ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 10 (2018) 394-401

Alzheimer's & Dementia

Diagnostic Assessment & Prognosis

Relationship between frailty and Alzheimer's disease biomarkers: A scoping review

Lindsay Wallace[a], Olga Theou[a], Kenneth Rockwood[a,b,*], Melissa K. Andrew[a,b]

[a]*Geriatric Medicine Research, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada*
[b]*Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada*

Abstract

Introduction: Frailty and dementia appear to be closely linked, although mechanisms remain unclear. The objective was to conduct a scoping review of the association between frailty and Alzheimer's disease (AD) biomarkers in humans.

Methods: Three databases, PubMed, PsycINFO, and Embase, were searched for articles using the following search terms: "frail elderly", "Alzheimer's disease", "dementia biomarkers" and their synonyms. Inclusion was limited to original research in humans published before 2017, which included a frailty measure and AD biomarker (fluid markers, neuroimaging, and neuropathology).

Results: Five hundred twenty-two articles were identified and screened; 10 were included. Most were cross-sectional (n = 6), measured the frailty phenotype (n = 6), and included people with dementia (n = 7). Biomarkers examined were postmortem AD pathology (n = 3), brain atrophy (n = 5), and in vivo fluid markers (n = 2). Eight studies reported that increased frailty was associated with at least one biomarker abnormality.

Discussion: Evidence is limited and suffers from design limitations but suggests that frailty and AD biomarkers are closely linked. Longitudinal research examining multiple biomarkers and frailty is warranted.

Keywords: Frail elderly; Neurodegeneration; Dementia; Neuropathology; Biomarkers; Alzheimer's disease; Frailty

1. Introduction

An intriguing challenge in understanding how Alzheimer's disease (AD) develops and is expressed is that the correlation between the so-called "neuropathological hallmarks" of AD (notably accumulation of abnormal amyloid-β [Aβ] and tau protein deposits) and cognitive decline is relatively weak. That is, cognitively intact people can exhibit high burdens of neuropathological lesions [1], and people with severe dementia may exhibit comparatively little neuropathology [2]. A promising opportunity therefore lies in understanding what influences an individual's ability to tolerate neuropathological features of AD; that is, to understand why some people with high neuropathological burden do not experience dementia.

Frailty and dementia are closely linked; both are strongly associated with age and adverse health outcomes [3–6]. Frailty has been described as physiologic vulnerability evidenced by reduced capability to repair/respond to internal or external stressors or insults and can be thought of as a measure of biologic aging [7,8]. Several studies have linked cognitive impairment or presence of dementia with frailty. A study by our group found that the frailer an individual, the more likely they were to exhibit dementia [9]. Similarly, studies from the Rush Memory and Aging Project (some of which are featured below) on the relationship between cognition and frailty have reported that baseline frailty level, as well annual change in frailty, was

*Corresponding author. Tel.: +1(902)473-8687; Fax: +1(902)473-1050.

E-mail address: Kenneth.rockwood@dal.ca

https://doi.org/10.1016/j.dadm.2018.05.002

associated with incident risk of AD [5], mild cognitive impairment [7], and rate of cognitive decline [8].

Frailty and AD might be related in many ways. They may share the underlying pathophysiology, such as inflammatory or stress responses. For example, inflammatory processes have been demonstrated to be intrinsic to both frailty [9,10] and cognitive decline [11]. Another intriguing idea is that both frailty and neuropathology may arise as a consequence of aberrant repair mechanisms [5,12]. That is, with time and environmental insults, redundancy in mechanisms that respond to and/or repair problems break down and therefore damage accumulates. The mechanism of interest is whether- and if so, how- frailty can impact the disease expression of AD, such that people can either reduce the presence of abnormal biomarkers, or somehow be better able to tolerate those abnormalities.

The evidence suggests the presence of these "biomarkers" is correlated with the development of dementia; but how they might cause it remains unclear. It is possible that frailty interacts with the pathophysiologic process to influence the "tolerability" of biomarkers (i.e., their ability to produce cognitive impairment), accounting for the heterogeneity seen clinically. Frailty as a conception model of dementia can integrate risk factors, progression, sensitivity and specificity, and high prevalence of mixed pathology; all of which have been challenging the traditional models of AD [13].

