Role of pre-operative frailty status in relation to outcome after carotid endarterectomy: a systematic review

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Abstract: Carotid endarterectomy (CEA) is a surgical treatment option to prevent ischemic cerebrovascular accidents. Patients that present with pre-operative frailty might have an elevated risk for unfavorable outcomes after the CEA. A systematic search, using Medline, Embase, Web of Science and Cochrane Database, was performed for relevant literature on frailty in patients undergoing CEA. The study protocol was registered with PROSPERO (CRD42020190345). Eight articles were included. The pooled prevalence for pre-operative frailty was 23.9% (95% CI: 12.98–34.82). A difference in the incidence of complications between frail and non-frail patients (6.4% *vs.* 5.2%, respectively) and a difference in hospital length of stay [2 (IQR: 2–3) days *vs.* 1 (IQR: 1–2) day, respectively] were described. The 30-day mortality after CEA was 0.6% for non-frail patients, 2.6% for frail patients, and 4.9% for very frail patients (P<0.001). For 3-year mortality, a >1.5-fold increased risk was found for frail patients (OR 1.7, 95% CI: 1.4–2.0) and a >2.5-fold increased risk for very frail patients (OR 2.6, 95% CI: 2.2–3.1). In conclusion, this review shows the impact of frailty on outcome after CEA. Pre-operative frailty assessment with a validated, multi-domain tool should be implemented in the clinical setting as it will provide information on post-operative surgical outcomes and mortality risk but also frailty trajectory and cognitive decline.

Keywords: Frailty; frail elderly; carotid endarterectomy (CEA)

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Introduction

Carotid endarterectomy (CEA) is a surgical treatment option to prevent ischemic cerebrovascular accidents (1). CEA has proven to be a successful treatment strategy, but remains a surgical procedure with the risk for adverse post-operative outcomes such as postprocedural disabling stroke, myocardial infarction and mortality (2). Advanced age, female gender and comorbidities in CEA patients are proved to be associated with such unfavorable outcomes (1,3,4).

As people age, cumulative declines in various physiological systems lead to decreased resistance to stressors, ultimately ending in an increased risk for adverse outcomes. This depletion in metabolic, physical and cognitive reserves is referred to as frailty, a multi-dimensional geriatric syndrome (5). As patients undergoing CEA are generally of older age, they may also considered to be more often frail (6). There are multiple frailty assessment tools, both validated and unvalidated, that have been used in the surgical population (7). Until today, no gold standard for the clinical assessment of frailty has been implemented.

Vascular surgery patients are especially at high risk

for being frail, given the advanced age and often present multimorbidity (8). Frailty and age have a mutual dependency, but are considered two different entities, with frailty being a stronger predictor for adverse outcomes than age alone (9-11). The prevalence of pre-operative frailty in the vascular surgery population ranges from 20–60%, compared to 10–37% for the general surgical population (12,13). However, its presence is not without risks in which frailty is proven to be associated with more post-operative complications and higher mortality after vascular surgery (14).

Patients that present with pre-operative frailty might have an elevated risk for unfavorable outcomes after the CEA. The aim of this systematic review was to identify the used frailty assessment tools and to investigate the prevalence of pre-operative frailty and its association with outcomes in CEA patients.

Methods

Protocol and registration

The protocol was registered in the International prospective register of systematic reviews (PROSPERO), registration number CRD42020190345. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements checklists and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist (15,16).

Search strategies

Medline, Embase, Web of Science and Cochrane Database were searched for articles from inception to June 2020. Articles should investigate frailty in patients undergoing CEA. The search strategies (Appendix 1) were developed in collaboration with an experienced clinical librarian. Search results were combined using Mendeley Reference Manager (Version 1.19.5, Elsevier, 2019, London, UK) and duplicate references were removed. The reference lists for potential articles meeting the inclusion criteria were manually examined.

