Mini-Review

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Alzheimer's disease with frailty: Prevalence, screening, assessment, intervention strategies and challenges

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SUMMARY Alzheimer's disease (AD) is a neurodegenerative disorder that affects millions worldwide and is expected to surge in prevalence due to aging populations. Frailty, characterized by muscle function decline, becomes more prevalent with age, imposing substantial burdens on patients and caregivers. This paper aimed to comprehensively review the current literature on AD coupled with frailty, encompassing prevalence, screening, assessment, and treatment while delving into the field's challenges and future trajectories. Frailty and AD coexist in more than 30% of cases, with hazard ratios above 120% indicating a mutually detrimental association.Various screening tools have emerged for both frailty and AD, including the Fried Frailty Phenotype (FP), FRAIL scale, Edmonton Frailty Scale (EFS), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), and General Practitioner Assessment of Cognition (GPCOG). However, none has solidified its role as the definitive gold standard. The convergence of electronic health records and brain aging biomarkers heralds a new era in AD with frailty screening and assessment. In terms of intervention, non-pharmacological strategies spanning nutrition, horticulture, exercise, and social interaction, along with pharmacological approaches involving acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, and anti-amyloid beta-protein medications, constituted cornerstones for treating AD coupled with frailty. Technological interventions like repetitive transcranial magnetic stimulation (rTMS) also entered the fold. Notably, multi-domain non-pharmacological interventions wield considerable potential in enhancing cognition and mitigating disability. However, the long-term efficacy and safety of pharmacological interventions necessitate further validation. Diagnosing and managing AD with frailty present several daunting challenges, encompassing low rates of early co-diagnosis, limited clinical trial evidence, and scarce integrated, pioneering service delivery models. These challenges demand heightened attention through robust research and pragmatic implementation.

Keywords Alzheimer's disease, frailty, epidemic, screening, intervention, challenge

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, representing a neurodegenerative disorder characterized by a gradual onset and the progressive deterioration of cognitive and functional capacities. According to the 2018 Global Alzheimer's Disease Report by Alzheimer's Disease International (ADI), the worldwide population living with dementia exceeded 50 million individuals, with projections estimating a surge to 152 million by 2050 (*1*). Approximately 60–70% of those cases can be attributed to AD. Frailty emerges as a syndrome denoting heightened vulnerability in older adults, encompassing factors like co-morbidities such as hypertension, diabetes, and heart disease (*2*).

Recent investigations have highlighted a robust correlation between frailty and AD. In their study, Kojima *et al.* unveiled a staggering 31.9% prevalence of frailty in patients exhibiting mild to moderate AD. Moreover, frailty exhibited strong links to cognitive decline, functional disability, mortality, and various other adverse health outcomes (*3*). A comprehensive systematic review led by Grande *et al*. underscored that the risk of dementia development surpassed fivefold

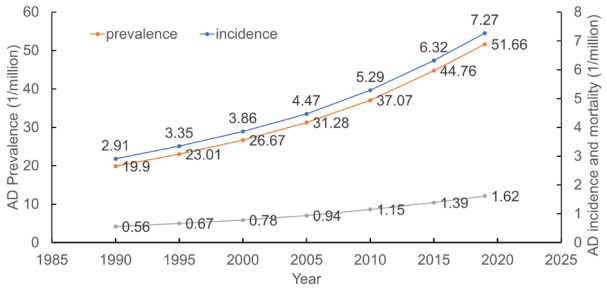

Figure 1. Epidemic of Alzheimer's disease (AD) from 1990-2019. Data source: *http://ghdx.healthdata.org/gbd-results-tool*

when cognitive impairment and frailty coexisted compared to individuals lacking either condition (*4*). The intersection of AD and frailty has rapidly evolved into a focal point of global research and preventative efforts, emerging as a significant public health concern.

This article encapsulates the present landscape concerning AD's prevalence, screening, and treatment in conjunction with frailty. As such, it offers a valuable reference for global prevention and management strategies in addressing the amalgamation of AD and frailty.

2. Epidemic situation of AD with frailty

The incidence, prevalence, and mortality of AD are on an escalating trajectory worldwide (*5*), as evidenced by the WHO's Global Burden of Disease (GBD) surveillance data (Figure 1). The prevalence of frailty escalates with advancing age and is distinctly influenced by socioeconomic disparities, with noticeably higher rates documented in low- and middle-income nations (*6*). The convergence of AD and heightened frailty substantially burden societal health. A comprehensive analysis of frailty prevalence in patients experiencing mild to moderate AD revealed a spectrum ranging from 11.1% to 50.0%, averaging 31.9% (*3*). Another systematic assessment focusing on frailty prevalence among dementia patients conducted in acute care environments observed rates spanning from 50.8% to 91.8%. In contrast, studies conducted in community-based residential settings indicated even higher prevalence rates. In such community residential settings, frailty prevalence spanned from 24.3% to 98.9% (*7*). Furthermore, an investigation encompassing older adults with limited cognitive capacity in Central Africa documented an estimated frailty prevalence of 64.9% (*8*). Employing the frailty index (FI), Heather *et al.* gauged frailty prevalence among participants in clinical trials targeting mild cognitive impairment (MCI) and dementia. the dementia trial noted a significantly higher rate of 48.6% (*9*). An additional retrospective evaluation, centering on patients aged 65 and older from two centers specializing in cognitive decline and dementia (CCDDs), disclosed that 40% of patients exhibited mild frailty. In contrast, 25% faced moderate to severe frailty. Intriguingly, the prevalence and severity of frailty exhibited a positive correlation with declining Mini-Mental State Examination (MMSE) scores and increasing age (*10*). Lee *et al.* assessed the prevalence of frailty within primary care settings among patients presenting memory complaints. Their findings showcased a frailty prevalence of 16% based on Fried's criteria and an elevated 48% according to the Clinical Frailty Scale (CFS). The collective findings of the aforementioned epidemiological investigations underscore the substantial prevalence of AD accompanied by frailty (*11*). Kasajima *et al.* harnessed a microsimulation methodology to forecast the prevalence and economic implications of dementia and frailty among the population aged 60 years and above in Japan from 2016 to 2043. Their projections anticipate an approximately 1.3-fold increase in frailty prevalence among individuals aged 75 and older by 2043. Alarming statistics reveal that nearly 29% of women aged 75 and above will grapple with dementia and frailty, precipitating an annual expenditure of $125 billion and $97 billion on dementia-related and frailty-related costs, respectively (*12*).