To date, the several reviews of the relationship between frailty and dementia [14,15] have yet to focus on the association between frailty and the neural correlates of dementia. Therefore, our objective in undertaking this scoping review was to summarize published evidence on the relationship between frailty and biomarkers of AD and to point out gaps in the literature.

2. Methods

2.1. Scoping review methodology

To map the existing literature, we chose to conduct a scoping review. A scoping review differs from a systematic review, in which instead of assessing the literature to provide an answer to a specific question, it systematically surveys the literature, quantitatively synthesizes what has been done, and summarizes the gaps in the literature of a certain field of research. As the area of biomarkers and frailty in dementia is relatively new, to date, there are no systematic reviews on this topic. A scoping review was therefore undertaken to examine the extent, range, and nature of research activity in this area, to draw attention to areas where more research is needed. The methodology does not significantly differ from a systematic review, though publications are not excluded based on study design, and quality assessments of each study are not undertaken. Typically, a scoping review precedes a systematic review to survey the literature and identify relevant research questions to be answered by a later systematic review. Furthermore, a scoping review does not aim to aggregate findings using meta-analysis but rather maps the literature to date to identify themes, trends, and gaps [16,17].

2.2. Search strategy

Three databases (PubMed, PsycINFO, and Embase) were searched for articles published as of January 2017. As the objective of our review was to identify articles that measured both frailty and AD biomarkers in the context of dementia, search terms were chosen accordingly; three arms of the search strategy ("frailty", "biomarkers" and "dementia" and their synonyms) were developed and intersected by using the Boolean term "AND". See Supplementary Table 1 for full list of search term combinations by database. The citations from the search strategy of the three databases were imported to DistillerSR (Evidence Partners Inc., student version) software to manage the screening process and data extraction.

2.3. Screening

Two sequential levels of article screening were undertaken (Fig. 1): (1) review of titles and abstracts; and (2) review of full-text articles. Two members of the review team independently screened all articles at each level. Any disagreement between reviewers was reconciled by consensus.

Inclusion criteria were as follows: (1) articles must be original research; (2) involve human subjects; (3) methods must identify measurement of an AD biomarker, as per the McKhann et al. [18] definition (i.e., Aβ or tau fluid or stain measurements, Pittsburgh compound-B positron emission tomography amyloid imaging, fluorodeoxyglucose positron emission tomography imaging, and structural magnetic resonance imaging showing atrophy [18,19]); and (4) articles must include a method or tool for assessing frailty, as stated by the author. As our purpose was to be as broad as possible, we included studies that used tools that the authors identified as a frailty measure, even if the tool was not specifically designed for that purpose. Articles were excluded if they were published in a language other than English or French.

2.4. Data extraction

Data extraction consisted of abstraction of 18 data points, including study design, sample size, average age of participants, how frailty and biomarkers were measured, and other pertinent variables for analysis (see Supplementary Table 2 for complete list). Data were extracted by both reviewers independently using a form in the Distiller program, with any disagreements resolved by consensus. Data were then exported to a database file (Microsoft Excel, version 15.18).

