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REVIEW ARTICLE

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Cognitive impairment in people with physical frailty using the phenotype model: A systematic review and meta analysis

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Abstract

Objective: We performed a systematic review and meta-analysis to study the relationship between cognitive functioning and phenotypic frailty status.

Methods: We searched Pubmed, Cochrane Library and Epistemonikos from 2000 until March 2022, and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Samples included both sexes, age ≥55 years, assessed with standardized measures of the different cognitive domains and the frailty phenotype model and analyzing the relationship between the frailty subtypes pre-frail, frail and robust and specific cognitive function.

Results: Eleven studies published from 2008 until March 2022 fulfilled the inclusion criteria, and 10 were included in our meta-analyses. Sample sizes varied from 104 to 4649 individuals. Mean Mini-Mental State Examination (MMSE) scores ranged from 17.0 to 27.6, with mean difference (MD) of −2.55 (95% confidence interval [CI] −3.32, −1.78) in frail compared to robust, MD −1.64 (95% CI −2.21, −1.06) in frail compared to prefrail and MD −0.68 (95% CI −0.94, −0.43) in prefrail compared to robust. In subgroup analyses, frail persons had lower scores in the memory domain with standardized mean difference (SMD) −1.01 (95% CI −1.42, −0.59).

Conclusion: MMSE scores were significantly lower in frail compared to robust and prefrail persons and in prefrail compared to robust persons. Subgroup analysis of memory revealed significantly poorer scores in frail compared to robust. The results indicate a strong relationship between physical frailty and cognitive impairment suggesting incorporation of cognitive function in frailty assessments.

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination; ADL, activities of daily living; BCSB, Brief Cognitive Screening Battery; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CASP, Critical Appraisal Skills Programme; CDR, clinical dementia rating; CEBM, Centre of Evidence Based Medicine; CHS, Cardiovascular Health Study; CRT, choice reaction time; CTT, color trails test; DST, digit span test; FIBRA, Frailty in Brazilian Older People; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HALST, Healthy Aging Longitudinal Study in Taiwan; HC UFMG, Hospital das Clínicas da UFMG Cohort; H-EPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; LBC1936, Lothian Birth Cohort; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; NR, not reported; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; RCT, randomized controlled trials; RTB, Robertson Test Battery; SART, sustained attention to response task; SD, standard deviation; SGS, Sasaguri Genkimon Study; TILDA, The Irish Longitudinal Study on Ageing; TMT, trail making test; WAIS-III, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

KEYWORDS
aging, cognitive domains, cognitive impairments, elderly, meta-analysis, older persons, physical frailty, systematic review

Key points

- Global cognitive function, as examined through Mini-Mental State Examination, shows poorer scores in frail compared to prefrail and robust persons.
- Frail persons also score poorer in cognitive domains memory, visuospatial function, executive function and psychomotor speed.
- The results indicate a strong relationship between physical frailty and cognitive impairment.
- Since both cognitive and physical frailty usually are present, frailty models which include both cognitive and physical functions should be used in clinical practice.

1 | INTRODUCTION

Frailty is a common clinical syndrome in older persons that may lead to an increased risk of falls, disability, hospitalization, and mortality.[1] Frailty has a significant impact on the quality of life for old persons and, additionally, poses a huge financial burden for health care systems worldwide.

The concept of frailty was proposed by Rockwood in 1994[3] and, since then, many definitions have emerged, the most commonly used are probably those published by Fried in 2001[1] and Rockwood in 2007.[4] Frailty is a multisystem reduction of the ability to cope with internal or external stress due to increased vulnerability resulting from the physiological aging process. Reduced physiological reserve can manifest itself as either a gradual or a sudden loss of activities of daily living (ADL) caused by a stressor that normally would not be expected to affect the patient's functional status. Age is the strongest risk factor for dementia as well.[5]

Fried's definition, also referred as the phenotype model, focuses mainly on physical function.[1] According to Fried, frailty is defined as having three or more of the following five phenotypic criteria: poor grip strength, reduced walking speed, low degree of physical activity, exhaustion, and unintentional weight loss. When only two of these criteria are identified, the person is classified as pre-frail with an increased risk of progress towards frailty, whereas a patient without any of these findings is considered robust. In the model developed by Rockwood, frailty is described as an accumulation of deficits representing risk for negative outcome.[6]