Study selection

Two authors (LB and SB) independently screened titles and abstracts based on the inclusion and exclusion criteria using the CADIMA evidence synthesis tool and database, and after that, the full texts likewise (17). Disagreements were resolved by a third reviewer (RP). The inclusion criteria consisted of the following: (I) original articles reporting either the pre-operative prevalence of frailty and/or the association of frailty with outcomes; (II) patients undergoing carotid enterectomy (CEA); (III) the measurement of frailty using a multi-domain assessment tool or multi-domain instruments (muscle mass, gait speed, grip strength, cognition, physical activity, psychosocial wellbeing and nutritional status). Articles were excluded if the frailty status was not measured before the CEA or when data for CEA patients was not reported separately.

Data extraction and quality assessment

Data extraction and quality assessment were performed by two independent reviewers (LB and SB). The quality of the included studies was assessed using an adapted version of the Newcastle Ottawa Scale (NOS), specified for cohort studies evaluating frailty status (18,19). The scale consists of the following domains: representativeness of the study population, use of frailty measures that were validated in the general population of older adults, frailty status determination, loss-to-follow-up or amount of missing outcome data, missing data on frailty measures, and validation of the risk prediction performance. If a domain was adequate, one point was given, if it was partially adequate, 0.5 point and if it was inadequate, zero points. An overall score of ≥4 points indicates a low risk of bias, a score of ≥3 and <4 points indicates a moderate risk of bias and a score of <3 points indicates a high risk of bias. The following study details were extracted from the included studies: first author, publication year, country, study design, use of a national database, sample size, frailty tool, prevalence of pre-operative frailty. If available, the post-operative outcomes were also extracted, including: post-operative complications (including stroke, myocardial infarction and 30-day mortality), hospital length of stay, 30-day readmission rate, discharge destination and long-term mortality. Disagreements were again resolved by a third reviewer (RP).

Data analysis

A pooled prevalence analysis was performed with the included articles. A subgroup analysis was performed to exclude studies conducted with data from the same national database. The chi-square heterogeneity test was used to report heterogeneity among studies, presented as I^2. An

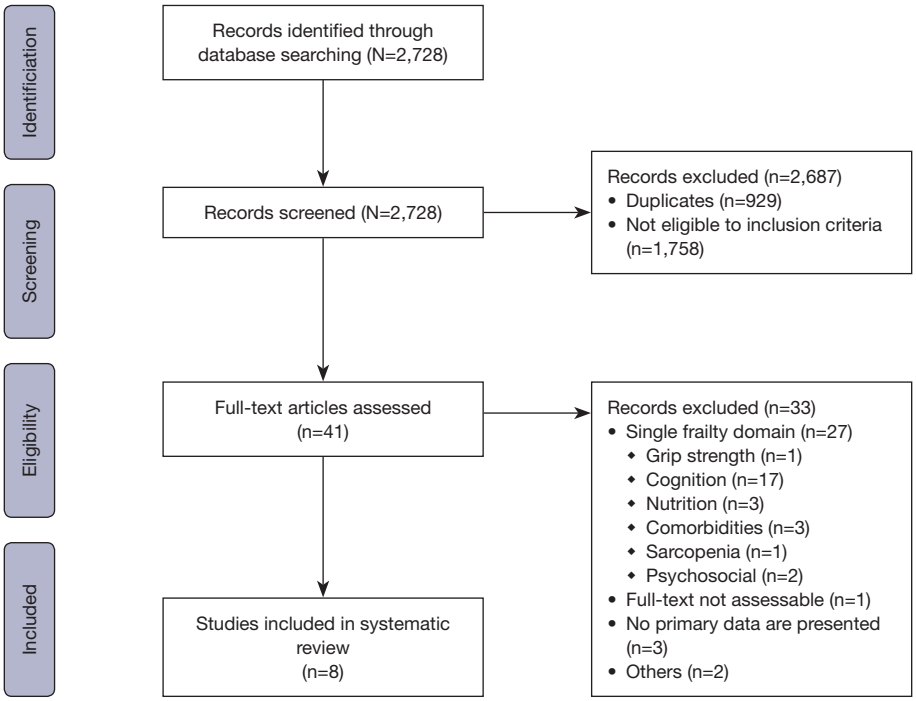

Figure 1 Flowchart of the included studies.