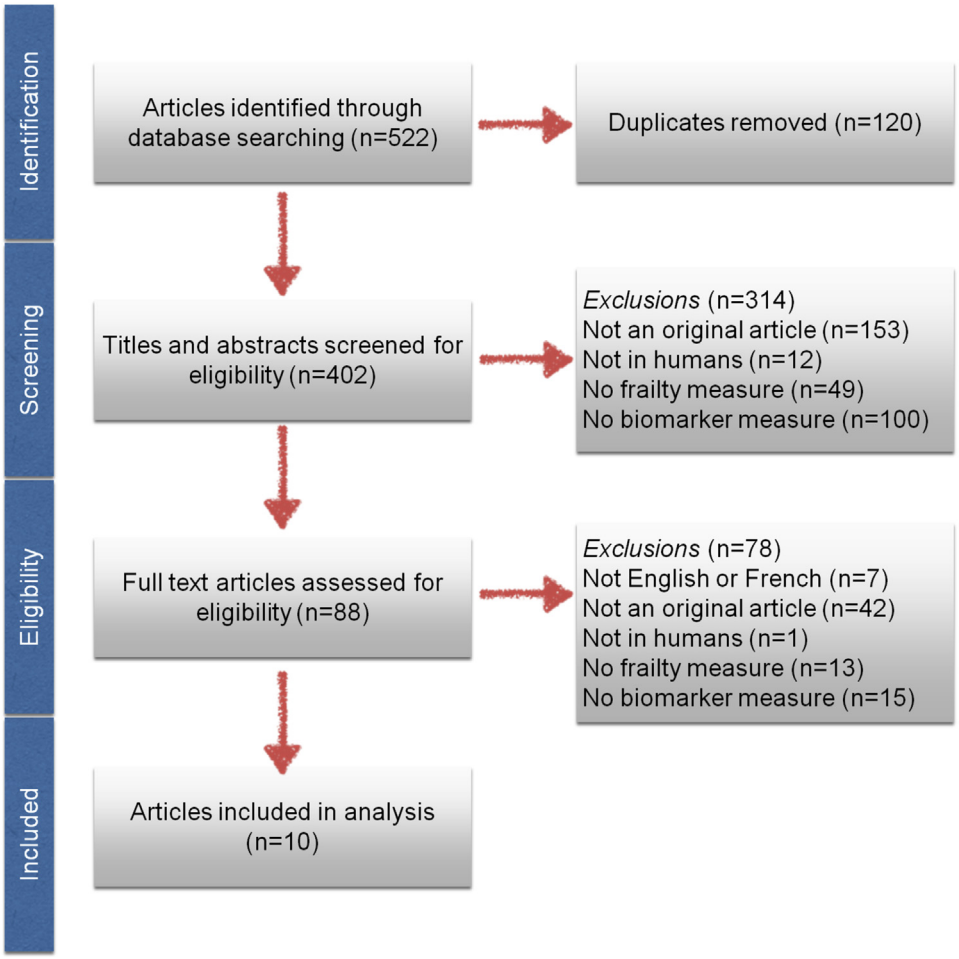

Fig. 1. Flowchart illustrating inclusion process.

3. Results

Our search strategy identified 522 articles from all three databases. After importing references to the systematic review manager, 120 articles were excluded due to duplication. Reviewers randomly hand checked these references to ensure whether the algorithm for duplicate detection was accurate. In the title and abstract (level 1) screening, 402 articles were screened, and 314 articles were excluded; in the full-text (level 2) screening, 88 articles were screened, of which 78 were excluded, leaving 10 published articles to be included for data extraction in this scoping review (Fig. 1).

3.1. Descriptive characteristics

A total of 2779 participants were included across the included studies, with the average age ranging from 50.6 [20] to 88.1 [21] years. Of the analyses that reported sex (9/10), the proportion of women ranged from 11% [20] to 74% [22]. Six were cross-sectional design [15–20], and all were published between 2008 and 2016. Two articles included participants with no dementia at baseline [11,21], three analyses included people with and without dementia at baseline [20,23,24], and three analyses restricted their participants to only those with some form of cognitive impairment [17,18,25]. Two additional analyses did not restrict their sample based on dementia status [15,20]. Most articles (8/10) examined the direct relationship between frailty and biomarkers [12,20–28]. Study characteristics and summaries obtained from data extraction can be found in Table 1.

3.2. Frailty measurement

Seven of the 10 studies utilized validated frailty measures, including the Fried frailty phenotype [11,15,16,21,22,25] and the Edmonton frail scale [20]; out of the six Fried phenotype measures, four modified the scale and did not appear to validate the modification [11,16,21,25]. Admittedly, the measurement of frailty, especially in relation to dementia, is not without its challenges. It has been previously demonstrated that modifications to the frailty phenotype may greatly affect prevalence estimates and outcomes [23]. Furthermore,