Global cognitive function is measured through brief cognitive test batteries to assess the overall cognitive ability of a person, usually when screening for cognitive disorders.[7] The global function of the brain can further be divided into cognitive domains. The concept of cognitive domains is used to classify cognitive performance in neuropsychiatry, for example, in dementia and other forms of cognitive impairment.[8] For each domain there has further been described subdomains, referring to component ability processes within the domain. Cognitive tests are primarily designed to assess one or more of the discrete abilities that the domain represents.[9] Cognitive domains are classified in different manners. General process classification sorts the domains as for instance memory, executive function, visuospatial function, and language,[10] while others are based on regional functions of the brain, identified through lesion studies, as stemming from the frontal lobe, parietal lobe, hippocampus, etc.[11] Additionally, the domains can be structured according to hierarchy, where more complex functions, such as reasoning, awareness, problem solving, and executive function are higher in the hierarchy, while more basic functions such as sensory function and perception are at the bottom.[12] According to the DSM-5, the following six cognitive domains should be evaluated: perceptual-motor function, language, earning and memory, complex attention, executive function, and social cognition.[10]

Impairments in cognitive domains and their association with frailty have largely been examined using a standardized battery of tests to assess cognitive functions according to the general domains, and frailty has been assessed through phenotype models according to Fried.

Studies have proposed that prefrail persons may present with poorer cognitive performance than non-frail in both memory and non-memory cognitive domains.[13] Frailty may be significantly associated with lower global scores on cognitive tests.[14]

In the frailty phenotype concept, functional impairments are essential.[1] Impaired cognitive function has been proposed to impact the development of frailty. Individuals with Alzheimer's disease have been classified as frail shortly before death, and frailty has been shown to be associated with a 60% increase in risk of developing mild cognitive impairment (MCI), and consequently, dementia.[15] Currently, the pathophysiologic mechanisms for both conditions are considered to overlap and synergistically increase one another, mainly through mechanisms that also promote neurodegeneration, such as chronic inflammation, oxidative stress and other clinical comorbidities as cardiovascular disease.[15] The level of evidence has, however, been deemed inadequate as the sample sizes have been small, and due to a lack of randomized controlled trials (RCT's).[16] Recently, some studies have emerged where frailty and pre-frailty are examined in people with deficits within specific cognitive domains. We have identified some systematic reviews, the most recent from 2019, though they did not perform meta-analyses of associations between physical frailty and cognitive impairment, as examined through cognitive testing of global cognitive function and subdomains.

While most studies have shown an association between frailty and cognitive decline, results vary in terms of the affected cognitive domains and the significance of pre-frailty. Thus, the aim of the present systematic review and meta-analysis was to study the relationship between degree of frailty and global cognitive functioning as well as specific cognitive domains.

2 | METHODS

2.1 | Inclusion criteria

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA).[17] We used the following prespecified inclusion criteria: (1) Population: persons of both sexes ≥55 years of age, (2) Intervention: cognitive investigation with a standardized test or test battery, (3) Comparisons: (a) global cognitive function: frail compared to robust and prefrail people, and prefrail compared to robust people; (b) cognitive domain memory: frail compared to robust people, (4) exposure: associations between cognitive function and degree of frailty, (5) Study design: cohort or cross-sectional studies.

Physical frailty had to be defined by the frailty phenotype model according to Fried, sometimes also referred to as the Cardiovascular Health Study (CHS) criteria.[1]

2.2 | Search strategy

We conducted a systematic literature search and retrieval in PubMed (1996), the Cochrane Library (1996) and Epistemonikos (2009), from the dates of inception of the databases until 29 January 2021, and, in addition, an updated search was performed 2 March 2022. The search was performed by trained information specialists. We used MeSH terms and free terms, "frail elderly," "frailty," "frail," "pre-frail," and "dementia," "cognition disorders," "cognition," "cognitive impairment," "cognitive dysfunction," "cognitive disorder," "cognitive decline," "dement," "Alzheimer," "cognitive domain." The search terms were combined with Boolean conjunction. In addition, we screened reference lists of systematic reviews for potential studies not identified through the literature search.

The present systematic review and meta-analysis was registered in the International prospective register of systematic reviews PROSPERO (CRD42021249448).[18]

The complete search strategy can be found in Supporting Information S1.

2.3 | Study selection and data extraction

To increase the comprehensiveness of the inclusion process, we manually sorted references, citations, and other related articles. Studies were included after independent screening of titles and abstracts and full-text reading of articles by two of the authors (AV and BF).

Data was extracted regarding year of publication, country, study design, setting, number of included research persons, age, sex and, if available, educational level. Additionally, we extracted outcomes in global cognitive function, function in specific cognitive domains when available and frailty assessment.

2.4 | Quality assessment

Quality assessment of included studies was performed using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies[19] and the Centre of Evidence Based Medicine (CEBM) checklist for cross-sectional studies.[20]

2.5 | Disagreement between reviewers

Any disagreement between reviewers regarding inclusion, quality assessment of individual studies or assessment of the evidence across studies using Grading of Recommendations Assessment, Development and Evaluation (GRADE), was resolved by consensus.