Conversely, multiple studies have established a substantial correlation between frailty and AD. An investigation into the interplay between frailty and dementia incidence within China unveiled that, over five years, the cumulative incidence of frailty coexisting with dementia markedly exceeded that of dementia without frailty. Different definitions of frailty yielded consistent results: 21.0% compared to 9.6%, 19.9% compared to 9.0%, and 22.8% compared to 8.9% (*13*). Cognitive capabilities among frail older adults generally register lower compared to their non-frail counterparts (*14*), with the occurrence of MCI 1.6 to 2.5 times more prevalent in the former group (*15,16*). Additionally, pre-frail subjects exhibited a higher prevalence of cognitive impairment than cognitively normal older adults, while the incidence of cognitive dysfunction was even greater among frail individuals than those who are pre-frail (*17*). Similar findings have been reported in several investigations of debilitating specialties, such as an investigation of the prevalence of MCI among patients with sarcopenia, which found that the prevalence of MCI among patients with sarcopenia was 20.5% (95% CI: 0.14–0.26) and that the overall adjusted ratio between MCI and sarcopenia was 1.46 (95% CI: 1.31–1.62). The prevalence of MCI was relatively high in patients with sarcopenia, and sarcopenia may be a risk factor for MCI (*18*). Furthermore, systematic evaluations have documented escalated instances of both debility and sarcopenia within dementia patients. A study targeting debility through the lens of swallowing quality of life (SwalQoL) underscored a noticeable escalation in frailty prevalence in tandem with declining cognitive status (*19*). Correspondingly, the prevalence of sarcopenia among individuals with dementia demonstrated an analogous elevation alongside cognitive deterioration (*20*).

3. Progress in screening and assessment of AD with frailty

3.1. Frailty screening tool

Globally, an array of assessment methods have emerged to facilitate routine frailty screening. Nevertheless, a universally recognized "gold standard" for frailty assessment remains elusive. The Fried Frailty Phenotype (FP), the FRAIL scale, and the Edmonton Frailty Scale (EFS) are among the more widely employed tools. The FP, introduced by Fried in 2001, comprises five criteria: weight loss, low physical activity, exhaustion, slowness, weakness (*21*). The FRAIL scale, devised by experts from the International Working Group on Nutrition, Health, and Ageing in 2008, incorporates the following five components: fatigue, resistance, ambulation, illness, and loss of weight (*22*). Another frequently utilized assessment tool, the EFS, was introduced by Rolfson *et al.* in 2006. It encompasses nine dimensions and eleven entries: cognition, general health status, self-reported health, functional independence, social support, polypharmacy, mood, continence, and functional performance (*23*). An appraisal by Han *et al.* regarding the consistency and applicability of these three scales for frailty screening among community-dwelling older adults revealed divergent outcomes. Notably, the EFS emerged as more suitable for comprehensively assessing frailty in this population, whereas the FP demonstrated greater efficacy than the FRAIL scale in gauging physical frailty (*24*). Another comparison conducted by Dent underscored certain limitations, such as the need for instrumental grip strength measurements in FP, potentially impeding its widespread use. Moreover, the FRAIL scale necessitated further validation efforts (*25*). Recent trends within the field signal a shift toward measurement tools integrated with electronic health records. Notable examples included the electronic frailty index (eFI) and the Hospital Frailty Risk Score (HFRS), both of which have demonstrated promising levels of differentiation in preliminary assessments (*26-28*).