Table 1
Characteristics of included studies

Article citation	Sample size (% female; % CI at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/database	Biomarker measured	Frailty measurement	Main finding
Koch et al., Neurolog Disorders 2013	72 (sex not reported; 100% mild-moderate AD)	69.9 ± 7.0	Cross-sectional	Tertiary Care Centre in Rome, Italy	CSF: $A\beta_{42}$, p-tau, t-tau levels	Rapid or slow progressing AD (based on MMSE)	AD progression significantly associated with t-tau, but not p-tau or $A\beta_{42}$ in one-way ANOVAs.
Gabelle et al., Alzheimers Dement 2014	1147 (60.0%; 43% MCI)	73.0 ± 4.9	Nested case-cohort; 5.7	French 3-City study (Bordeaux, Dijon, Montpellier)	Blood plasma: Aβ (40,42,40/42) levels	Fried Phenotype	Frailty did not significantly influence the relationship between plasma Aβ and mortality in Cox regression models.
Burns et al., Neurology 2008	121 (54%; 47% early AD)	73.5 ± 6.5	Cross-sectional	Brain Aging Project (Kansas, USA)	Normalized whole brain volume	Physical Performance Test	Frailty did not influence the relationship between whole brain atrophy and cardiorespiratory fitness (VO_2 peak) in linear regression models.
Yamada et al., Geriatr Gerontol Int 2013	31 (74%; 35% MCI, 65% mild AD)	78.9 ± 7.3	Cross-sectional	Memory clinic data from Kyoto, Japan	Global brain atrophy index (VBM)	Physical Performance Test	Global brain atrophy was significantly correlated with frailty.
Tay et al., J Nutr Health Aging 2015	99 (35.4%; 16% MCI, 69% mild AD, 15% moderate AD)	76.6 ± 6.7	Prospective cohort study, 1.0	Memory clinic data from Singapore	Medial temporal atrophy (T1 MRI, consensus based 0-4 score)	Modified Fried Phenotype	Baseline frailty and medial temporal atrophy were significantly related, but 1-year change in frailty was not associated with baseline atrophy in regression models.
Kallianpur et al., Open Med J 2016	35 (11%; all with HIV for 15.3 ± 7.3 years)	50.6 ± 6.8	Cross-sectional	Hawaii Aging with HIV Cohort-Cardiovascular Disease Study	12 normalized regional volumes (T1 MRI)	Fried Phenotype	Regional brain volumes (thalamus and caudate) were positively and negatively associated with grip strength, respectively; while cerebellar white matter and subcortical gray matter were negatively associated with walking time.
Del Brutto et al., Geriatr Gerontol Int 2016	298 (57%; not reported)	70 ± 8	Cross-sectional	The Atahualpa Project	Global Cortical Atrophy (1.5T T1 MRI), White Matter Hyperintensity (T2 MRI)	Edmonton Frail Scale	More cortical atrophy was associated with increased frailty; age appeared to produce an interaction at 67 years.
Buchman et al., Neurology 2008	164 (56.4%; 35.8% MCI or AD)	88.1 ± 5.7	Cross-sectional	Religious Orders Study/Memory and Aging Project (USA)	Post mortem index of AD pathology	Modified Fried Phenotype	AD pathology was significantly associated with frailty status in adjusted linear regression models, no interaction with dementia diagnosis.
Buchman et al., Neurology 2013	791 (65.7%; 0% AD)	81.5 ± 6.7	Longitudinal cohort; 6.0	Religious Orders Study/Memory and Aging Project (USA)	Postmortem index of AD pathology	Modified Fried Phenotype	AD pathology was associated with frailty progression over 1 year in adjusted mixed effects models, no interaction with dementia diagnosis. AD pathology explained 8% of the variance in frailty progression.
Buchman et al., J Gerontol A Biol Sci Med Sci 2014	976 (72.5%; 0% AD)	78.5 ± 7.7	Longitudinal cohort; 6.4	Religious Orders Study/Memory and Aging Project (USA)	Postmortem index of AD pathology	Modified Fried Phenotype	Rate of frailty progression, and rate of cognitive decline were both significantly associated with AD pathology, and their change was correlated, suggesting a shared pathologic basis.

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; Aβ, amyloid β; CI, cognitively impaired; CSF, cerebrospinal fluid; MMSE, Mini–Mental State Examination; MRI, magnetic resonance imaging; p-tau, phosphorylated tau; t-tau, total tau; VBM, voxel based morphometry.

many of the items in the frailty phenotype have been individually linked with dementia risk, which impedes the ability to accurately capture whether multisystem impairment and physiologic vulnerability are truly the culprits [3].