2.6 | Statistical analysis

Data regarding global cognitive function and specific cognitive domains for different degrees of frailty was entered into Review Manager 5.4.[21] We performed meta-analyses using random effects models due to heterogeneity across studies. Mean difference was applied when the same instrument was used across included studies; otherwise standardized mean difference was used.[22]

2.7 | Confidence in the evidence

We used the GRADE tool to assess our confidence in the evidence for each outcome across all the included studies.[23]

3 | RESULTS

The studies were published between 2008 and 2021 and had sample sizes varying from 104 to 4649 included persons, with a total of 12,489 persons across all studies, see Table 1.

The samples varied in mean age between 61.8 (±8.4) and 78.4 years (±7.9) (55–86 years), and even though they differed in gender distribution, they mostly contained a larger female proportion with a mean of 63.2% (±13.15). Education was presented in varying ways, spanning from a mean of 2.99 (±2.76) to as long as 13.6 years (±3.6) of education, and 3.3%–36.9% of the samples having undergone tertiary education, defined as college, university,

TABLE 1 Background variables of included studies

Source	Year	Country	Study design	Cohort	Setting	Sample size, *N*	Age, mean (SD)	Sex *F*, %	Education, %	Education in years, mean (SD)
Samper-Ternent	2008	United States of America	Cohort	H-EPESE	Community-based	1370	74.0 (5.44)	58.9	NR	5.56 (3.96)
Macuco	2012	Brazil	Cohort	FIBRA	Community-based	384	72.3 (5.8)	67.19	NR	3.4 (2.8)
Alencar	2013	Brazil	Cross-sectional	HC UFMG	Outpatient clinic, University hospital	207	78.4 (7.9)	76.3	NR	2.99 (2.76)
Robertson	2014	Ireland	Cross-sectional	TILDA	Home and health-center based	4649	61.8 (8.4)	53.6	36.9 Tertiary[b]	NR
Chen	2016	Japan	Cross-sectional	SGS	Community-based	1565	73.3 (6.0)	60.0	NR	11.1 (2.5)
Gale	2017	Scotland	Cohort	LBC 1936	Community-based	594	69.5 (0.82)	48.98	NR	NR
Hsieh	2018	Taiwan	Cohort	HALST	Community-based	2386	73.2 (5.71)	51.26	42.33 Secondary[a]	
Yoon	2018	Korea	Cross-sectional	NR	Community-based	104	73.5 (5.43)	77	NR	5.1 (4.17)
Murukesu	2019	Malaysia	Cross-sectional	NR	Institutions	302	68.9 (7.24)	31.3	3.3 Tertiary[b]	NR
Chen	2021	Taiwan	Cohort	TIGER I	Outpatient clinic, University hospital	521	72.2 (5.3)	52.4	NR	13.6 (3.6)
De Mello	2021	Brazil	Cross-sectional	NR	Outpatient clinic, University hospital	407	70.9 (7.6)	49.9	55%[c]	NR

Abbreviations: FIBRA, Frailty in Brazilian Older People; HALST, Healthy Aging Longitudinal Study in Taiwan; HC UFMG, Hospital das Clínicas da UFMG Cohort; H-EPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; LBC1936, Lothian Birth Cohort; NR, not reported; SGS, Sasaguri Genkimon Study; TIGER I, Taiwan Initiative for Geriatric Epidemiological Research; TILDA, The Irish Longitudinal Study on Ageing.

[a]Six years of education.

[b]≥9 years of education.

[c]1–4 years of education.

*Estimation from mean and range.

TABLE 2 Diagnostic criteria of frailty and cognitive function in included studies

Source	Year	Frailty criteria	Global cognitive tests	Memory tests	Psychomotor tests	Visuospatial/ executive tests
Samper-Ternent	2008	Phenotype (fried)	MMSE	NR	NR	NR
Macuco	2012	Phenotype (fried)	MMSE	From MMSE	NR	NR
Alencar	2013	Phenotype (fried)	MMSE, BCSB, CDR	NR	NR	NR
Robertson	2014	Phenotype (fried)	MMSE, MoCA, RTB	CAMDEX memory subtest, 10-word recall	CTT-A, SART, CRT	CTT-B, CAMDEX subtest
Chen	2016	Phenotype (fried)	MMSE, MoCA	WMS-III	NR	NR
Gale	2017	Phenotype (fried)	WAIS-III, NART, WTAR	NR	NR	NR
Hsieh	2018	Phenotype (fried)	MMSE	NR	NR	NR
Yoon	2018	Phenotype (fried)	MMSE	Rey 15-item memory test, DST	TMT-A	TMT-B
Murukesu	2019	Phenotype (fried)	MMSE, ACE-III	NR	NR	NR
Chen	2021	Phenotype (fried)	MoCA	WMS, DST	TMT-A	TMT-B
De Mello	2021	Phenotype (fried)	MMSE	SVF	NR	NR

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination; BCSB, Brief Cognitive Screening Battery; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; CDR, clinical dementia rating; CRT, choice reaction time; CTT, color trails test; DST, digit span test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NART, National Adult Reading Test; NR, not reported; RTB, Robertson Test Battery; SART, Sustained Attention to Response Task; SVF, semantic verbal fluency test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

or other corresponding forms of education. The cohorts recruited community-dwelling people, with the exception of one cohort which recruited hospital workers. The cohorts were initiated between 1993 and 2011 and recruited people from 50 to 65 years and above.

