Supplementary Material

Digital Biomarkers for the Assessment of Non-Cognitive Symptoms in Patients with Dementia with Lewy Bodies: A Systematic Review

DATABASE SEARCH STRATEGIES

Embase <1974 to 2023 February 28>

1 "dementia with lewy bod*".ab,kf,ti,tw. 8329
2 DLB.ab,kf,ti,tw. 5919
3 lewy body dementia*.ab,kf,ti,tw. 2394
4 LBD.ab,kf,ti,tw. 4791
5 DLBD.ab,kf,ti,tw. 193
6 diffuse lewy body disease.ab,kf,ti,tw. 485
7 diffuse Lewy body disease/ 11443
8 1 or 2 or 3 or 4 or 5 or 6 or 7 18554
9 portable.ab,kf,ti,tw. 48358
10 "digital*".ab,kf,ti,tw. 246398
11 "digitiz*".ab,kf,ti,tw. 19801
12 smart.ab,kf,ti,tw. 45253
13 watch.ab,kf,ti,tw. 15488
14 digital biomarker*.ab,kf,ti,tw. 618
15 "electronic biomarker*".ab,kf,ti,tw. 8
16 "pupil*".ab,kf,ti,tw. 43433
17 "actigraph*".ab,kf,ti,tw. 15354
18 "electronic device*".ab,kf,ti,tw. 14291
19 (speech pattern or speech recog*).ab,kf,ti,tw. 5676
20 "biosens*".ab,kf,ti,tw. 58898
21 (wore or wear*).ab,kf,ti,tw. 123158
22 "sens*".ab,kf,ti,tw. 3010091
23 "app".ab,kf,ti,tw. 51948
24 "tablet".ab,kf,ti,tw. 55082
25 accelerometer/ or accelerometry/ 24924
26 wearable sensor/2196
27 ambulatory monitoring/ 12169
28 activity tracker/ or exp actigraph/ or exp smart watch/ 10112
29 digital technology/ 3298
30 exp mobile application/ 23803
31 speech analysis/ 9123
32 automatic speech recognition/ 1322
33 ambulatory monitoring/ 12169
34 home monitoring/ 5600
35 body temperature monitoring/ 851
36 physiologic monitoring/ 6626
37 sensor/ or exp biosensor/ or electronic sensor/ or inertial sensor/ or motion sensor/ or

thermal sensor/ or wearable sensor/ 144817
38 remote sensing/ 14206
39 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 3570439
40 8 and 39 2525

Ovid MEDLINE(R) ALL <1946 to February 28, 2023>

1 Lewy Body Disease/ 4217
2 "dementia with lewy bod*".ab,kf,ti,tw. 5210
3 DLB.ab,kf,ti,tw. 3299
4 lewy body dementia*.ab,kf,ti,tw. 1308
5 LBD.ab,kf,ti,tw. 3292
6 DLBD.ab,kf,ti,tw. 133
7 diffuse lewy body disease.ab,kf,ti,tw. 359
8 1 or 2 or 3 or 4 or 5 or 6 or 7 10329
9 exp Accelerometry/ 11879
10 wearable electronic devices/ or fitness trackers/ or smart glasses/ or digital technology/ 9062
11 mobile applications/ or speech recognition software/ 11868
12 exp electroencephalography/ or olfactometry/ or exp monitoring, ambulatory/ or remote sensing technology/ 204540
13 portable.ab,kf,ti,tw. 38856
14 "digital*".ab,kf,ti,tw. 194575
15 "digitiz*".ab,kf,ti,tw. 16494
16 smart.ab,kf,ti,tw. 38387
17 watch.ab,kf,ti,tw. 10705
18 digital biomarker*.ab,kf,ti,tw. 430
19 "electronic biomarker*".ab,kf,ti,tw. 6
20 "pupil*".ab,kf,ti,tw. 33922
21 "actigraph*".ab,kf,ti,tw. 9038
22 "electronic device*".ab,kf,ti,tw. 13756
23 (speech pattern or speech recog*).ab,kf,ti,tw. 5027
24 "biosens*".ab,kf,ti,tw. 53119
25 (wore or wear*).ab,kf,ti,tw. 101363
26 "sens*".ab,kf,ti,tw. 2385922
27 "app".ab,kf,ti,tw. 37230
28 "tablet".ab,kf,ti,tw. 30844
29 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 3008256
30 8 and 29 1480