Three studies did not use validated frailty tools to measure frailty; two studies used the Physical Performance Test [17,19], and one created their own AD progression measure for the purpose of their study [25]. Although the Physical Performance Test is a validated tool, it does not meet the criteria for a frailty tool as it is limited to one domain of physical health. Some studies have shown that mobility may be an appropriate screening tool for frailty, though consensus on this has not been established [29].

Overall, measurement of frailty was limited in the studies reviewed here; some measures of frailty focused on only one system or domain of function (e.g., mobility), whereas others modified previously established and validated tools without repeating validation.

3.3. Biomarker measurement

Biomarkers included in the articles analyzed here were roughly drawn from the recommendations report published in 2011 [18]. This list includes dementia biomarkers that have the most evidence for links with the AD pathophysiological process. Of the ten included articles from which data were extracted, three examined postmortem neuropathological data, (although all originated from the Religious Orders Study and Memory and Aging Project [12,21,27]), and five examined magnetic resonance imaging data to obtain brain atrophy estimates [20,22,23,26,28]. The other two examined protein levels in cerebrospinal fluid [25] and blood plasma [24].

3.4. Relationship between frailty and biomarkers

We examined the relationship of each biomarker class (fluid, neuroimaging, and neuropathological) with frailty for two main reasons: (1) to understand whether the relationship between frailty and dementia biomarkers differed according to when each biomarker appears in the pathophysiologic trajectory [30]; and (2) to better appreciate how frailty and dementia biomarkers may influence each other along the disease course.

Of the studies that measured the direct relationship between AD biomarkers and frailty [12,20–22,25–28], all reported positive relationships: that is, increased frailty was associated with increased levels of AD biomarker abnormality, but the strength of this evidence varied by biomarker type. Correlations between frailty and fluid markers were weak, though more research is needed in this area to facilitate any sort of firm conclusion. In four studies [20,22,26,28] measures of brain atrophy were significantly associated with frailty. Despite the limitations of the individual studies, this consistent finding is not surprising: measures of brain atrophy likely reflect broad neurodegenerative processes and are less specific than fluid markers. Postmortem neuropathology was more closely related to frailty of all the biomarkers. This should be interpreted with caution given that all results were obtained from the same study (Rush MAP). Even so, AD pathology has also been found to predict cognition in individuals with and without cognitive impairment [28,29,31], which may suggest that neuropathology is more closely related to frailty and ageing than clinical dementia. The two studies that examined indirect relationships, that is, how frailty influenced the relationship between AD biomarkers and mortality [24] and cardiorespiratory fitness [23], were more equivocal and reported no effect of frailty. This warrants further research to better understand how frailty interacts with neuropathology to produce adverse health outcomes.

Many of the studies summarized here overlook the complex nature of the interaction between biomarkers of AD and frailty over time. Given the evidence, it is likely that their interactions are bidirectional, and the nature of these interactions changes over time and are influenced by other internal and external factors [32]. Although investigations by the Rush group have examined some of these dynamics, further work is necessary in longitudinal data sets to examine directions and rates of change and how changes are related. Embracing the complexity of interactions between brain and bodily health over the life course is a crucial step in improving the design of dementia studies in the future and maximizing clinically relevant outputs [33].

3.5. Limitations of included studies

Most studies included this review were cross-sectional. Cross-sectional studies are limited in only being able to establish correlative and not causative relationships. While they still contribute to the literature and give a useful snapshot of a relationship at crucial time points, longitudinal analyses are needed to better understand how disease develops and progresses. Given the hypothesis that neuropathology, frailty, and some forms of cognitive decline begin decades before clinical dementia is apparent [34], understanding interactions between these variables over time will be a key to understanding dementia etiology and expression over the life course.

Of the studies included in this review, many suffer from small sample size and therefore it is possible that they are underpowered. It must be noted that when drawing samples for biomarkers, whether it be magnetic resonance imaging, cerebrospinal fluid, blood plasma, or postmortem brain autopsy, large numbers of participants are difficult to achieve for two main reasons: (1) they are relatively invasive and require a significant commitment on behalf of the participant; and (2) they are very costly.