The studies were performed in eight countries, Brazil (n = 3), Taiwan (n = 1), Ireland (n = 1), Japan (n = 1), Korea (n = 1), Malaysia (n = 1), and United States of America (n = 1) and were either cohort or cross-sectional studies. The Mini-Mental State Examination (MMSE)[24] was used across the nine studies included in the main meta-analyses, one used, in addition, Montreal Cognitive Assessment (MoCA) and one used Wechsler Adult Intelligence Scale (WAIS), though other diagnostic tools were used as well to measure global cognitive functions and cognitive subdomains such as memory, see Table 2.

3.1 | Characteristics and quality of included studies

The literature search yielded 5175 results, and after duplicates were removed, 4869 remained. In total, 36 studies fulfilled the inclusion and exclusion criteria of the study design, and subsequently were retrieved in full text, where all were read but one, as it was unavailable to acquire.[25] Of these, eleven[26-36] fulfilled our inclusion criteria, see flow chart in Figure 1. No additional study was identified through screening of reference lists in previously published systematic reviews. Reasons for excluding studies were that the results were not presented according to frailty groups, and thus could not be properly assessed according to the research question (n = 18), one frailty group omitted (n = 2), non-representative population (n = 1), results of MMSE not reported (n = 1), results of cognitive testing not including standard deviations (n = 1), cognitive testing not performed systematically (n = 1) and article unavailable for retrieval (n = 1). The 25 studies excluded after full text reading can be found with explanations for exclusion in Supporting Information S2.

3.2 | Quality assessment

Critical appraisal using the CASP tool[19] yielded high quality across the assessed cohort studies,[26,28,29,33,36] see Supporting Information S2.

The cross-sectional studies[27,30-32,34,35] were assessed through the CEBM tool,[20] resulting in an overall poor appraisal, see Supporting Information S3. The cross-sectional studies were assessed to be of lower quality due to poor internal validity with an inclusion process that could introduce selection bias in several studies. In addition, in some studies, it was questionable whether the sample was representative and, hence, the external validity satisfactory. It was clearly stated in only one study[30] that the sample size was based on pre-study calculations of statistical power.

3.3 | Confidence in the evidence

Our confidence in the estimates was assessed using the GRADE tool,[23] see Table 3. According to GRADE, we have low confidence in the estimates from the main meta-analyses involving MMSE and very low confidence in the estimates from the subgroup analyses involving

