early signs and symptoms. MCI was required at baseline in the Devier et al study, (20) with memory complaints six months to ten years prior to enrolment. The study began long before the Petersen et al (42) MCI criteria definition. Prior to enrolment, memory loss was observed on average 38.5; depressed mood 37.4; performance 36.8; personality 32.1; behaviour deficits 31.1; language deficits 29.2; disorientation 29.1 and psychosis 14.0 months before diagnosis.

For the ten converters in the Fox et al study,(26) 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 deficit in 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 higher early sensitivity than the semantic memory and cognitive changes 2-3 years before the symptomatic phase. There was no difference observed between cases and non-converters in terms of age, gender, handedness or MMSE at initial assessment and symptomatic assessment.

In the Schmidt et al (27) study, the median disease duration was 26.4 months and the median age at clinical onset was 73 years. The authors were unable to obtain a summary of the data from the onset of the symptoms to disease diagnosis.

All the studies were diagnosed with the NINCDS-ADRDA diagnostic criteria and symptoms measured with the neuropsychiatry inventory score.

Discussion

Four studies met the inclusion criteria which had heterogeneous objectives, diagnosis, and participants. The four studies had a total of 593 people who were followed for conversion to AD. All the studies assessed the timing of the signs and symptoms of AD prior to a formal diagnosis and/or case fatality, but with different participants and type of AD.

Studies were assessed methodologically with the QUADAS-2 tool. Three of the included studies (20, 26, 27) validated their results via the NINCDS-ADRDA and one study(27) via post-mortem examination.

Even though there were differences in timing, objectives, participants and type of AD, the Fox et al(26) study on FAD identified a participant with MMSE score of 25/30, the lowest in the group, that remained the same for two years, similar to family members that remained well throughout. This supports the evidence that the MMSE offers a reasonably good diagnosis and classification of AD,(43) especially the accuracy of the MMSE baseline score. However, critics advised that the measurement should be interpreted with caution.(44,45) Furthermore, Schmidt et al(27) discovered additional focal neurological symptoms consistent with CJD; AD was misdiagnosed as CJD until the post-mortem study proved AD as the cause of the presentations. This finding is in line with Mega et al (29) and Zahodne et al,(43) who reported that there are measurable behavioural changes in AD, and suggested that focal neurological symptoms are associated with poor prognosis.(46)

Memory disturbances remain the predominant differentiating factor between early AD and normal ageing in all of the studies. Verbal memory was more vulnerable than non-verbal in

the EOFAD.(26) The memory test for words indicated significant differences in scores, 1-5 years before becoming symptomatic, against the notion of 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. However, memory loss presented early and frequently in this group too.(20,40) The rapidly progressive LOAD (42) presented predominantly with myoclonus (75%), disturbed gait (66%) and rigidity (50%). These symptoms were also early in the presentation process occurring before apathy. Neurological and depressive behavioural presentations are an early occurrence in EOAD.(20) This calls for further studies 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.

The main limitation of this systematic review was the dearth of data and heterogeneity in methodology and findings in the included studies. Moreover, pooled estimate or statistical analysis for the signs and symptoms was not possible to be calculated and several other potential sources of heterogeneity like the age of onset, gender and education could not be investigated given the paucity of relevant data.

We excluded studies on individual symptoms and signs, as well as other types of dementia, where it was not possible to isolate AD. Further and rigorous research is needed to understand the timing and sequence of the appearance of the signs and symptoms that elude to AD prior to diagnosis, with the aim of supporting as early an AD diagnosis as possible.

Conclusions

There is a proposition of multiple definitions including MCI and subjective cognitive decline (SCD) to capture the intermediate stage between ageing and mild cognitive changes, which is in line with the effort to diagnose AD early, by recognising the signs and symptoms as reliable predictive markers of the disease.(47,48)

There are currently insufficient published data on the sequence and timing of the early signs and symptoms of AD. We advocate that more research should be undertaken in this area.

This review is important to general practitioners, researchers, health policymakers the pharmaceutical industry and the public. The review is also of importance to neurologists and other practitioners dealing with dementing disorders.

Abbreviations

AD: Alzheimer's disease; CJD: Creutzfeldt-Jacob disease; DSM-5: Diagnostic and Statistical Manual-5; EOAD: Early Onset Alzheimer's disease; FAD: Familial Alzheimer's disease; LOAD: Late Onset Alzheimer's disease; MCI: mild cognitive impairment; MeSH: Medical Subject Headings; MMSE: Mini Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communication Disorders and Stroke- Alzheimer's Disease and Related Disorders Association; QUADAS: Quality Assessment and Diagnostic Accuracy Studies; RPAD: Rapidly Progressive AD ; SCD: Subjective Cognitive Decline ; SD: Standard Deviation.

Declarations:

Authors' contributions

FB and BG conceived the study and participated in the design and drafting of the manuscript. DP participated in the analysis and helped to draft the manuscript. YP suggested the design, participated in the selection of studies, design and drafting of the manuscript. FB developed the protocol of the study, conducted the analysis and drafted the manuscript. FB, DP, BG and YP read and approved the final manuscript for this publication.