Another important feature missing in many of the studies presented here is a range of baseline cognitive profiles; many only sample participants of the same cognitive

status. When considering how dementia comes about, it is impossible to ignore that it largely occurs in people who are older and have several other health problems. Typically, in epidemiological and basic science studies, as well as clinical trials, people with multiple interacting health problems are excluded from study because they threaten the purity of the mechanism being studied (considering that most of these inquiries are examining single-mechanisms in the first place). The relative lack of variation in cognitive and physical profiles at baseline limits the generalizability of the findings.

In the studies reviewed here, measurement of frailty was limited; some measures of frailty focused on only one system or domain of function (i.e., mobility or cognition), whereas others modified previously established and validated tools (i.e., frailty phenotype). This may significantly influence results as differences in frailty measurement greatly affect prevalence estimates and outcomes [31].

4. Discussion

4.1. Summary of findings

This scoping review suggests that evidence relating AD biomarkers and frailty in this area is at only an early stage of understanding. Ten studies (including all eight that examined their direct relationship) suggest that frailty and AD biomarkers are positively related and interact over time. The gaps in literature that this review identified include the lack of studies that are large and longitudinal in design and measure multiple biomarker types and have broad inclusion criteria (i.e., not limiting inclusion to people who have dementia). Data sharing and collaborative studies will be useful to address these gaps.

Although very few studies have evaluated the relationship between AD biomarkers and frailty, their findings are important as they may help account for the vast heterogeneity seen in AD; frailty may explain some of the variance in the relationship between AD biomarkers and the cognitive and clinical symptoms. This review supports an emerging theme in AD research: the transition from the view of AD as a single-cause disease entity to a multidimensional phenomenon with complex and heterogeneous etiology [3]. Our findings here also highlight the dearth of evidence in this area, and we hope that this serves as a catalyst in moving this research area further to better understand mechanisms and therefore, improve prevention, treatment, and management.

4.2. Limitations of scoping review

Our findings should be interpreted with caution. Our review excluded seven articles not written in English or French, potentially biasing results. Furthermore, we chose to do a scoping review, an approach that omits quality assessments of the articles. Likely, the largest limitation of this review is the dearth of evidence available for review.

4.3. Comparison with other literature

This is the first article to our knowledge to examine the relationship between AD biomarkers and frailty. This work builds on previous bodies of work linking cognitive decline with AD biomarkers, and with frailty. Specifically, poorer cognition has been linked with increased levels of Aβ using cerebrospinal fluid markers [35] and positron emission tomography in cognitively intact [36] and demented individuals [37,38], as well as increased levels of Aβ deposition on autopsy [39]. Similarly, epidemiological studies have demonstrated that cognition and dementia incidence has been associated with increased frailty in community-dwelling [9,11,40] and continuing care populations [9,11]. Our work here demonstrates that these constructs are importantly linked and begs the question of how and/or what mechanisms are responsible for this relationship? Previous frailty research suggests that aberrant repair mechanisms may show some promise in understanding the failure of higher order systems in the body [32]. Similarly, systemic factors such as chronic inflammation and cellular senescence may provide additional insight [41]. This will be an important area of future research to better understand cognitive decline and dementia development in AD.

4.4. Gaps in research and future directions

The dearth of longitudinal evidence here points to a need to invest in longitudinal observational studies of dementia development that consider ageing. One of the most expedient ways to accomplish this goal will likely be to include measurement of dementia biomarkers (neuroimaging and autopsy option) in existing population-based ageing studies such as the Canadian Longitudinal Study on Aging, the English Longitudinal Study on Aging, the Survey of Health And Retirement in Europe, and the Beijing Longitudinal Study on Aging, among others. Along these lines, data sharing will become an inevitable feature of continued quality research in this area.

As mentioned previously, most studies here to do not examine a range of baseline cognitive and physical profiles, which limits the generalization of their results and makes it harder to understand the complex mechanisms of AD development. A proper antidote to this challenge will be to examine community and population-based samples of individuals with a wide range of cognitive function and health status, to better understand how dementia arises in a more ecologically sound manner.

As noted in the results, frailty measurement in the included studies was a significant limitation. Future investigations of dementia biomarkers and frailty should consider using standardized and validated multi-system frailty

measures. Of particular interest will be how deficit accumulation is related to the manifestation of dementia biomarkers and how they may interact to influence dementia expression.