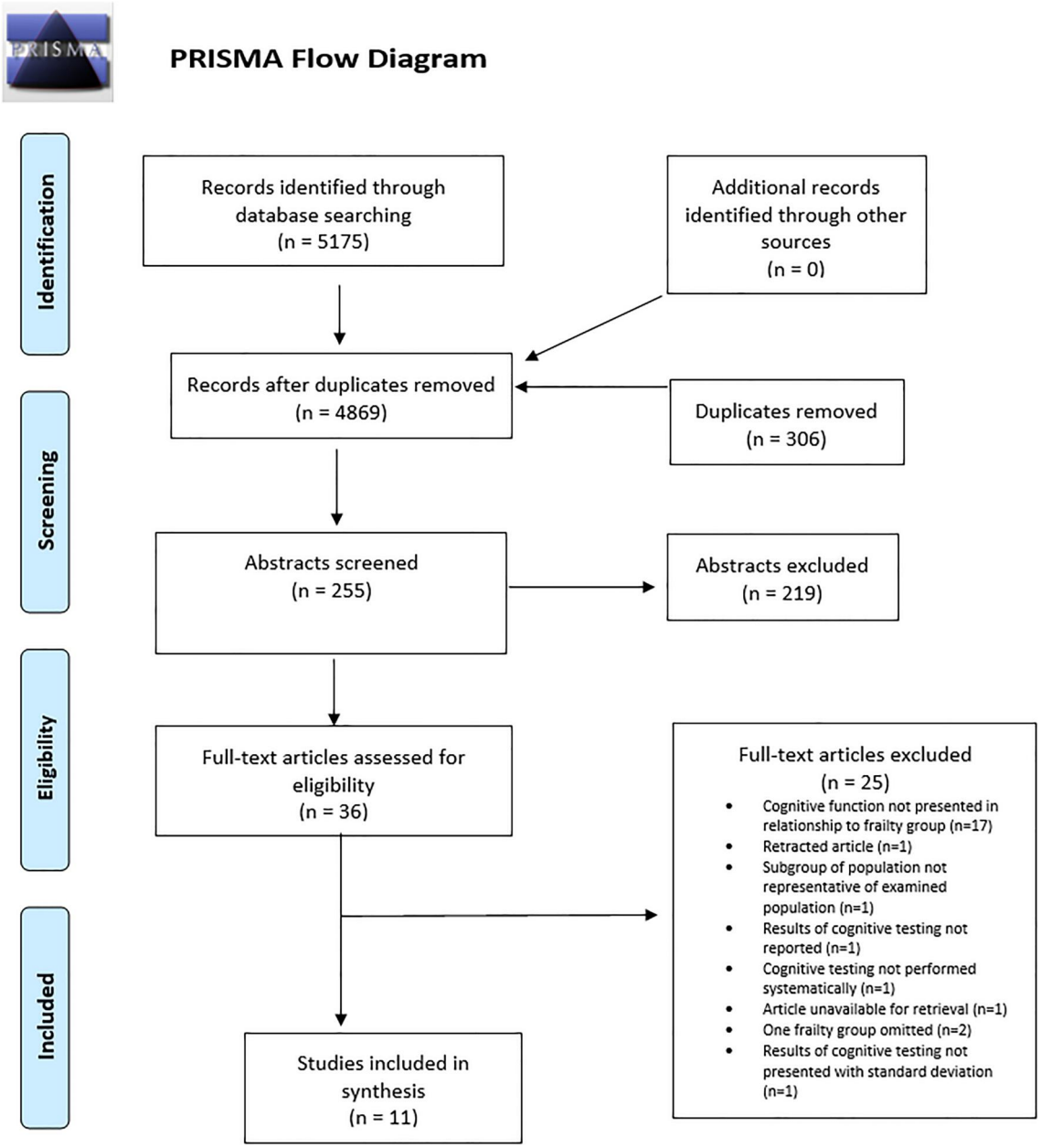

FIGURE 1 PRISMA flow chart for the inclusion process

specific cognitive domains. Reasons for downgrading our confidence were mainly risk of bias and imprecision, with small studies and wide confidence intervals (CIs) across studies. Our confidence in the estimates were upgraded due to strong associations and a "dose-response gradient," that is, a lower MMSE score in frail than in prefrail people and a lower MMSE score in prefrail than in robust people. We agree with the GRADE assessment.

3.4 | Meta-analyses

We performed meta-analyses of global MMSE scores across each frailty subtype, that is, frail, prefrail, and robust, including nine of the studies,[26,27,29–35] with a total of 10,855 persons. We used a 95% fixed CI.

The global MMSE scores were significantly lower in the frail group when compared to the robust, with a mean difference of −2.55 (95% CI −3.32, −1.78) MMSE points. Comparing MMSE scores in frail and prefrail, we found a significantly lower MMSE score in frail people, with a mean difference of −1.64 (95% CI −2.21, −1.06), as well as a lower MMSE score in prefrail than in robust people with a mean difference of −0.68 (95% CI −0.94, −0.43), see Figure 2.

Results extracted from MoCA in Chen et al.[36] showed the same pattern, where frail people scored 26.2 ± 2.4, prefrail 26.8 ± 2.3 and robust 27.1 ± 2.0, indicating that MoCA scores decrease with increasing frailty. This study was not included in the main meta-

TABLE 3 Our confidence in the estimates across all included studies according to Grading of Recommendations Assessment, Development and Evaluation

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frailty	Robust	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
MMSE in frail versus Robust people												
9	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	Strong association dose response gradient	708	5723	-	MD **2.49 MMSE pts. lower** (3.31 lower to 1.68 lower)	⨁⨁◯◯ LOW	IMPORTANT
MMSE in frail versus prefrail people												
9	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	Strong association dose response gradient	708	4536	-	MD **1.45 MMSE pts. lower** (1.98 lower to 0.91 lower)	⨁⨁◯◯ LOW	IMPORTANT
MMSE in prefrail versus Robust people												
9	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	Strong association dose response gradient	4536	5723	-	MD **0.73 MMSE pts. lower** (0.99 lower to 0.46 lower)	⨁⨁◯◯ LOW	IMPORTANT
Memory in frail versus Robust people												
6	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	None	374	4244	-	SMD **0.71 SD lower** (0.88 lower to 0.53 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations: CI, confidence interval; MD, mean difference; SMD, standardized mean difference.

[a]Selection bias, selective reporting, lack of representativeness in selection.

[b]Small studies, wide confidence intervals.