3.2. Screening tools for cognitive impairment

Numerous cognitive assessment scales were employed both domestically and internationally within clinical contexts. Among these, MMSE stands out as the most prevalent, alongside other tools like the Montreal Cognitive Assessment Scale (MoCA), the Clock Drawing Test (CDT), and the General Practitioner Cognitive Functioning Assessment Gauge (GPCOG), among others (*29,30*). The MMSE, introduced by Folstein *et al.* in 1975, is particularly prominent due to its brevity and applicability across various subject profiles. The scale evaluates five domains: orientation, memory, attention, language, and visuospatial skills (*31*). Developed by Nasreddine *et al.* in Canada in 2005, the MoCA proves invaluable in swiftly screening for MCI. While the MoCA exhibits enhanced sensitivity towards MCI compared to the MMSE, it necessitates a higher literacy level due to its more intricate assessment content. This tool encompasses eight primary cognitive domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation (*32*). First introduced in 1989 for detecting structural dysfunctions, the CDT is lauded for its ease of administration, brevity (typically 1–3 minutes), and reduced susceptibility to factors like cultural disparities and educational levels. It delves into a broad spectrum of cognitive functions beyond spatial structural skills, encompassing visuospatial structural capacities, verbal memory, and executive functions. This test emerges as highly sensitive in screening early cognitive dysfunction. It tasks the patient with drawing a clock according to specific instructions, serving as a single-item assessment primarily targeting executive functions. It also evaluates cognitive domains such as visuospatial and executive capabilities, auditory-verbal skills, attentional focus, and structural functionality (*33*). Introduced in 2002, the GPCOG is tailored for application within primary care settings. The assessment comprises two components: a patient test and an informant survey. The patient test features six items: orientation, memory, attention, language, visuospatial skills, and executive function. The informant survey consists of 6 questions, generating scores of 9 out of 9 for the patient test and 6 out of 6 for the informant survey. Typically, administration takes less than 2 minutes (*34*) (Table 1). Recently, the Chinese Aging Marker Research Consortium has pioneered the exploration and proposal of brain aging biomarkers, striving to achieve a scientific measurement of biological age within the population. The Consortium has constructed markers spanning behavioral and functional realms, imaging parameters, and humoral indicators (*35*).

3.3. Developments in the evaluation of AD with frailty

Although frailty and AD are inextricably linked, current evaluation approaches primarily focus on isolated measures or translational analyses of each condition. For instance, a FI may be created by combining results from cognitive tests with activities of daily life. However, as revealed by Ward *et al.*, it is worth noting that the association between frailty and dementia risk was attenuated after certain early core dementia symptom factors were eliminated (*36*). This underscores the intricate relationship between these factors. Engvig *et al.* adopted a data-driven approach to evaluating health deficits, aiming to enhance the predictive accuracy of the FI concerning both current cognitive status and the likelihood of future dementia. This effort brings to light the potential shortcomings of the traditional FI when applied to dementia risk assessment (*37*). Li *et al*., on the other hand, devised a nomogram integrating risk factors

Table 1. Frailty and AD screening instruments

Field	Name	Items	Type and scope of scoring	Evaluation method	Advantage	Shortcomings
Frailty	FP	weight loss, low physical activity, exhaustion,slowness, weakness	0–5 points, ≥ 3 points indicates frailty	Face to face, professional equipment required	TUGT, grip strength, and other objective markers are included, and it is also more sensitive to physical weakness. It is straightforward and simple to use.	Only takes into account physical dimension. ignores additional contributing elements like emotion and cognition.
Frailty	FRAIL	fatigue, resistance, ambulation, illness, loss of weight	0–5 points, ≥ 3 points indicates frailty	self-reporting	straightforward and simple to use; contains both subjective and objective metrics.	Only takes into account physical dimension. Due to cognitive impairment, senior persons may have an erroneous assessment of their physical state.
Frailty	EFS	cognition; general health status: self-reported health: functional independence: social support; polypharmacy; mood; continence; and functional performance	0–17 points, ≥ 5 indicates frailty	Face to face, professional training required	Several physiological and disease-related indicators are present; can be used to assess the effects of interventions.	The examination is rather intricate and is only applicable to hospital circumstances; Some indicators might be affected by illnesses.
Cognitive Disorder	MMSE	orientation, memory, attention, language, and visuospatial skills	0–30, < 24 indicates frailty	Face to face, professional training required	The diagnostic sensitivity and specificity for dementia are respectively 85% and 90%; relatively valuable for identifying AD.	False negative or false positive findings are noticeable and are dependent on the subject's education level; The questions are easy. There is a ceiling effect, which lowers the sensitivity of detecting MCI.
Cognitive Disorder	MoCA	visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation	0–30, ≥ 26 indicates normal cognitive function;	Face to face, professional training required	The specificity for detecting MCI is decent, with sensitivity for moderate AD and MCI being 90% and 100%, respectively.	The inquiries are time-consuming and quite challenging; many nations do not have a normative understanding of language and cultural variations.
Cognitive Disorder	CDT	Draw a closed circle, the position of the numbers is correct, all 12 numbers are not missing, and the position of the minute and hour hands is correct.	0–4 points, scoring 3–4 points indicate normal cognitive level	Face to face, professional training required	The highest sensitivity and specificity for diagnosing cognitive disorders are 97.9% and 94.2%, respectively; the method is simple to use and unaffected by cultural differences, educational attainment, or other variables.	Being unable to identify a patient's precise type of cognitive dysfunction
Cognitive Disorder	GPCOG	orientation, memory, attention, language, visuospatial skills, and executive function	0-9 points, ≥ 5 indicates normal	Face to face, professional training required	Simple to use; high reliability and validity; the Chinese version's sensitivity and specificity for detecting AD are up to 98.08% and 91.94%; It is appropriate for AD screening at the community level	When screening for MCI, there is still a chance of missing diagnosis or misdiagnosis, hence it is required to integrate different scales for screening.

