PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for validating an algorithm to identify neurocognitive disorders in Canadian Longitudinal Study on Aging participants; an observational study
AUTHORS	Mayhew, Alexandra; Hogan, David; Raina, Parminder; Wolfson, Christina; Costa, Andrew P; Jones, Aaron; Kirkland, Susan; O'Connell, Megan; Taler, Vanessa; Smith, Eric E; Liu-Ambrose, Teresa; Ma, Jinhui; Thompson, Mary; Wu, Changbao; Chertkow, Howard; Griffith, Lauren

VERSION 1 – REVIEW

REVIEWER	Inagawa, Takuma National Center of Neurology and Psychiatry, Department of Psychiatry
REVIEW RETURNED	24-Mar-2023

GENERAL COMMENTS	Thank you for giving me the opportunity to review this manuscript. I think this manuscript was well written. 1) Please describe the novelty of this study more clearly. I think there have been many studies to assess the prevalence of dementia worldwide. 2) Please describe how missing data were addressed. 3) I cannot understand well, but was this a study protocol for a longitudinal diagnostc accuracy study? If this is a accuracy study, it is better to describe the followings. a) Index test and reference standard, in sufficient detail to allow replication. b)Definition of and rationale for test positivity cut-offs or result categories of the index test and the reference standard, distinguishing pre-specified from exploratory. c) Whether clinical information and reference standard results/index test results were available to the performers/readers of the index test. 4) If this study is a cohort study, please attach the STROBE checklist. If this study is a diagnostic accuracy study, please attach the STARD 2015 checklist.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Takuma Inagawa, National Center of Neurology and Psychiatry
Comments to the Author:
Thank you for giving me the opportunity to review this manuscript.
I think this manuscript was well written.

Thank you Dr. Inagawa for taking the time to review our manuscript and provide feedback.

1) Please describe the novelty of this study more clearly. I think there have been many studies to assess the prevalence of dementia worldwide.

We agree that there have been many studies which have assessed the prevalence of dementia. The novelty of our work is in developing an algorithm to identify dementia cases in a large, population-based study (the Canadian Longitudinal Study on Aging) to understand the epidemiology and burden of diagnosed and undiagnosed mild and major NCD. As highlighted in our background, previous studies such as the Health and Retirement Study as well as the Personality and Total Health Through Life Project have shown that algorithms are a valid and cost-effective way to determine neurocognitive disorder status in large, epidemiological studies. Algorithms circumvent the limitations of self-reported neurocognitive disorder status which are unable to capture the estimated 64% of people living with a neurocognitive disorder that have not seen a doctor regarding their cognition.

Due to the variability in the studied populations and the data collected on them, cohort-specific validation of algorithms is required. This protocol paper describes the validation study we are conducting to validate a neurocognitive disorder algorithm in the Canadian Longitudinal Study on Aging. If our algorithm proves to be valid, it will allow for other researchers to address a wide range of epidemiological questions related to neurocognitive disorders, far beyond estimates of prevalence.

2) Please describe how missing data were addressed.

We have addressed missing data in several spots in the manuscript;

In the “Study clinician” section, we have indicated that all participant that have completed the medical assessment will have a provisional clinical determination of : 1) no evidence of cognitive impairment; 2) mild NCD (MCI); or, 3) major NCD (dementia) based on DSM-5 criteria. Therefore, there will not be any missing data for the reference standard.

In the “***Participant categorization based on CLSA ascertainment algorithm”*** section, we have added; “Two versions of the algorithm will be run. The first will have an indeterminate category for participants with missing data that prevents the algorithm from making a final classification of 1) no evidence of cognitive impairment; 2) mild NCD (MCI); or, 3) major NCD (dementia). The second version will use imputed data which considers other waves of data collection and missing data patterns and will not have an indeterminant category.”

In the “**Statistical analyses and sample size determination**” section we have added:

> "We will conduct the analyses using the version of the algorithm with the indeterminate category for participants with missing data as well as using the version of the algorithm with imputed data."

3) I cannot understand well, but was this a study protocol for a longitudinal diagnostc accuracy study? If this is a accuracy study, it is better to describe the followings.

Thank you for these suggestions. As this paper is a protocol paper for which the work is currently ongoing, we cannot provide all the information you have requested, but have done our best to address these comments.

a) Index test and reference standard, in sufficient detail to allow replication.

We have provided a detailed explanation of the reference standard in the "**Measurements**" section. For clarity, we have explained that this section refers to the reference standard by adding the following;

> "This information will be used to provide a provisional study diagnosis of 1) no evidence of cognitive impairment; 2) mild NCD (MCI); or, 3) major NCD (dementia) based on DSM-5 criteria which will be used as the reference standard for which the algorithm will be compared."

However, we do not have a final algorithm (index test) to publish. We have provided the most up to date information regarding the content of the algorithm **in Supplementary Appendix 9**. We will provide sufficient information about the algorithm to allow for replication when we publish the results of this project.

b) Definition of and rationale for test positivity cut-offs or result categories of the index test and the reference standard, distinguishing pre-specified from exploratory.

We have clarified what the result categories will be of the algorithm (index test) in the "**Participant categorization based on CLSA ascertainment algorithm"** section:

> "Two versions of the algorithm will be run. The first will have an indeterminate category for participants with missing data that prevents the algorithm from making a final classification of 1) no evidence of cognitive impairment; 2) mild NCD (MCI); or, 3) major NCD (dementia). The second version will use imputed data which considers other waves of data collection and missing data patterns and will not have an indeterminant category."

These are the same categories as the reference standard which we have clarified in the "**Measurements"** section:

> The CLSA Memory Study includes a clinical assessment of the study participant and a phone interview with the informant which will take place between September 2022 and March 2024. This information will be used to provide a provisional study diagnosis of 1) no evidence of cognitive impairment; 2) mild NCD (MCI); or, 3) major NCD (dementia) based on DSM-5 criteria which will be used as the reference standard for which the algorithm will be compared.

As this is a study protocol, these categories are pre-specified.

c) Whether clinical information and reference standard results/index test results were available to the performers/readers of the index test.

> The “index test” for our upcoming analyses will be an algorithm. The algorithm will not include any of the information collected as part of our reference standard assessment.

4) If this study is a cohort study, please attach the STROBE checklist. If this study is a diagnostic accuracy study, please attach the STARD 2015 checklist.

> Thank you for these suggestions. This manuscript is not a cohort study or a diagnostic accuracy study. Rather, this manuscript is a protocol paper. Referring to the BMJ Open website – “*Protocol manuscripts should report planned or ongoing research studies. … Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study*.” Consequently, we can not use the STROBE check list of STARD 2015 checklist as we have not conducted any analyses and do not have any results to report.

Reviewer: 1
Competing interests of Reviewer: I declare no conflict of interests.

VERSION 2 – REVIEW

REVIEWER	Inagawa, Takuma National Center of Neurology and Psychiatry, Department of Psychiatry
REVIEW RETURNED	29-Jul-2023

GENERAL COMMENTS	I think this manuscript would be suitable for publication in this journal.