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Consent for publication: Not applicable.

Data sharing: No additional data available.

Competing interest: "We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests".

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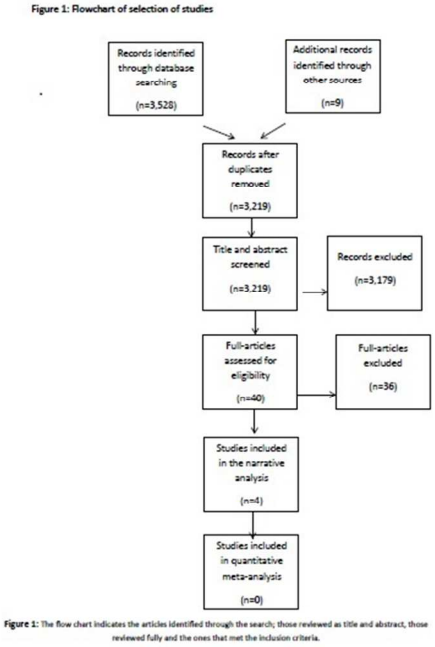
FIGURE TITLE AND LEGEND SECTION:

Figure 1: Flowchart indicating the process for the selection of studies. The flow chart indicates the articles identified through the search; those reviewed as title and abstract, those reviewed fully and the ones that met the inclusion criteria.

Figure 2: Graph representing the risk of bias and applicability concerns. Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

Figure 3: The summary of the risk of bias and applicability concerns. The reviewer's judgment on each domain for the included studies is shown with a high risk of bias and applicability concerns on index test for.(32)



69x50mm (300 x 300 DPI)

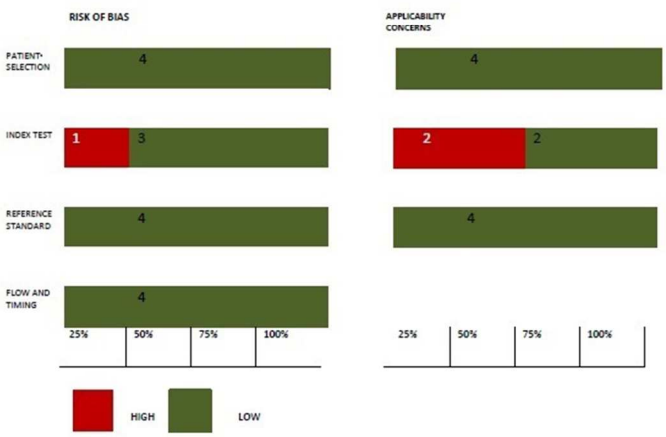


Figure 2: Proportion of studies with the risk of bias and applicability concerns: Each domain is represented as a percentage across included studies for the review; the red colour indicates high risk, while the green indicates low risk. However, none of the studies was given an unclear risk of bias and applicability concerns (QUADAS-2 tool).

69x50mm (300 x 300 DPI)

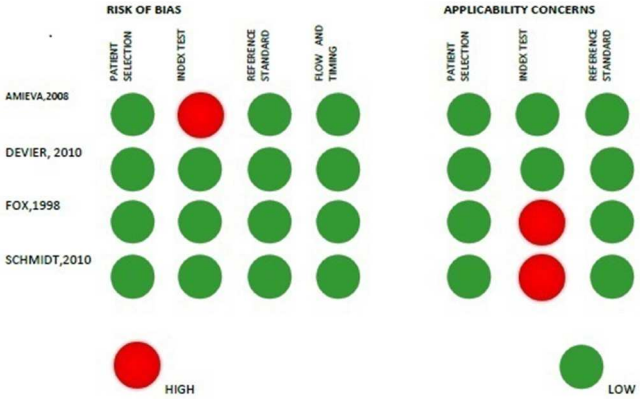


Figure 3: The summary of the risk of bias and applicability concerns; reviewer's judgement on each domain for the included studies is shown with high risk of bias on the index test for study 25 and applicability concerns on index test for study 26 and 27.

69x50mm (300 x 300 DPI)

Appendix 1

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.

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.

Grey Literatures:

Dates for search: 9th May 2016. Included terms were AD, terms for cognitive impairment and limit same as databases limits.

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Systematic scoping review- 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and Implications of key findings; systematic review registration number.	2&3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5&6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Supplementary list
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5&6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6 & 25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21-26
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5&6
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and	7

Section/topic	#	Checklist item	Reported on page #
		any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5&6
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7&8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not undertaken due to dearth of data and heterogeneity in studies.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11&12
Additional analysis	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not done; same as response 13.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7&8 ;table 1; figure 2&3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
Synthesis of	21	Present results of each meta-analysis done,	Same as

Section/topic	#	Checklist item	Reported on page #
results		including confidence intervals and measures of consistency.	response 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11&12
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Same as response 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	11&12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N.A

From: Moher et al (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.