 # Web of Science Search Strategy (v0.1)
Database: Web of Science Core Collection

Entitlements:

- WOS.IC: 1993 to 2023
- WOS.CCR: 1985 to 2023
- WOS.SCI: 1900 to 2023
- WOS.AHCI: 1975 to 2023
- WOS.BHCI: 2005 to 2023
- WOS.BSCI: 2005 to 2023
- WOS.ESCI: 2005 to 2023
- WOS.ISTP: 1990 to 2023
- WOS.SSCI: 1956 to 2023
- WOS.ISSHP: 1990 to 2023

Searches:

Search: #1 AND #2 Date Run: Thu Mar 02 2023 09:59:08 GMT+0100

Results: 2961

Search: ((((((ALL=(dementia with lewy bod*)) OR ALL=(DLB)) OR ALL=(lewy body disease)) OR ALL=(DLBD)) OR ALL=(diffuse lewy body disease)) OR ALL=(LBD)) OR ALL=(lewy body dementia) Date Run: Thu Mar 02 2023 09:59:07 GMT+0100
Results: 22810

Search: ((((((((((((((((((ALL=(digital)) OR ALL=(digitiz*)) OR ALL=(smart)) OR ALL=(watch)) OR ALL=(actigraph*)) OR ALL=(electronic biomarker)) OR ALL=(pupil*)) OR ALL=(speech pattern)) OR ALL=(speech recog*)) OR ALL=(biosens*)) OR ALL=(sens*)) OR ALL=(app)) OR ALL=(mobile app*)) OR ALL=(tablet)) OR ALL=(portable)) OR ALL=(ambulatory monitoring)) OR ALL=(remote sensing technology)) OR ALL=(digital technology)) OR ALL=(wearable)) OR
ALL=(fitness track*) Date Run: Thu Mar 02 2023 09:59:07 GMT+0100
Results: 7380143

Modified check list based on the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [1]

Criteria	Yes	No
1. Was the research question or objective in this paper clearly stated?		
2. Was the study population clearly specified and defined?		
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		
4. Was a sample size justification provided?		
5. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		
6. Were the outcome assessors blinded to the exposure status of participants?		
7. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientificpaper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interestat the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were inthe nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriategroup in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population.This increases the risk of bias.

Question 3. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the samesection of

the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic.This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 4. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of thestudy? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecifiedquestion–i.e., it may have been an exploratory, hypothesis-generating study.

Question 5. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with ameasure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (ifbody weight is the outcome of interest).

Results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 6. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is tolook for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants'

exposure status. The committee wouldthen be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 7. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or otherregression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the researchquestion–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, bloodcholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

REFERENCE

[1] Study Quality Assessment Tools, NHLBI, NIH.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	*Last in title*
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	*See below*
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	*Para. 1-2*
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	*Final para.*
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	*2.1*
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	*2.2*
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	*2.2*
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	*2.3*
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	*2.4*
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	*2.5*
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	*2.5*
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	*2.6*
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	*2.7*
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	*2.7*
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	*3., Figure 1*
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	*3.*
Study characteristics	17	Cite each included study and present its characteristics.	*3.1, Table 1*
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	*3.7, Figure 3*
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	*3.2 to 3.6*
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	*Not applicable*
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	*4.*
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	*4. (penultimate paragraph)*
	23d	Discuss implications of the results for practice, policy, and future research.	*4. (final para.)*
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	*Below abstract*
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	*Below abstract*
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	*In PROSPERO*
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	*Under funding*

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	*Under COI*
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	*Under supplementary*

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	YES
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	YES
Registration	12	Provide the register name and registration number.	YES

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/