I^2 of <25% shows a low chance and an I^2 of >50% a high chance of heterogeneity. If heterogeneity was expected to be high, a random-effects model was used, and if heterogeneity was expected to be low, a fixed-effect model was used. Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, 2020, Copenhagen, Denmark) was used to perform the pooled prevalence analysis in our study.

Results

In total, 2,728 articles were identified using the primary search string (*Figure 1*). After applying the in- and exclusion criteria, 2,686 articles were excluded. Out of the remaining 41 full-texts, 27 studies were excluded because of using a single-domain frailty tool, and six for miscellaneous reasons (i.e., full-text not accessible or no primary data presented), resulting in eight articles that were included in this systematic review (20-27).

Study characteristics

After quality assessment, six studies were identified as having low risk of bias (22-27) and two studies as having moderate risk of bias (20,21) (*Table 1*). All studies focused on pre-operative frailty status (*Table 2*). Seven were retrospective cohort studies (20,22-27) and one was a prospective cohort study (21). All studies were performed in the USA and six studies (20,22-25,27) used the same national database from the National Surgical Quality Improvement Project (NSQIP) to retrieve their data. The three different frailty tools used by the included studies are presented in *Table 3* and consist of the Clinical Frailty Scale (CFS) to prospectively collect patient-reported data, and the Risk Analysis Index (RAI) and Modified Frailty Index (MFI) to retrospectively collect data, retrieved from medical records.

Prevalence of pre-operative frailty

Seven out of eight studies (20,22-27) included the pre-operative prevalence of frail and non-frail CEA patients and were therefore included in the pooled prevalence analysis (*Figure 2*). The pooled prevalence for pre-operative frailty was 22.07% (95% CI: 16.35–27.79), with a high level of heterogeneity (I^2=100%, P<0.01). After excluding the studies that used the same database (20,23-25,27), the pooled prevalence for pre-operative frailty was estimated at 23.9% (95% CI: 12.98–34.82) with a high level of

Table 1 Results of quality assessment of included cohort studies

Author	Year	Represen-tativeness	Validation of frailty assessment	Determination of frailty status	Loss to follow-up	Missing data	Prediction on model validation	Overall score*	Risk of bias
Arya *et al.*	2016	●	●	●	●	●	●	3.5	Moderate
Donald *et al.*	2018	●	●	●	●	●	●	3.5	Moderate
Ehlert *et al.*	2016	●	●	●	●	●	●	4.0	Low
Melin *et al.*	2015	●	●	●	●	●	●	4.0	Low
Pandit *et al.*	2018	●	●	●	●	●	●	4.0	Low
Pandit *et al.*	2020	●	●	●	●	●	●	4.0	Low
Rothenberg *et al.*	2020	●	●	●	●	●	●	5.0	Low
Rothenberg *et al.*	2020	●	●	●	●	●	●	4.0	Low

*, according to the Newcastle Ottawa Scale (NOS). Each component was assigned 1 point for adequate (green), 0.5 points for partially adequate (yellow), and 0 points for inadequate (red). Overall score of ≥4 points for low risk of bias, of ≥3 and <4 points for a moderate risk of bias, and <3 points for a high risk of bias.

Table 2 Summary of studies included in the systematic review

Author	Year	Country	Design	National database	Tool	Sample size	Age, years	Gender[a]
Arya *et al.*	2016	USA	Retrospective Cohort study	2011–2012 NSQIP[b]	MFI[c]	5,933	-	–
Donald *et al.*	2018	USA	Prospective Cohort study	–	CFS[d]	25	-	–
Ehlert *et al.*	2016	USA	Retrospective Cohort study	2006–2012 NSQIP	MFI	40,803	72 (IQR 65–78)	41%
Melin *et al.*	2015	USA	Retrospective Cohort study	2005–2011 NSQIP	RAI[e]	44,832	-	41%
Pandit *et al.*	2018	USA	Retrospective Cohort study	2005–2012 NSQIP	MFI	36,133	74.9±6.3	32%
Pandit *et al.*	2020	USA	Retrospective Cohort study	2005–2012 NSQIP	MFI	36,000	74.6±5.9	32%
Rothenberg *et al.*	2018	USA	Retrospective Cohort study	Vascular Quality Initiative	RAI	42,869	71.2±9.5	41%
Rothenberg *et al.*	2020	USA	Retrospective Cohort study	2007–2013 NSQIP	RAI	51,978	–	–

[a], percentage (%) female; [b], national surgical quality improvement project; [c], modified frailty index; [d], clinical frailty scale; [e], risk analysis index.

heterogeneity (I^2=100%, P<0.01).