Furthermore, when considering which dementia biomarkers may be plausible in the context of AD, it is crucial to consider the criteria for a candidate biomarker. A true biomarker should be internally and externally valid [42]. It is unlikely that any of the proposed indicators actually constitute veritable biomarkers, and attention should be drawn to the clinical utility of this biomarker search [39,40]. Given the complexity, heterogeneity, harms, and cost of measuring many of these biomarkers, we should consider whether the pursuit of tools such as this to detect risk for AD early is a valuable one.

Overall, future research should focus on longitudinal data collection in population-based samples, where biomarkers of all stages (fluid, imaging, and pathological) are collected and analyzed to establish the veracity of the continuum approach [30]. Embracing the complexity of interactions between brain and bodily health over the life course is a crucial step in improving the design of dementia studies in the future and maximizing clinically relevant outputs [33].

5. Conclusions

This scoping review of frailty and dementia biomarkers is meant to be a starting point to summarize research in this area, generate hypotheses, and direct future research. Briefly, it has uncovered three critical points: (1) there is a dearth of evidence in this area; (2) the few studies that have investigated this suffer from important challenges that limit generalizability; and (3) despite this, there does appear to be a relationship between frailty and AD biomarkers and more work in this area requires thoughtful design to uncover novel mechanistic insights regarding AD etiology and expression; and (4) gaps in the current literature suggest that large, longitudinal studies of adults with varying cognitive profiles (i.e., not just those who are already suffering from dementia) and measure frailty as well as multiple biomarkers will be needed to better understand how dementia develops and how frailty may be implicated. The field of AD research is ripe for a change in conceptualization of the process leading to dementia expression and examining the influence of frailty may be a useful way to achieve this.

Acknowledgments

This work was supported by the Canadian Consortium on Neurodegeneration in Aging which receives funding from the Canadian Institutes of Health Research and several partner organizations including the Alzheimer Society of Canada, Nova Scotia Health Research Foundation, and the Women's Brain Health Initiative. This study is part of a CCNA investigation into how multi-morbidity modifies the risk of dementia and the patterns of disease expression (Team 14). L.W. is supported by a biomedical doctoral fellowship awarded by the Alzheimer's Society of Canada Research Program in partnership with the CCNA.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2018.05.002.

RESEARCH IN CONTEXT

1. Systematic review: Frailty and dementia are closely linked; previous reports have demonstrated a strong relationship between frailty and cognitive decline. Furthermore, cognitive impairment and dementia are significantly related to Alzheimer's disease (AD) neuropathology. A dearth of evidence exists on how these mechanisms may interact, that is, how frailty may influence disease expression in the context of AD.
2. Interpretation: Our findings suggest that frailty and AD biomarker abnormalities are positively associated. Furthermore, it is clear that more research is needed in this area to make more supported mechanistic conclusions.
3. Future directions: An undertaking of longitudinal population-based studies where biomarkers of all stages are analyzed will allow us to better elucidate how frailty may influence AD expression.

References

[1] Bennett DA, Launer LJ. Editorial longitudinal epidemiologic clinical-pathologic studies of aging and Alzheimer's disease. Curr Alzheimer Res 2012;9:617–20.
[2] Mendez MF, Mastri AR, Sung JH, Frey WH. Clinically diagnosed Alzheimer disease: neuropathologic findings in 650 cases. Alzheimer Dis Assoc Disord 1992;6:35–43.
[3] Wallace LMK, Theou O, Kirkland SA, Rockwood MRH, Davidson KW, Shimbo D, et al. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. PLoS One 2014;9:e90475.
[4] Searle SD, Rockwood K. Frailty and the risk of cognitive impairment. Alzheimers Res Ther 2015;7:54.
[5] Song X, Mitnitski A, Rockwood K. Age-related deficit accumulation and the risk of late-life dementia. Alzheimers Res Ther 2014;6:54.
[6] Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323–36.
[7] Morley JE, Vellas B, Abellan van Kan G, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392–7.
[8] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–62.