Abbreviations: AD, Alzheimer's disease; CDT, Clock Drawing Test; EFS, Edmonton Frailty Scale; FP, The Fried Frailty Phenotype; GPCOG , the General Practitioner Cognitive Functioning Assessment Gauge; MCI, mild cognitive impairment ; MMSE, Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment Scale.

for frailty within the elderly Chinese AD population. Their findings elucidated that factors such as older age, irregular exercise habits, substantial cognitive decline, and insufficient social support played pivotal roles in contributing to physical frailty among AD patients. The constructed nomogram exhibited a C-index of 0.884, indicative of robust differentiation and calibration capabilities. These insights collectively underscore the intricate relationship between frailty and AD, further emphasizing the need for more refined assessment tools to capture their complex interplay (*38*).

4. The improvement of AD with frailty therapy and intervention

4.1. Non-pharmacological treatment

Nutrition, horticultural treatment, physical activity, and social interaction are just a few of the disciplines that are combined in non-pharmacological therapies. A study conducted in Hyogo Prefecture, Japan, introduced a multifactorial Frailty Prevention Curriculum (FPC) within the community. This curriculum encompassed resistance exercise, nutritional education, and a psychosocial program overseen by trained geriatric professionals. Encouragingly, results revealed that older adults participating in the FPC exhibited significantly diminished risks of functional disability, notably attributable to dementia, over a 6.8-year observation period (*39*). A separate investigation undertaken in a New Zealand community randomized pre-frail older adults into distinct class combinations: a nutrition education and cooking class (SC), a strength and balance exercise program (SAYGO), a combined program (COMBINED), or a social activity program (CONTROL). While no significant disparities were initially observed among the four groups based on Fried frailty scores during the 2-year tracking phase, the SAYGO group demonstrated a noteworthy improvement compared to the control group at the 6-month mark (*40*). Other studies have delved into the impacts of horticultural therapy on physical functionality and psychological well-being among older adults. Horticultural therapy dramatically improves upper extremity flexibility and aerobic endurance in elderly cancer patients, according to this study. Additionally, it promotes subjective social relationships, overall quality of life, and emotional well-being (*41*). Salzman *et al.* systematically evaluated the effects of multidomain interventions on cognitive functioning among MCI patients. This examination, encompassing 28 randomized controlled trials (RCTs), unveiled that multidomain interventions yielded substantial enhancements in overall cognition, executive functions, memory, and verbal fluency. However, the study observed no significant differences in attention and processing speed. The multidomain intervention also correlated with improved scores on specific cognitive assessments like the MMSE, Category Verbal Fluency Test, Trail Making Test-B, and Wechsler Memory Scale-Logical Memory I and II. Ultimately, the study deduced that short-term multidomain interventions (spanning less than one year) can ameliorate cognitive functioning in individuals with MCI. However, additional research is necessary to ascertain the ideal intervention duration (*42*).

4.2. Drugs and physical therapy

Acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, anti-amyloid -protein (A) medications, and novel targeted therapeutic agents were all thoroughly examined in the World Alzheimer Report of 2022 (*43*). While AChEIs and NMDA receptor antagonists exhibit cognitive function enhancement, they are accompanied by increased adverse effects. Aβ Drugs show the ability to delay cognitive aging, but stronger proof is still needed to support this claim. Novel targeted therapies, although promising, necessitate further studies to validate their safety and efficacy (*44,45*). Seibert *et al.* contributed to the discourse by investigating the efficacy and safety of pharmacotherapy in older AD patients grappling with debilitating or impaired function. Their findings indicated that AChEIs marginally improved cognitive function yet exhibited no substantial effect on functional status or behavioral and psychological symptoms (BPSD). Antidepressants demonstrated limited improvement in depressive symptoms. Antipsychotics and anticonvulsants exhibited mild effects on select BPSD facets, albeit accompanied by heightened adverse effects (*46*). Thapaliya *et al.* conducted a longitudinal cohort study evaluating medication usage among older women in Australia between 2003 and 2015. They observed that women with dementia residing in nursing homes displayed elevated rates of medication reviews (MR), although the usage remained below 50% (*47*). Wei *et al.* embarked on a systematic evaluation and Bayesian network meta-analysis to compare the effectiveness of repetitive transcranial magnetic stimulation (rTMS) with medication among AD patients. Their investigation highlighted rTMS as superior to placebo and multiple medications in enhancing cognitive function while exhibiting the lowest incidence of adverse effects (*48*). Okahara *et al.* delved into the effects of the multi-component drug "ginseng nourishing broth" (Ninjin'yoeito) on debilitating symptoms in patients with MCI and mild AD. Their research demonstrated how Ninjin'yoeito's anorexia early on improved anorexia scores on the Neuropsychiatric Symptoms Scale. After 24 weeks, there was no sign of frailty and significant improvements in the Cardiovascular Health Study scores were seen. Moreover, scores on the fatigue

Table 2. Treatment type and effectiveness of Alzheimer's disease (AD) accompanied by frailty

