PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Signs and Symptoms Preceding the Diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937-2016.
AUTHORS	BATURE, FIDELIA; Guinn, Barbara; Pang, Dong; Pappas, Yannis

VERSION 1 - REVIEW

REVIEWER	Raudino Francesco Valduce Hospital Dept. of Neurology. Como ITALY
REVIEW RETURNED	16-Jan-2017

GENERAL COMMENTS	This is a good review regarding a topic not well know but with possible interesting implications. The old version (from page 38) will be deleted.

REVIEWER	Catherine M. Roe Washington University School of Medicine
REVIEW RETURNED	05-Feb-2017

GENERAL COMMENTS	Fidelia et al. set out to review the literature on the signs and symptoms of AD specifically. For persons with diagnosed AD, they examined the first symptom reported at presentation, the average sequence of symptoms across participants included in the review, the time of symptom occurrence prior to diagnosis, the approximate timing of cognitive decline prior to a diagnosis of probably AD, and signs and symptoms of AD. Overall, I believe that this is an outstanding paper. I found the methodology to be impeccable and extremely rigorous. The amount of detail regarding the methodology was excellent, as evidenced by the Systematic Review Protocol. The question is an important one, as knowledge of the early signs and symptoms of AD can signal clinicians, loved ones, and the individuals themselves, that the possibility that AD is present, or impending. This would in turn increase the likelihood of early diagnosis, enabling early treatment, better understanding of what the individual is experiencing, and planning for the future. Highlights of the paper include examination of longitudinal studies, as opposed to cross-sectional reports, excellent choice of outcomes, review of the literature over a period of approximately 80 years, and clear explanation of the limitations of the findings and conclusions that can be taken from the review.

	As noted by the authors, the biggest limitation of this report is the fact that only 4 studies were available for review. Although I understand and agree with the authors reasoning in confining their review to "clean" AD samples, I believe that it would have been informative to have also reviewed (separately) the 4 studies cited that examined dementia generally. Since most dementia is due to AD, it is likely that the results would have been similar to those found in the clean AD samples, which to my mind would have added greater power to the findings. If the results had varied from the clean samples, that would presumably help to inform knowledge about the specificity of the signs and symptoms of AD. I have a specific remark regarding the last paragraph on page 8. The second sentence reports on the first symptoms presented. The next sentence talks about the sequence of symptom presentation. I initially found this to be quite confusing, since depression was the second-most often symptom at first presentation, but appeared to be relatively late in the sequence of symptom development. Perhaps this paragraph could be clarified.

REVIEWER	Tobi Van den Bossche, MD VIB - UAntwerp Center for Molecular Neurology, Belgium
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	Bature et al. have performed a systematic scoping review of the literature to identify the timing/sequence of early signs and symptoms associated with Alzheimer's disease. This study is certainly of interest, since early diagnosis is an important step in improving patient care and selection for (developing) therapeutic interventions, as well as further elucidation of AD pathophysiology. After review and quality assessment of the literature, they describe - some - of the early features that have been observed in different forms of AD, but conclude that there is a paucity in the currently available data and that further research in this area should be conducted. General comments: some parts of the manuscript can be confusing. However, the 'systematic review protocol' does clarify a lot – can it be incorporated more in the main text? Though more research is certainly needed, it seems a bit strange that only four papers can be included. This way, it does not accurately reflect the current state-of-the-art. Too much excluded with screening of the titles? The remainder of the methodology has however been performed meticulously and the outcomes (though limited) are of interest and clearly described. The abstract results and conclusion paragraphs need to be rewritten to be more in line with the objectives. With 'AD diagnosis' – do you mean dementia due to AD or (as current biomarkers allow) identification of underlying AD pathophysiology (thus also encompassing prodromal AD, MCI due to AD,…)? The introduction could at least mention the well described predementia phase of Mild Cognitive Impairment (and some even advocate the recognition of a predementia Mild Behavioral Impairment stage). Since different forms of AD are included (ie. LOAD vs EOAD, autosomal dominant AD,...) the introduction or discussion could elaborate a bit more on the differences between these forms (for example the diagnostic approach and differential diagnosis in EOAD is not the same as in LOAD). Please review the text again for correct use of language and punctuation.