Association of frailty with post-operative complications

Three studies have investigated the association between pre-operative frailty and post-operative complications. One study found that 6.4% of the frail patients developed a complication in comparison with 5.2% of the non-frail patients, the hospital length of stay of frail patients was 2 (IQR: 2–3) days [in comparison with 1 (IQR: 1–2) day] and the 30-day readmission rate was 4.0% (in comparison with 2.6%) (24). Frail patients had a higher risk than non-frail patients to be discharged to a non-home destination after CEA (OR 2.8, 95% CI: 2.0–3.9) (20). A linear correlation between frailty status, according to the RAI, and increased risk of stroke (P<0.001) and myocardial infarction (MI) (P<0.001) was also found (23).

Association of frailty with mortality after carotid enterectomy

Five studies have investigated the association between pre-operative frailty and mortality, both short- and long-term, after CEA. An in-hospital mortality of 1.4% in frail

Table 3 Summary of Frailty Assessment Tools used by included studies

Tool	Mobility	Function	Comorbidity	ADLs	Strength	Nutrition	Cognition	Psychosocial	Score	Frail
MFI[a]	–	–	◆	◆	–	–	–	–	0–1	≥0.25
CFS[b]	–	◇	◇	◇	–	–	–	–	1–9	≥5
RAI[c]	–	◆	◆	◆	–	◆	◆	–	0–75	≥11

Assessment method for individual domains: ◆ medical record; ◇ patient-reported. [a], modified frailty index; [b], clinical frailty scale; [c], risk analysis index.

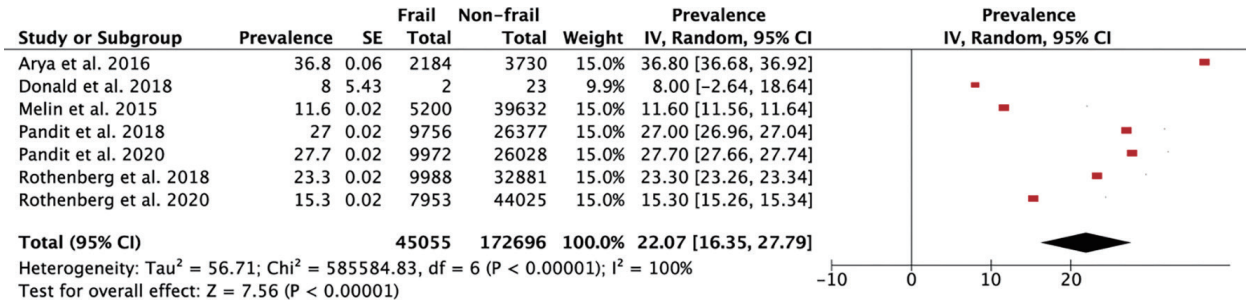

Figure 2 Pooled prevalence of the included studies.

patients in comparison with 0.8% in non-frail patients was found (24). There is a difference in frailty severity and CEA outcome in which 0.6% of the non-frail patients, 2.6% of the frail patients and 4.9% of the very frail (RAI ≥35) patients died within 30 days after the CEA (P<0.001) (26). They also found that the RAI was a good predictor for 30-day mortality after CEA (C-statistic: 0.70), with a linear correlation between an increasing RAI score and 30-day mortality (23). The domain "impaired sensorium" in the MFI was the strongest predictor for 30-day mortality in CEA patients (22). For 3-year mortality, a >1.5-fold increased risk was found for frail patients (OR 1.7, 95% CI: 1.4–2.0) and a >2.5-fold increased risk for very frail (RAI ≥35) patients (OR 2.6, 95% CI: 2.2–3.1) (27).