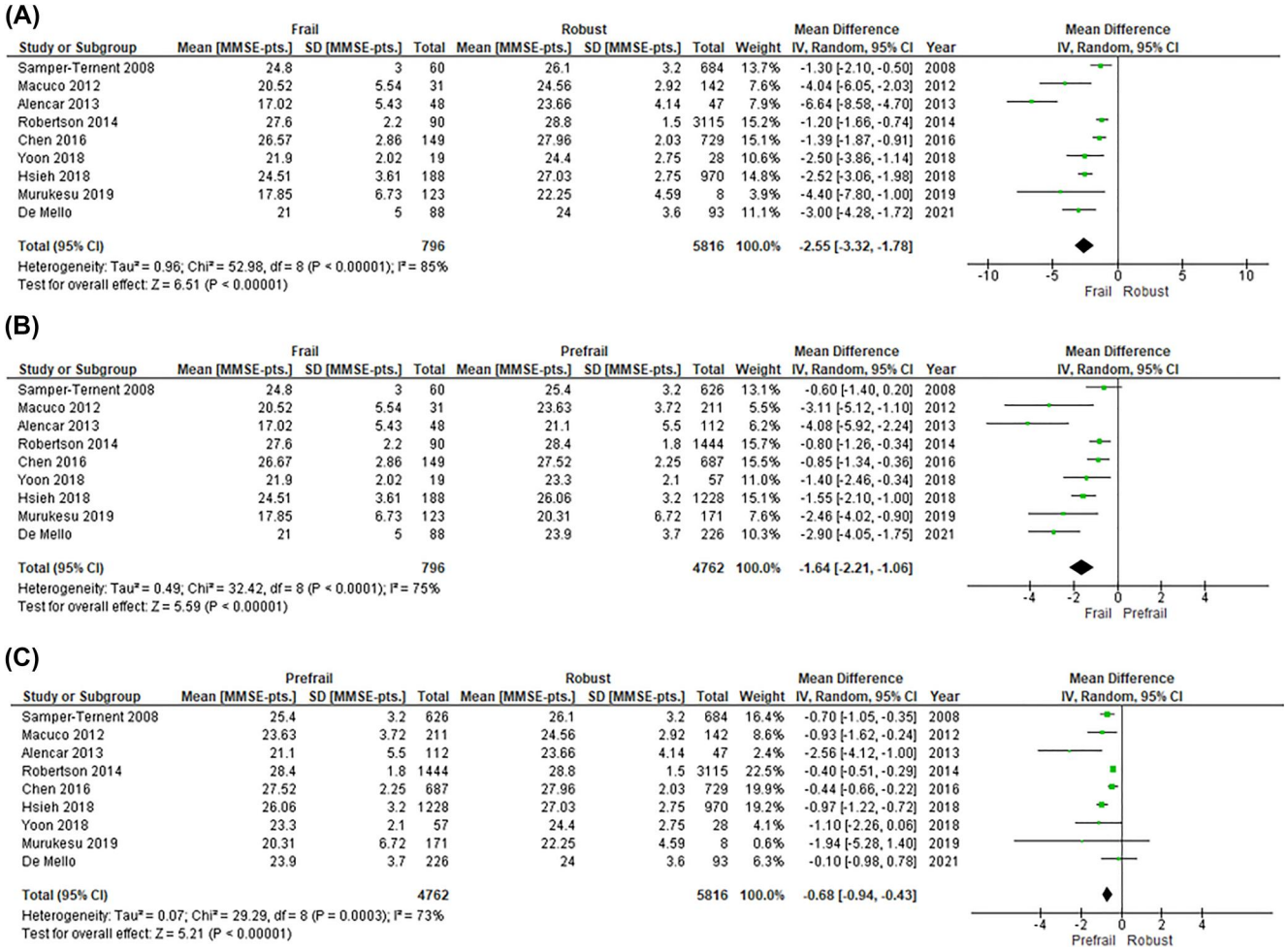

FIGURE 2 Global MMSE score between frailty groups. (A) Global MMSE scores in frail versus robust, (B) Global MMSE scores in frail versus prefrail, (C) Global MMSE scores in prefrail versus robust. MMSE, Mini-Mental State Examination

analyses since only MoCA was used for evaluating global cognitive function and not MMSE.

Subgroup analyses were designed to assess the memory subdomain between the frail and the robust.

Data from memory subtests were extracted from MMSE in Macuco et al.[30] and De Mello et al.[35] Robertson Test Battery in Robertson et al.[32] MoCA in Chen et al.[27] WAIS in Gale et al.[28] and Rey 15-item Memory test in Yoon et al.[34] with a total of 5537 included persons. There was a significantly lower score in memory subtests in frail compared to robust people, with a standardized mean difference of −1.01 (95% CI −1.42, −0.59), see Figure 3.