	Specific comments: Objective (page 2/53): do you want to determine the sequence and timing of already established early signs/symptoms, or also establish what these early signs/symptoms encompass? If so, the latter should be mentioned in the abstract objective. If this is not the case, the introduction (5/53) should elaborate a bit more on the current knowledge on prodromal/early AD and the range of associated symptomatology/signs (eg. it is more clearly stated in the 'Outcomes' and 'Index symptoms' paragraph of the methodology, but this should be more clear in the objective/introduction). Results (2/53 - line 37): 'some individuals' is not clear and too much open for interpretation. Is it a rare occurrence (which it is not) or is the predominant early presentation of AD? Same line: is 'memory loss' not a part of 'cognitive impairment' (line 36)? Do you mean memory complaints (SCI) or objective memory impairment (MCI)? Line 42: these (ie. rigidity, myoclonus) are signs, not symptoms. Line 46: it is not clear which participant you mean (lowest MMSE across all the cohorts you investigated?), and what the implication of this result is (still remains unclear to me in further reading of the manuscript), or how this fits in the objective. In general, the results should be more reflective of the outcomes described nicely further in the manuscript. Conclusions (2/53): the conclusion in the abstract does not aptly reflect the objective, or the conclusion as stated on 12/53. Also, in the results you mention depression/cognitive impairment in LOAD, but in the conclusion you speak of EOAD? Introduction (5/53): line 12-13: there are indeed challenges in early diagnosis, but cognitive and functional decline is a consequence of the neurodegeneration – not the missed diagnosis. You could elaborate a bit more on the consequences of a missed diagnosis eg. distress in patients/family due to the uncertainty associated with lack of a diagnosis, delay of advanced care planning, inappropriate treatment, etc. Summary of findings (7/53): line 57: not clear what you mean with 'red-flag or easier to diagnose' patients. Outcome IV (9/53): it should be more clear that this is in the specific setting of autosomal dominant AD. Discussion (11/53): line 27: maybe mention the criteria that were used for neuropathological diagnosis. Line 32-37: I do not understand this part on the MMSE, as it has been shown that the MMSE has very poor sensitivity for early stage AD. And how does this contribute to 'classification'? Page 12/53, first line: has it been taken into account that depression can also lead to cognitive impairment? Line 13: what do you mean with 'neurological presentation' (is an EOAD presentation not always 'neurological' in nature)? Conclusions (12/53): line 42: can you elaborate on these proposed 'multiple definitions' or more clearly define them in the discussion? Line 52: it seems these finding are also of relevance to neurologists and other practitioners dealing with dementing disorders.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO COMMENT FROM DR. RAUDINO FRANCESCO:
This is a good review regarding a topic not well known but with possible interesting implications.
The old version (from page 38) will be deleted.
RESPONSE: Thank you.

RESPONSE TO COMMENTS FROM DR. CATHERINE M. ROE:
Fidelia et al. set out to review the literature on the signs and symptoms of AD specifically. For persons with diagnosed AD, they examined the first symptom reported at presentation, the average sequence of symptoms across participants included in the review, the time of symptom occurrence prior to diagnosis, the approximate timing of cognitive decline prior to a diagnosis of probably AD, and signs and symptoms of AD.