Discussion

This review shows that pre-operatively, 24% of the patients undergoing CEA are frail, and of that nature more prone for adverse outcomes such as post-operative complications and mortality. The MFI is the most frequently used frailty assessment tool in CEA patients.

As highlighted before, the prevalence of pre-operative frailty in the vascular surgery population is higher than in the general surgery population (12,13). The 24% is on the low side of the spectrum with respect to the general vascular surgery population which may be explained by the differences in patient characteristics between the patient groups. To illustrate, carotid patients are less dependent in activities of daily living than patients with peripheral arterial disease and are younger than patients treated for aneurysms, possibly leading to a relatively less frail population (22,26).

To surgically treat patients with carotid disease, carotid stenting (CAS) is an endovascular alternative to the open CEA procedure, especially for patients with an increased surgical risk profile (for example with multi-morbidity, high carotid bifurcation or previous neck irradiation or surgery) (28). Therefore, it is expected that patients undergoing CAS are more often frail at time of intervention, although this is not unequivocally demonstrated in the literature (24,29). When considering treatment options, age and comorbidities should be taken into account since carotid stenting has an increased risk of adverse cerebrovascular events in elderly patients but with a similar mortality rate compared to younger patients (1).

The role of frailty in relation to outcome after vascular surgery has been thoroughly investigated over the years (14,30,31). Consistent with our findings, a recently published systematic review and meta-analysis found that frailty in the vascular surgery population leads to an increased risk for post-operative complications and short- and long-term mortality (14). Another study found that frail

patients were discharged to a care facility more often, which is also in accordance with a previous paper published by our group (30).

When considering frailty in its individual domains, CEA patients differ from the general vascular patients. In the majority of patients, deterioration in mobility and/or functional dependency is an important contribution to becoming frail (26). In CEA patients, impaired cognition has a pivotal role in becoming frail (32). Ten percent of the carotid patients have impaired cognition compared to approximately 4% of the other vascular surgery patients (26). Likewise, in our review, it was shown that when measuring frailty with a single-domain tool in CEA patients, the domain cognition had the best representation in the literature (*Figure 1*). Some studies suggest that sarcopenia, a loss of muscle mass, can be used as a surrogate for frailty to determine the risk for adverse outcomes (31). But when choosing a single domain tool, it is necessary to realize that in a sense it is not frailty which is determined but a variation or approximation of the syndrome (33). According to Fried, the frailty syndrome consists of five biological components, including unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity (5). Over the years, cognition and psychosocial wellbeing have been added to the domains of frailty (34). Despite this addition, there are still numerous frailty assessment tools that do not represent all the domains of frailty. The MFI is the most frequently used frailty assessment tool in CEA patients, but does not include the domain cognition (*Table 2*).These data support the belief that a multi-domain approach is desirable when it comes to assessing frailty or determining the effect of an intervention (9).

Information about the individual composition of the frailty syndrome will aid in achieving a personalized treatment to pre-operatively enhance the patients' condition. Over the past years, more attention has been paid to pre-habilitation, which is the process to increase a patients' capacity to withstand a forthcoming stressor, for example a vascular intervention (35). The improvement of the psychophysiological reserves might help them to stay out of the so-called "critical zone" after the intervention, ultimately decreasing the risk for adverse outcomes and even mortality (36). Pre-habilitation could for example consist of medical optimization, physical exercise, help from a dietician and psychological support (37).

This review has some limitations that need to be reported. First, no formal meta-analysis was possible on the intended outcome measures due to variations in methods to investigate all types of post-operative outcomes and because six studies used the same national database. However, we did perform a pooled prevalence analysis, including a subgroup analysis to exclude the studies with the same database. Second, because studies used data from the same database, the results should be interpreted with caution. Third, all the studies were performed in the USA. To obtain a broader global view of the role of frailty in CEA patients, more diversity in studied populations is desirable. And finally, 7 out of 8 studies used retrospectively collected data to determine the frailty status. Since frailty is a dynamic condition that fluctuates in time, it is difficult, if not impossible, to reliably interpret retrospectively collected results (38,39).