4 | DISCUSSION

We found significant differences in global cognitive function, assessed by MMSE scores, and frailty according to the frail phenotype model, with frail persons scoring significantly lower than robust persons. The same difference was present when comparing frail and prefrail persons, where frail scored lower than prefrail people, and, subsequently, prefrail scored lower than robust people did. Subgroup analyses, designed to assess cognitive subdomains, that is, memory, visuospatial function, executive function, and psychomotor speed, showed significantly lower scores in frail compared to robust people in all assessed domains.

A previous systematic review by Brigola et al. concluded that there might be an association between frailty and cognitive impairment, as frail persons scored lower in MMSE score than did robust persons, with the main cognitive domain impaired being memory.[37] Specific subdomains were thought to be linked to specific criteria of physical frailty.[37] The severity of cognitive impairment was suggested to be influenced by higher levels of frailty, especially when viewed as a physical syndrome.

Another systematic review by Kiiti Borges et al. studied the relationship between physical frailty and MCI, defined as cognitive impairment without concomitant impairment in ADL.[38] Physical frailty was, in line with the results of the present systematic review and meta-analysis, associated with MCI, with a potentially bidirectional association, that is, poorer cognition was, reversely, significantly associated with physical frailty. However, according to

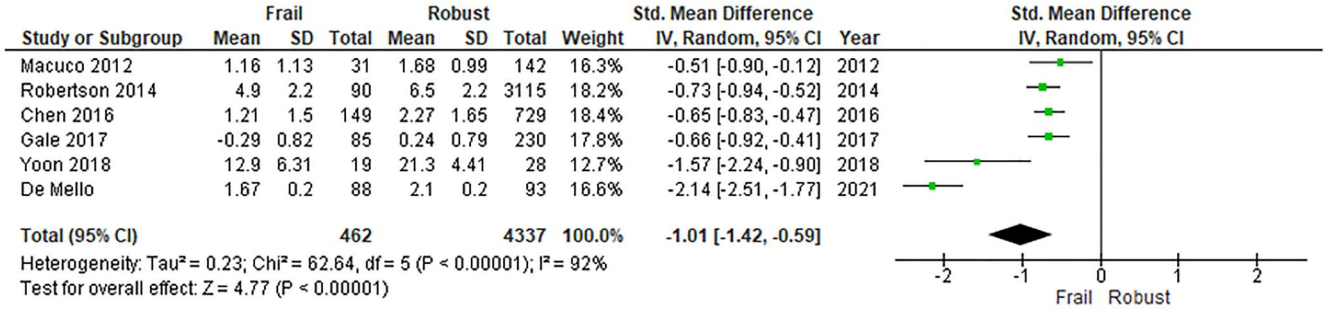

FIGURE 3 Memory in frail compared to robust people

diagnostic criteria, changes in cognitive function have to interfere with ADL-performance for a dementia diagnosis.[39]

A recent cross-sectional study by Lorenzo-López et al. did not observe any significant differences in global cognitive performance according to MMSE,[13] when comparing the prefrail to the robust. MoCA scores, however, were overall lower in the prefrail group, as well as scores on immediate and delayed memory subtests. Delayed episodic memory was the only cognitive subdomain significantly associated with a pre-frail state after adjusting for age, sex, and educational level, contradicting previous studies concluding that non-memory domains generally were the first domains influenced in the prefrail.

Robertson et al. found frailty to be significantly associated with global cognition and perceptual speed, but not with episodic memory, semantic memory or working memory.[39] Also, in a systematic review by Robertson et al. it has been suggested that the domains executive functioning and attention, but not memory, are related to frailty.[40] Hence, although there seems to be an agreement regarding the relationship between global cognitive function and frailty, the association between specific cognitive domains and frailty is still under discussion.

In accordance with other systematic reviews, we also found that the level of physical frailty may correspond to the level of cognitive impairment. In clinical practice, this may imply that physically frail individuals should be tested cognitively, for example, when a patient presents with frequent falls or weight loss, two criteria of the frailty syndrome, there is a risk of coexisting cognitive impairments. Although there are, at present, no effective curative treatment options against MCI and dementia, cholinesterase inhibitors have been shown to be associated with persistent albeit small cognitive benefits in AD.[41] Non-pharmacological interventions may be effective in people with cognitive impairments, such as support in economic management, improvement of personal and instrumental ADL through tools and aids, and advance care planning.[42,43] Conversely, interventions against frailty in the form of improved nutrition, managing drugs with adverse effects, managing risk factors for vascular disease and interventions to reduce systemic inflammation could retard the frailty process, and, thus, cognitive decline. In addition, physical exercise might reverse frailty, and potentially, attenuate cognitive decline.[44] However, this might be difficult in patients with severe cognitive impairment, as the patient's motivation is affected, a key component in physical training and rehabilitation.[45]