Overall, I believe that this is an outstanding paper. I found the methodology to be impeccable and extremely rigorous. The amount of detail regarding the methodology was excellent, as evidenced by the Systematic Review Protocol. The question is an important one, as knowledge of the early signs and symptoms of AD can signal clinicians, loved ones, and the individuals themselves, that the possibility that AD is present, or impending. This would in turn increase the likelihood of early diagnosis, enabling early treatment, better understanding of what the individual is experiencing, and planning for the future.
Highlights of the paper include examination of longitudinal studies, as opposed to cross-sectional reports, excellent choice of outcomes, review of the literature over a period of approximately 80 years, and clear explanation of the limitations of the findings and conclusions that can be taken from the review.
RESPONSE: Thank you.
As noted by the authors, the biggest limitation of this report is the fact that only 4 studies were available for review. Although I understand and agree with the authors reasoning in confining their review to "clean" AD samples, I believe that it would have been informative to have also reviewed (separately) the 4 studies cited that examined dementia generally. Since most dementia is due to AD, it is likely that the results would have been similar to those found in the clean AD samples, which to my mind would have added greater power to the findings. If the results had varied from the clean samples that would presumably help to inform knowledge about the specificity of the signs and symptoms of AD.I have a specific remark regarding the last paragraph on page 8. The second sentence reports on the first symptoms presented. The next sentence talks about the sequence of symptom presentation. I initially found this to be quite confusing, since depression was the second-most often symptom at first presentation, but appeared to be relatively late in the sequence of symptom development. Perhaps this paragraph could be clarified.
RESPONSE: The paragraph has now been edited for clarification. The bottom of page 9 and the top of page 10 (line 240-42) now read: ‘When considering the occurrence of depression, reverse causation 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.’

RESPONSES TO COMMENTS FROM DR. TOBI VAN DEN BOSSCHE
Bature et al. have performed a systematic scoping review of the literature to identify the timing/sequence of early signs and symptoms associated with Alzheimer’s disease. This study is certainly of interest, since early diagnosis is an important step in improving patient care and selection for (developing) therapeutic interventions, as well as further elucidation of AD pathophysiology. After review and quality assessment of the literature, they describe - some - of the early features that have been observed in different forms of AD, but conclude that there is paucity in the currently available data and that further research in this area should be conducted.
RESPONSE: Thank you.
General comments: some parts of the manuscript can be confusing. However, the ‘systematic review

protocol' does clarify a lot – can it be incorporated more in the main text?
RESPONSE: We have now added more elements of the 'systematic review protocol' in the main text to explain the QUADAS tool as follows: The tool consist of fourteen items that rates the risk of bias, source of variation (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 (Line 178-84, page 7); and explain the findings in outcome 1: 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 (Line 239-41,page 9).

Though more research is certainly needed, it seems a bit strange that only four papers can be included. This way, it does not accurately reflect the current state-of-the-art. Too much excluded with screening of titles?
RESPONSE: We faithfully followed our protocol and specifically the exclusion/inclusion criteria in the process of screening.
The remainder of the methodology has however been performed meticulously and the outcomes (though limited) are of interest and clearly described.
RESPONSE: Thank you.
The abstract results and conclusion paragraphs need to be rewritten to be more in line with the objectives.
RESPONSE: The abstract, results and conclusions have been rewritten in line with the objectives in pages 2 and 3, lines 28-29, 31, 42-43, 45, 52-53. However, the finding of interest of MMSE score of 25 prior to clinical diagnosis of AD is included in the abstract to help discriminate the converters from non-converters in FAD.
With 'AD diagnosis' – do you mean dementia due to AD or (as current biomarkers allow) identification of underlying AD pathophysiology (thus also encompassing prodromal AD, MCI due to AD,…)?
RESPONSE: We mean the diagnosis at pre-dementia stage (intermediate phase) with a cluster of early signs and symptoms and the dementia phase of the disease. This has now been clarified on page 5 lines 118-22.
The introduction could at least mention the well described pre-dementia phase of Mild Cognitive Impairment (and some even advocate the recognition of a pre-dementia Mild Behavioral Impairment stage). Since different forms of AD are included (ie. LOAD vs EOAD, autosomal dominant AD,...) the introduction or discussion could elaborate a bit more on the differences between these forms (for example the diagnostic approach and differential diagnosis in EOAD is not the same as in LOAD).
Please review the text again for correct use of language and punctuation.
RESPONSE: Thank you. We have included the types (lines 106-10), stages (lines 119-22) and diagnostic approach (lines 115-19) of AD and the text in the introduction section on page 5 was reviewed for correct use of language and punctuation.