Types of Intervention	Content of Intervention	Effectivness of Intervention
Non-pharmacological interventions	Program to prevent frailty that takes a multifaceted approach that incorporates resistance training, nutrition education, and psychosocial interventions	Functional disability risk was significantly lower (HR = 0.53, 95% CI: 0.38–0.75), notably for functional disability brought on by dementia (HR = 0.47, 95% CI: 0.25–0.86).
	Combining lessons, such as classes on nutrition education and cooking, classes on strength and balance, and both	At six months, the SAYGO group outperformed the Friend control group (-0404, 95% CI: -068 to -0123).
	Horticultural therapy	Improvement in aerobic endurance (SMD = 0.79, 95% CI: 0.41–1.16) and upper body flexibility (SMD = 0.26, 95% CI: 0.03–0.50) as well as an improvement in general quality of life.
	Multiple exercise or cognitive therapies, dietary supplements, cognitive, physical, and social activities, joint cognitive training with transcranial direct current stimulation, *etc*. are examples of multidomain interventions	Among other things, there was a substantial improvement in executive function (SMD = 0.20; 95% CI: 0.04–0.36) , memory (SMD = 0.29; 95% CI: 0.14–0.45), verbal fluency (SMD = 0.30; 95% CI: 0.12–0.49), and global cognition (SMD = 0.41; 95% CI: 0.23–0.59).
Pharmacological interventions	Acetylcholinesterase Inhibitors (AChEIs)	Donepezil, rivastigmine, and galantamine are cholinesterase inhibitors that are cognitively beneficial in mild to severe Alzheimer's disease (Class A).
	Memantine	In patients with mild to moderate Alzheimer's disease, memantine is cognitively successful (Class A), and combination therapy with cholinesterase inhibitors may be helpful (Class B).
	Anti-amyloid-beta (Aβ) drugs	Particularly Aducanumab and Lecanemab, anti-A monoclonal antibodies significantly enhanced cognitive and biomarker outcomes. The use of these medications alone is unlikely to fundamentally alter the development of AD in a clinically relevant way because the cognitive effects were minor. Second, these medications significantly up the chance of adverse effects such headaches and cerebral edema (ARIA-E).

visual analog scale significantly increased (*49*) (Table 2).

4.3. Innovative intervention models

Suharya's research focuses on combining medical and social care techniques to provide post-diagnosis support to people in Korea who are dealing with cognitive impairment (*50*). Three different service categories are identified in the article: *i*) A year-long, individualized support system is provided by specialists as part of the Post-Diagnostic Support Program for Cognitive Impairment (PDS). This all-encompassing help entails providing knowledge, instruction, psychological assistance, encouraging social activity, and assisting with legal planning. *ii*) Individuals and families dealing with cognitive disorders can get comprehensive help from the Community Cognitive Disability Centers (CDCs). Comprehensive assessments, counseling, therapy, childcare, in-home care, and emergency response are all included in these services. *iii*) Specialized Cognitive Disorder Hospitals (SDHs) focus on providing patients with cognitive impairments with specialized medical care. Their services span medication administration, surgical interventions, rehabilitation, and inpatient care. The authors underscore that these services collectively contribute to delaying cognitive decline, mitigating social expenses and hospitalization rates, curbing complications and mortality, and enhancing the overall quality and safety of care, among other benefits. Lorimer provides insights into the Scottish model of care, which includes aspects of diagnosis, post-diagnostic support, community assistance involving the coordination of medical and social agencies, and provision for hospital and institutional care (*51*). Oliveira's work focuses on Brazilian reforms and innovative approaches to diagnosing and treating cognitive disorders within the primary health care system. Notably, the primary health care system offers access to both pharmacological and non-pharmacological treatments, incorporating cognitive stimulation, psychosocial support, and exercise interventions. Specialized memory clinics have been established to conduct multidisciplinary assessments and management with primary health care teams. Moreover, primary health care workers receive training and support to enhance their knowledge and competence in addressing cognitive impairment and facilitating communication with specialists. Additionally, digital technologies, such as teleconsultation, electronic health records, and mobile applications, have been leveraged to improve accessibility and efficiency in diagnosing and treating cognitive impairment (*52*).