[9] Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. Neurology 2011;77:227–34.
[10] Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483–9.
[11] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc 2010;58:248–55.
[12] Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. J Gerontol A Biol Sci Med Sci 2014; 69:1536–44.
[13] Khachaturian ZS, Mesulam MM, Khachaturian AS, Mohs RC. The special topics section of Alzheimer's & dementia. Alzheimers Dement 2015;11:1261–4.
[14] Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a predictor of Alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: a systematic review and meta-analysis. J Am Med Dir Assoc 2016;17:881–8.
[15] Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment? A review of the evidence and causal mechanisms. Ageing Res Rev 2013;12:840–51.
[16] Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69.
[17] Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8:19–32.
[18] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.
[19] Lawrence E, Vegvari C, Ower A, Hadjichrysanthou C, De Wolf F, Anderson RM. A systematic review of longitudinal studies which measure Alzheimer's disease biomarkers. J Alzheimers Dis 2017;59:1359–79.
[20] Kallianpur KJ, Sakoda M, Gangcuangco LMA, Ndhlovu LC, Umaki T, Chow D, et al. Frailty characteristics in chronic HIV patients are markers of white matter atrophy independently of age and depressive symptoms: a pilot study. Open Med J 2016;3:138–52.
[21] Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology 2008;71:499–504.
[22] Yamada M, Takechi H, Mori S, Aoyama T, Arai H. Global brain atrophy is associated with physical performance and the risk of falls in older adults with cognitive impairment: global brain atrophy and falls. Geriatr Gerontol Int 2013;13:437–42.
[23] Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology 2008;71:210–6.
[24] Gabelle A, Schraen S, Gutierrez LA, Pays C, Rouaud O, Touchon J, et al. Plasma beta-amyloid 40 levels are positively associated with mortality risks in the elderly. Alzheimers Dement 2015;11:672–80.
[25] Koch G, Belli L, Lo Guidice T, Di Lorenzo F, Sancesario GM, Sorge R, et al. Frailty among Alzheimer's disease patients. CNS Neurol Disord Drug Targets 2013;12:507–11.
[26] Del Brutto OH, Mera RM, Cagino K, Fanning KD, Milla-Martinez MF, Nieves JL, et al. Neuroimaging signatures of frailty: a population-based study in community-dwelling older adults (the Atahualpa Project). Geriatr Gerontol Int 2017;17:270–6.
[27] Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. Neurology 2013;80:2055–61.
[28] Tay L, Lim W, Chan M, Ye R, Chong M. The independent role of inflammation in physical frailty among older adults with mild cognitive impairment and mild-to-moderate Alzheimer's disease. J Nutr Health Aging 2016;20:288–99.
[29] Matsuzawa Y, Konishi M, Akiyama E, Suzuki H, Nakayama N, Kiyokuni M, et al. Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol 2013;61:1964–72.
[30] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16.
[31] Theou O, Cann L, Blodgett J, Wallace LMK, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. Ageing Res Rev 2015;21:78–94.
[32] Howlett SE, Rockwood K. New horizons in frailty: ageing and the deficit-scaling problem. Age Ageing 2013;42:416–23.
[33] Armstrong JJ, Mitnitski A, Andrew MK, Launer LJ, White LR, Rockwood K. Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. Alzheimers Res Ther 2015;7:38.
[34] Salthouse TA. When does age-related cognitive decline begin? Neurobiol Aging 2009;30:507–14.
[35] Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924–38.
[36] Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. JAMA 2017; 317:2305–16.
[37] Quigley H, Colloby SJ, O'Brien JT. PET imaging of brain amyloid in dementia: a review. Int J Geriatr Psychiatry 2011;26:991–9.
[38] Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al. Imaging β-amyloid burden in aging and dementia. Neurology 2007; 68:1718–25.
[39] Cummings BJ, Pike CJ, Shankle R, Cotman CW. β-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease. Neurobiol Aging 1996;17:921–33.
[40] Godin J, Armstrong JJ, Rockwood K, Andrew MK. Dynamics of frailty and cognition after age 50: why it matters that cognitive Decline is mostly seen in old age. J Alzheimers Dis 2017;58:231–42.
[41] Fulop T, McElhaney J, Pawelec G, Cohen AA, Morais JA, Dupuis G, et al. Frailty, inflammation and immunosenescence. Interdiscip Top Gerontol Geriatr 2015;41:26–40.
[42] Rockwood K. Con: can biomarkers be gold standards in Alzheimer's disease? Alzheimers Res Ther 2010;2:16.