Specific comments:

Objective (page 2/53): do you want to determine the sequence and timing of already established early signs/symptoms, or also establish what these early signs/symptoms encompass? If so, the latter should be mentioned in the abstract objective. If this is not the case, the introduction (5/53) should elaborate a bit more on the current knowledge on prodromal/early AD and the range of associated symptomatology/signs (eg. it is more clearly stated in the 'Outcomes' and 'Index symptoms' paragraph of the methodology, but this should be more clear in the objective/introduction).
RESPONSE: We determined the sequence and timing of already established early signs and symptoms. We have added the term 'established' to distinguish this fact in the objective on page 2, line 31.

Results (2/53 - line 37): ‘some individuals’ is not clear and too much open for interpretation.
RESPONSE: Thank you. The terms ‘some individuals’ have been removed and the percentage is stated instead in the results on page 2, lines 42-3.
Is it a rare occurrence (which it is not) or is the predominant early presentation of AD?
RESPONSE: Here, we mean predominantly early presentation of AD, as specified in the objective on page 2, line 31.
Same line: is ‘memory loss’ not a part of ‘cognitive impairment’ (line 36)? Do you mean memory complaints (SCI) or objective memory impairment (MCI)?
RESPONSE: Memory loss is part of cognitive impairment in MCI and the sentence has now been edited for clarity: ‘Memory loss presented early and was experienced 12 years before the clinically defined AD dementia in the LOAD’, on page 2, lines 43-4.
Line 42: these (ie. rigidity, myoclonus) are signs, not symptoms.
RESPONSE: This has been corrected on page 2, lines 44-6 as follows: However, the rapidly progressive late onset AD (RPLOAD), presented predominantly with 35 non-established focal symptoms and signs and including myoclonus (75%), disturbed gait (66%) and rigidity.
Line 46: it is not clear which participant you mean (lowest MMSE across all the cohorts you investigated?), and what the implication of this result is (still remains unclear to me in further reading of the manuscript), or how this fits in the objective. In general, the results should be more reflective of the outcomes described nicely further in the manuscript. Conclusions (2/53): the conclusion in the abstract does not aptly reflect the objective, or the conclusion as stated on 12/53.
RESPONSE: We mean the lowest MMSE score ‘25’ in the FAD study; although not part of the objective, this finding of interest, could support the diagnosis, by discriminating converters from non-converters in FAD, as MMSE is part of AD diagnostic criteria in the clinical practice. However, we would be delighted to take this finding out of the manuscript.

Also, in the results you mention depression/cognitive impairment in LOAD, but in the conclusion you speak of EOAD?
RESPONSE: The results section has been clarified to state that ‘depressive and cognitive symptoms were early occurrence in LOAD as well as EOAD but in different measures and type of memory decline’ on page 2 lines 51 to page 3 line 53.

Introduction (5/53): line 12-13: there are indeed challenges in early diagnosis, but cognitive and functional decline is a consequence of the neurodegeneration – not the missed diagnosis. You could elaborate a bit more on the consequences of a missed diagnosis e.g. distress in patients/family due to the uncertainty associated with lack of a diagnosis, delay of advanced care planning, inappropriate treatment, etc.
RESPONSE: We have added the following statement to make it clearer: ‘late diagnosis can result to non-reversible symptoms progression, that lead to institutionalisation and high mortality rate among this group’. There is also the emotional and physical burden to the care givers as well as emotional, physical and financial burden to the health care system on page 5, lines 114-17.

Summary of findings (7/53): line 57: not clear what you mean with ‘red-flag or easier to diagnose’ patients.
RESPONSE: The term has been removed to avoid confusion and now reads: ‘For the case studies, (20, 38,39) the exclusion criteria were appropriate and sample selection was consecutive, which reduced the risk of selection bias’ on page 8 lines 206-8.