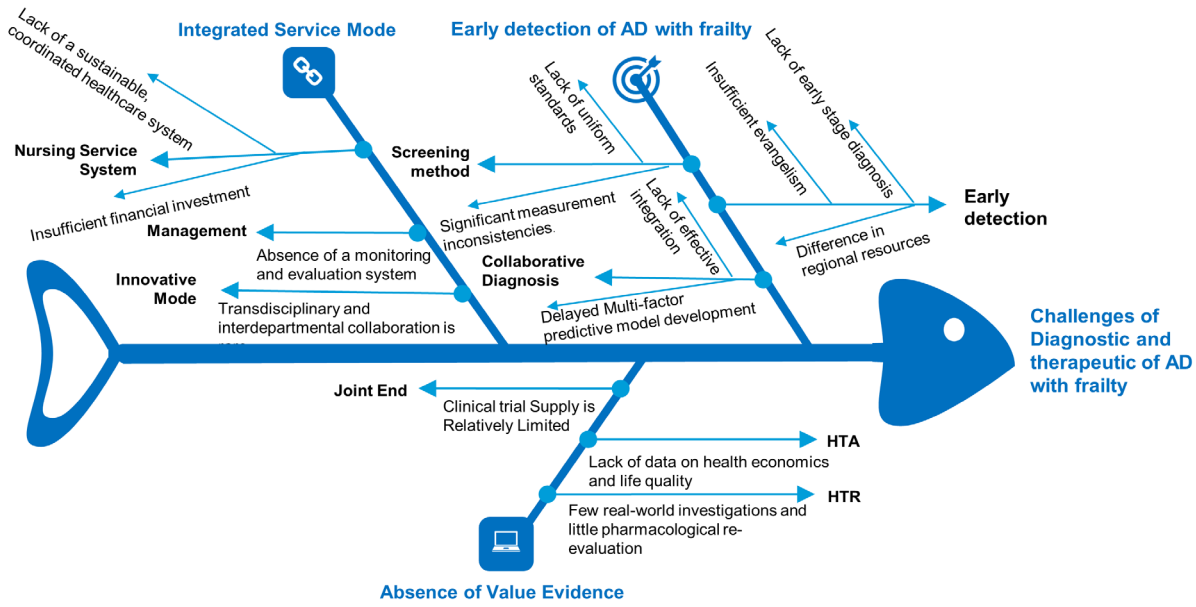

Figure 2. Diagnostic and therapeutic challenges for Alzheimer's disease (AD) with frailty. HTA, health technology assessment; HTR, health technology reassessment.

5. Diagnostic and therapeutic problems for AD with frailty

5.1. Improving the early detection of AD with frailty

Recent studies have gradually shown the higher frequency of frailty and AD, showing the complex interactions between the two. Within the current clinical intervention paradigms, this emergent element has now taken the lead: *i*) The key to addressing the urgent issue is early detection of AD during its asymptomatic and severe stages. It is crucial to find solutions to the problems caused by varying diagnostic standards, resource constraints, cultural differences, and ethical considerations in various countries. *ii*) Because there aren't many standardized tests available, current screening techniques suffer from significant measurement inconsistencies. *iii*) The integration of current diagnostics is still far from perfect. Although they are in use, predictive models often struggle with small sample numbers and frequently overlook potential confounding factors including patient history and the more recent contributions of biomarkers, imaging methods, and genetic testing technologies. These factors all work together to reduce the accuracy, dependability, and accessibility of diagnostic information. Addressing these issues becomes crucial as the therapeutic landscape develops.

5.2. The value of therapies and drugs for AD with debilitation are not supported by clinical trial

Clinical trials for senior patients with AD who exhibit frailty or functional impairment are noticeably lacking at the moment. In addition, there is a dearth of thorough evaluation data that considers factors like quality of life, financial impact, and social benefits for both patients and caregivers. Improvements in biological diagnostic accuracy, dependability, and accessibility of recently produced medications are also necessary. The need to increase the body of research pertaining to the cost-effectiveness, adherence, and safety of routine medication injection delivery is also widely acknowledged. The fact that just a small portion of drug use has been reviewed is notable and emphasizes the pressing need for stronger real-world evidence to demonstrate the effectiveness of these therapies.

5.3. To be developed: Integrated AD with frailty service model

Frailty and AD are serious public health issues that have an effect on both families and society. However, it is still clear that there is a lack of an egalitarian, sustainable, integrated, and high-quality care delivery system. The lack of specialized policies and uniform guidelines makes this shortfall even worse, which causes an insufficient allocation of human, material, and financial resources, particularly for preventative treatments during the pre-AD phase. The continued improvement of care service quality and efficacy is negatively impacted by the absence of efficient monitoring and evaluation systems at the managerial level. Another major obstacle is the insufficient support for cross-sectoral and interdisciplinary collaboration and coordination. This lack of cooperation prevents the field from spreading innovative concepts and outstanding practices. Consequently, it is necessary to to provide a comprehensive service model to handle this task (Figure 2).

6. Conclusion

Due to the significant and rising prevalence of AD and frailty, this situation poses a serious public health challenge that calls for preventative, regulatory, and therapeutic approaches. Evidently, there is still a sizable gap in the areas of screening, assessment, therapy, and intervention for people coping with the combination of frailty and AD. This unmet demand emphasizes the urgent need for more resources and ground-breaking solutions to be swiftly deployed.