Several shared mechanisms have been proposed as explanations for the link between physical frailty and cognitive impairment. Systemic inflammation, depression, impaired sleep, exposure to toxic compounds such as medicines, vascular and genetic risk factors, collectively described as a "deficit accumulation," may cause a state where the body is unable to remove, or repair accumulated damage.[46] A recent systematic review by Sargent et al. identified overlapping risk factors such as cardiovascular risk factors, nutritional, renal, hematologic, and hormonal biomarkers, and neuroinflammatory proteins.[47] When summarizing the results, the hypothesis of multi-system dysfunction is supported, as immunological system dysfunction, environmental exposures and toxicities, genetic factors, and chronic neuroinflammation all seem to play a part in the development of both the frailty syndrome and cognitive decline.

The present systematic review has some weaknesses. The studies included were few and relatively small in sample size. The cohorts were from varying settings, socioeconomic background, age range, varying follow-up time and educational levels. Cognitive subdomains were generally assessed with differing instruments across studies. Moreover, MMSE that was used as a measure of global cognition in the included studies, does not include assessment of executive function and psychomotor speed.[48] Instead, MoCA has been proposed to be more appropriate, as this instrument contains subtests for both these cognitive domains[49] and is more sensitive than MMSE to assess MCI.[50-52] Other weaknesses were the exclusion of persons who were wheelchair-bound, bedridden and visually or hearing impaired across most studies. Thus, those with most comorbidities and disabilities were not included in our meta-analyses, which subsequently leads to reduced generalizability of our results in clinical practice. Other frailty models, such as the Rockwood or Frailty Index, were not included, which might affect the generalizability as well. Our confidence in the estimates were low, according to GRADE, due to small sample sizes, selection bias, selective reporting, lack of representativeness in selection, and results with wide confidence intervals.

There is a discussion regarding the use of different observational study designs, such as cross-sectional and cohort studies, in the same

meta-analysis. No consensus has been reached in this topic.[53] Although study designs differ, we have exclusively introduced cross-sectional data into our analyses, and, in addition, assessed the methodological quality of all included studies, using customized and validated checklists for cross-sectional and cohort studies, respectively.[53] Cross-sectional data is data from a population from a single point in time,[54] and this is a proper description of the type of data pooled from the cohort studies, where data was collected in different points in time.

There has also been discussion regarding meta-analyses of results of different diagnostic instruments measuring the same outcome, as we have performed in the subgroup analysis.[55] However, according to the Cochrane Handbook, the use of standardized mean difference is a well-established and accepted part of meta-analyses.[22]

We considered conversion of global MoCA scores to MMSE scores[56] from Chen et al.[36] but opted not to due to the risk of introducing more heterogeneity in the analysis.

This systematic review also has some strengths. First, trained information specialists performed the literature search, reducing the risk of not identifying all relevant studies. Second, a transparent methodology for sorting and including studies was used. Third, quality assessments were done using a validated check lists for individual studies and the GRADE tool for assessing our confidence in each outcome across included studies. Fourth, in the main meta-analyses, the same cognitive instrument, that is, MMSE, was used in all included studies allowing a pooled mean difference in MMSE points to be calculated.

5 | CONCLUSION

We found a significantly lower score on global cognition, measured by MMSE, in persons with frailty compared to robust people as well as in frail compared to prefrail people and in prefrail compared to robust people. We also found significantly lower scores on instruments measuring the cognitive domains memory, visuospatial function, executive function, and psychomotor speed in frail compared to robust people. Although we have low and very low confidence in the estimates according to GRADE, the results suggest that physical frailty and cognitive impairment seem to coexist. Thus broader definitions and concepts of frailty that incorporate cognition, such as the widely used Frailty Index by Rockwood et al.[57] are needed. We propose additional studies on large and representative samples from multicentre trials, long follow-up times, clear diagnostic criteria, and validated instruments. Further research is needed to study the relationship between frailty and different cognitive subdomains, and the shared pathophysiological mechanisms of physical frailty and cognitive impairment.

AUTHOR CONTRIBUTIONS

Ali Vahedi and Brynjar Fure developed the idea behind the review, set the PICO, screened abstracts, and articles, extracted data, performed the analyses, assessed quality with check lists and GRADE. Maria Eriksdotter, Torgeir Bruun Wyller, Hege Ihle-Hansen, and Anne Rita Øksengård, contributed with reviewing the manuscript, including inputs regarding the interpretation of results and discussion of the findings.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data generated or analyzed during this systematic review are included in the article. The data can also be accessed through the individual included studies.

ETHICS STATEMENT

The study was conducted in accordance with the World Medical Associations Declaration of Helsinki. Only published work was used.

CONSENT FOR PUBLICATION

Not applicable.

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