Outcome IV (9/53): it should be clearer that this is in the specific setting of autosomal dominant AD.
RESPONSE: This has been clarified that the result is based on a setting of FAD study (of the 63 subjects in the Fox et al (38) 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 to include) in outcome IV, page 10 line 254.

Discussion (11/53): line 27: maybe mention the criteria that were used for neuropathological diagnosis.
RESPONSE: The criteria for the neuropathological diagnosis have been added to line 295 on page 12, to indicate that participants in all of the studies were diagnosed with the NINCDS-ADRDA diagnostic criteria
Line 32-37: I do not understand this part on the MMSE, as it has been shown that the MMSE has very poor sensitivity for early stage AD. And how does this contribute to 'classification'?
RESPONSE: MMSE has poor sensitivity for early stage AD and even though there is no evidence supporting the test as a stand-alone single diagnostic test, the findings of 25 MMSE score could support an additional and extensive test to early discriminate converters in autosomal dominant AD.
Page 12/53, first line: has it been taken into account that depression can also lead to cognitive impairment?
RESPONSE: Thank you. This is now reflected on page 10 lines 239-41 as follows: 'When considering the occurrence of 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.'
Line 13: what do you mean with 'neurological presentation' (is an EOAD presentation not always 'neurological' in nature)?
RESPONSE: EOAD presentations are always neurological, however, we understand that depression is not necessary a neurological presentation but could be a risk for the development of severe neurological conditions. Hence we suggest in this review that neurological and depressive behaviours are an early occurrence in early-onset AD (EOAD), with depressive and cognitive symptoms in the assessment of semantic memory and conceptual formation in LOAD, on page2 lines 51-53 on page 3.
Conclusions (12/53): line 42: can you elaborate on these proposed 'multiple definitions' or more clearly define them in the discussion?
RESPONSE: A line has been added as highlighted in the conclusions to include: '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' on page 13 lines 348-49.
Line 52: it seems these findings are also of relevance to neurologists and other practitioners dealing with dementing disorders.
RESPONSE: Thank you. This has now been added in lines 353-54 on page 14 as follows: 'The review is also of importance to neurologists and other practitioners dealing with dementing disorders'.
Thank you.

VERSION 2 – REVIEW

REVIEWER	Francesco Raudino Valduce Hospital. Como. ITALY
REVIEW RETURNED	12-Apr-2017

GENERAL COMMENTS	An interesting and well written paper. Only two minimal correction: page 4 line 25 and page 13 line 1 The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Tobi Van den Bossche VIB-UAntwerp Center for Molecular Neurology, Belgium
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	The methodology and results of this paper are sufficient, however parts of the manuscript still remain too unclearly written to be fit for

	scientific publication. This has not been adequately addressed in the revision. NB: though stated in the scoring sheet that the abstract is accurate, the last sentence of the result section regarding the MMSE score is still strange to me. I would leave this out of the manuscript.

VERSION 2 – AUTHOR RESPONSE

RESPONSE TO COMMENT FROM DR. RAUDINO FRANCESCO:
An interesting and well-written paper.
Only two minimal corrections: page 4 line 25 and page 13 line 1
RESPONSE Thank you Dr. Raudino. Pardon me; the corrections have been made on page 4 line 25 to delete the additional 'a' to state institutionalisation and page 13 line 1 to change it to study 20,25,26 instead of 20,25,25.

RESPONSES TO COMMENTS FROM DR. TOBI VAN DEN BOSSCHE
The methodology and results of this paper are sufficient, however, parts of the manuscript still remain too unclearly written to be fit for scientific publication. This has not been adequately addressed in the revision. NB. Though stated in the scoring sheet that the abstract is accurate, the last sentence of the result section regarding the MMSE score is still strange to me. I would leave this out of the manuscript.
RESPONSE Thank you for your review; we have not acted on this comment, sir.
Thank you.