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References

1. Alzheimer's Disease International. World Alzheimer Report 2018 - The state of the art of dementia research: New frontiers. *https://www.alzint.org/resource/world-alzheimer-report-2018* (accessed August 3, 2023).
2. Koch G, Belli L, Giudice TL, Lorenzo FD, Sancesario GM, Sorge R, Bernardini S, Martorana, A. Frailty among Alzheimer's disease patients. CNS Neurol Disord Drug Targets. 2013; 12:507-511.
3. Kojima G, Liljas A, Iliffe S, Walters K. Prevalence of frailty in mild to moderate Alzheimer's disease: A systematic review and meta-analysis. Curr Alzheimer Res. 2017; 14:1256-1263.
4. Grande G, Haaksma ML, Rizzuto D, Melis RJF, Marengoni A, Onder G, Welmer AK, Fratiglioni L, Vetrano DL. Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: Systematic review and meta-analysis. Neurosci Biobehav Rev. 2019; 107:96-103.
5. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci. 2022; 14:937486.
6. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: Implications for clinical practice and public health. Lancet. 2019; 394:1365-1375.
7. Koria LG, Sawan MJ, Redston MR, Gnjidic D. The prevalence of frailty among older adults living with dementia: A systematic review. J Am Med Dir Assoc. 2022; 23:1807-1814.
8. Gbessemehlan A, Kehoua G, Helmer C, Delcourt C, Tchalla A, Mbelesso P, Ndamba-Bandzouzi B, Dartigues JF, Houinato D, Preux PM, Guerchet M. Self-Reported Vision Impairment and Frailty among Older People with low cognitive performance in central Africa: EPIDEMCA population-based study. Dement Geriatr Cogn Disord. 2021; 50:326-332.
9. Wightman H, Quinn TJ, Mair FS, Lewsey J, McAllister DA, Hanlon P. Frailty in randomised controlled trials for dementia or mild cognitive impairment measured *via* the frailty index: Prevalence and prediction of serious adverse events and attrition. Alzheimers Res Ther. 2023; 15:110.
10. Bellelli G, Zucchelli A, Benussi A, Pinardi E, Caratozzolo S, Ornago AM, Cosseddu M, Stella V, Turrone R, Massariello F, Marengoni A, Padovani A. Assessing frailty at the centers for dementia and cognitive decline in Italy: Potential implications for improving care of older people living with dementia. Neurol Sci. 2023; doi: 10.1007/s10072-023-06885-8.
11. Lee L, Jones A, Patel T, Hillier LM, Heckman GA, Costa AP. Frailty prevalence and efficient screening in primary care-based memory clinics. Fam Pract. 2023; cmad035. doi: 10.1093/fampra/cmad035.
12. Kasajima M, Eggleston K, Kusaka S, Matsui H, Tanaka T, Son BK, Iijima K, Goda K, Kitsuregawa M, Bhattacharya J, Hashimoto H. Projecting prevalence of frailty and dementia and the economic cost of care in Japan from 2016 to 2043: A microsimulation modelling study. Lancet Public Health. 2022; 7:e458-e468.
13. Li M, Huang Y, Liu Z, Shen R, Chen H, Ma C, Zhang T, Li S, Prince M. The association between frailty and incidence of dementia in Beijing: Findings from 10/66 dementia research group population-based cohort study. BMC Geriatr. 2020; 20:138.
14. Canevelli M, Cesari M, van Kan GA. Frailty and cognitive decline: How do they relate? Curr Opin Clin Nutr Metab Care. 2015; 18:43-50.
15. Jang JY, Kim J. Association between handgrip strength and cognitive impairment in elderly Koreans: A population-based cross-sectional study. J Phys Ther Sci. 2015; 27:3911-3915.
16. 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; 58:248-255.
17. Sharifi F, Khoiee MA, Aminroaya R, Ebrahimpur M, Shafiee G, Heshmat R, Payab M, Shadman Z, Fakhrzadeh H, Arzaghi SM, Mehrdad N, Ostovar A, Sheidaei A, Fahimfar N, Nabipour I, Larijani B. Studying the relationship between cognitive impairment and frailty phenotype: A cross-sectional analysis of the Bushehr Elderly Health (BEH) program. J Diabetes Metab Disord. 2021; 20:1229-1237.
18. Yang Y, Xiao M, Leng L, Jiang S, Feng L, Pan G, Li Z, Wang Y, Wang J, Wen Y, Wu D, Yang Y, Huang P. A systematic review and meta-analysis of the prevalence and correlation of mild cognitive impairment in sarcopenia. J Cachexia Sarcopenia Muscle. 2023; 14:45-56.
19. Waite SJ, Maitland S, Thomas A, Yarnall AJ. Sarcopenia and frailty in individuals with dementia: A systematic review. Arch Gerontol Geriatr. 2021; 92:104268.
20. Güner M, Baş AO, Ceylan S, Kahyaoğlu Z, Çöteli S, Ünsal P, Çavuşoğlu Ç, Özsürekci C, Doğu BB, Cankurtaran M, Halil MG. Dysphagia is closely related to frailty in mild-to-moderate Alzheimer's disease. BMC Geriatr. 2023; 23:304.
21. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146-M156.
22. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008; 12:29-37.
23. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton

Frail Scale. Age Ageing. 2006; 35:526-529.
24. HAN J, WANG JQ, XIE BQ, WANG Y. Comparison of consistency and validity of Fried frailty phenotype, Frail scale and Edmonton frailty scale for frailty screening among community-dwelling older adults. Chinese General Practice, 2021; 24:2669-2675. (in Chinese)
25. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. Eur J Intern Med. 2016; 31:3-10.
26. Ambagtsheer RC, Beilby J, Dabravolskaj J, Abbasi M, Archibald MM, Dent E. Application of an electronic Frailty Index in Australian primary care: Data quality and feasibility assessment. Aging Clin Exp Res. 2019; 31:653-660.
27. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, Mohammed MA, Parry J, Marshall T. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016; 45:353-360.
28. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, Arora S, Street A, Parker S, Roberts HC, Bardsley M, Conroy S. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: An observational study. Lancet. 2018; 391:1775-1782.
29. Cai M, Hu QR, Jia SH, Yang RY, Wang LY, Hu JY, Wang XJ, Chen XY. Strategy for the choice of appropriate mild cognitive impairment screening scales for community-dwelling older adults. Chinese General Practice. 2022; 25:3191-3195. (in Chinese).
30. Chen Y, Yu D, Ma L, Lu Y, Community-based application of six common cognitive impairment screening tools at home and abroad. Chinese General Practice. 2018; 21:1392-1396. *(in Chinese)*
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189-198.
32. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53:695-699.
33. Hazan E, Frankenburg F, Brenkel M, Shulman K. The test of time: A history of clock drawing. Int J Geriatr Psychiatry. 2018; 33:e22-e30.
34. Brodaty H, Pond D, Kemp NM, Luscombe G, Harding L, Berman K, Huppert FA. The GPCOG: A new screening test for dementia designed for general practice. J Am Geriatr Soc. 2002; 50:530-534.
35. Ren J, Song M, Zhang W, *et al.* The aging biomarker consortium represents a new era for aging research in China. Nat Med. 2023. doi: 10.1038/s41591-023-02444-y.
36. Ward DD, Wallace LMK, Rockwood K. Frailty and risk of dementia in mild cognitive impairment subtypes. Ann Neurol. 2021; 89:1221-1225.
37. Engvig A, Maglanoc LA, Doan NT, Westlye LT; Alzheimer's Disease Neuroimaging Initiative. Data-driven health deficit assessment improves a frailty index's prediction of current cognitive status and future conversion to dementia: Results from ADNI. Geroscience. 2023; 45:591-611.
38. Li Q, Zhang S, Wang X, Du M, Zhang Q. Risk factors and a nomogram for frailty in Chinese older patients with Alzheimer's disease: A single-center cross-sectional study. Geriatr Nurs. 2022; 47:47-54.
39. Nofuji Y, Seino S, Abe T, Yokoyama Y, Narita M, Murayama H, Shinkai S, Kitamura A, Fujiwara Y. Effects of community-based frailty-preventing intervention on all-cause and cause-specific functional disability in older adults living in rural Japan: A propensity score analysis. Prev Med. 2023; 169:107449.
40. Teh R, Barnett D, Edlin R, Kerse N, Waters DL, Hale L, Tay E, Leilua E, Pillai A. Effectiveness of a complex intervention of group-based nutrition and physical activity to prevent frailty in pre-frail older adults (SUPER): A randomised controlled trial. Lancet Healthy Longev. 2022; 3:e519-e530.
41. Lin Y, Lin R, Liu W, Wu W. Effectiveness of horticultural therapy on physical functioning and psychological health outcomes for older adults: A systematic review and meta-analysis. J Clin Nurs. 2022; 31:2087-2099.
42. Salzman T, Sarquis-Adamson Y, Son S, Montero-Odasso M, Fraser S. Associations of multidomain interventions with improvements in cognition in mild cognitive impairment: A systematic review and meta-analysis. JAMA Netw Open. 2022; 5:e226744.
43. Alzheimer's Disease International. World Alzheimer Report 2022, Life after diagnosis: navigating treatment, care and support. *https://www.alzint.org/resource/world-alzheimer-report-2022* (accessed August 3, 2023).
44. O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, McKeith I, Mittler P, Passmore P, Ritchie C, Robinson L, Sampson EL, Taylor JP, Thomas A, Burns A. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol. 2017; 31:147-168.
45. Jeremic D, Navarro-López JD, Jiménez-Díaz L. Efficacy and safety of anti-amyloid-β monoclonal antibodies in current Alzheimer's disease phase III clinical trials: A systematic review and interactive web app-based meta-analysis. Ageing Res Rev. 2023; 90:102012.
46. Seibert M, Mühlbauer V, Holbrook J, Voigt-Radloff S, Brefka S, Dallmeier D, Denkinger M, Schönfeldt-Lecuona C, Klöppel S, von Arnim CAF. Efficacy and safety of pharmacotherapy for Alzheimer's disease and for behavioural and psychological symptoms of dementia in older patients with moderate and severe functional impairments: A systematic review of controlled trials. Alzheimers Res Ther. 2021; 13:131.
47. Thapaliya K, Harris ML, Byles JE. Use of medication reviews among older women with dementia, 2003-2015: A longitudinal cohort study. Australas J Ageing. 2020; 39:e552-e558.
48. Wei N, Liu H, Ye W, Xu S, Lu C, Dai A, Hou T, Zeng X, Wu J, Chen J. Repetitive transcranial magnetic stimulation may be superior to drug therapy in the treatment of Alzheimer's disease: A systematic review and Bayesian network meta-analysis. CNS Neurosci Ther. 2023; doi: 10.1111/cns.14228.
49. Okahara K, Ohsawa M, Haruta-Tsukamoto A, Miyoshi R, Funahashi H, Fukutani Y, Makita S, Matsuo H, Ishida Y. Frailty improvement by multicomponent drug, ninjin'yoeito, in mild cognitive impairment and mild Alzheimer's disease patients: An open-label exploratory study (FRAMINGO). J Alzheimers Dis Rep. 2023; 7:107-117.
50. Suharya D. "Integrating medical and social care at a local level: Post-diagnostic support in South Korea" in World

Alzheimer report 2022: Life after diagnosis: Navigating treatment, care and support. Alzheimer's Disease International, London, England, 2022; pp.356-357. *https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf* (accessed August 3, 2023).
51. Lorimer N. "Post-diagnostic support in Scotland" in World Alzheimer report 2022: Life after diagnosis: Navigating treatment, care and support. Alzheimer's Disease International, London, England, 2022; pp.125-126. *https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf* (accessed August 3, 2023).
52. Oliveira D, da Mata FAF, Brucki S, Ferri CP. 'Post-diagnostic support for people living with dementia and their family carers in Brazil' in World Alzheimer report 2022: Life after diagnosis: Navigating treatment, care and support. Alzheimer's Disease International, London, England, 2022; pp.103-104. *https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf* (accessed August 3, 2023).

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