To develop a full overview of the role of frailty in CEA patients, future studies should use a validated multi-domain tool, preferably prospectively collected at various time point before and after treatment, to retrieve the most reliable results and to provide a view on the trajectory.

In conclusion, this review shows that the presence of frailty has an important role in relation to outcome after CEA. Frail CEA patients have an increased risk for post-operative complications and mortality. In patients with carotid disease, there is a lot of attention for the cognition of a patient, but in terms of the frailty syndrome and tools used, this domain is often neglected. In the future, pre-operative frailty assessment with a validated, multi-domain tool should be implemented in the clinical setting as it will provide information on post-operative surgical outcomes and mortality risk but also frailty trajectory and cognitive decline.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7225). The series "Carotid Artery Stenosis and Stroke–Prevention and Treatment Part II" was

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Detailed search strategies per database, until 15th of June 2020

PubMed

("Endarterectomy, Carotid"[Mesh] OR "Carotid Stenosis"[Mesh] OR "Carotid Artery Diseases/surgery"[Majr] OR “carotid endarterectomy”[tiab] OR “carotid stenosis”[tiab] OR “carotid artery stenting”[tiab] OR “carotid revascularization”[tiab] OR “carotid surgery”[ti]) AND (“frail elderly”[Mesh] OR “frailty”[Mesh] OR “geriatric assessment”[Mesh] OR “frail*”[tiab] OR “geriatric assessment”[tiab] OR “sarcopenia”[Mesh] OR “cognition”[Mesh] OR “physical fitness”[Mesh] OR “walking speed”[Mesh] OR “nutritional status”[Mesh] OR “hand strength”[Mesh] OR “sarcopenia”[tiab] OR “low muscle mass”[tiab] OR “muscle loss”[tiab] OR “muscle atrophy”[tiab] OR “cognit*”[tiab] OR “physical fitness”[tiab] OR “physical activity”[tiab] OR ”walking speed”[tiab] OR “gait speed”[tiab] OR “slowness”[tiab] OR “weakness”[tiab] OR “nutrition*”[tiab] OR “unintentional weight loss”[tiab] OR “oldest patient*”[tiab] OR “oldest old”[tiab] OR “vulnerable elder*”[tiab] OR “hand grip”[tiab] OR “grip strength”[tiab])

EMBASE

(‘carotid endarterectomy’/exp OR ‘carotid artery surgery’/exp OR ‘carotid endarterectomy’:ab,ti OR ‘carotid stenosis’:ab,ti OR ‘carotid artery stenting’:ab,ti OR ‘carotid revascularization’:ab,ti OR ‘carotid surgery’:ab,ti) AND (‘frailty’/exp OR ‘frail elderly’/exp OR ‘geriatric assessment’/exp OR ‘frail*’:ab,ti OR ‘geriatric assessment’:ab,ti OR ‘sarcopenia’/exp OR ‘cognition’/exp OR ‘walking speed’/exp OR ‘nutritional status’/exp OR ‘grip strength’/exp OR ‘sarcopenia’:ab,ti OR ‘low muscle mass’:ab,ti OR ‘muscle loss’:ab,ti OR ‘muscle atrophy’:ab,ti OR ‘cognit*’:ab,ti OR ‘physical fitness’:ab,ti OR ‘physical activity’:ab,ti OR ‘walking speed’:ab,ti OR ‘gait speed’:ab,ti OR ‘slowness’:ab,ti OR ‘weakness’:ab,ti OR ‘nutrition*’:ab,ti OR ‘unintentional weight loss’:ab,ti OR ‘oldest patient*’:ab,ti OR ‘oldest old’:ab,ti OR ‘vulnerable elder*’:ab,ti OR ‘hand grip’:ab,ti OR ‘grip strength’:ab,ti)

Web of Science

TS=((“carotid endarterectomy” OR “carotid stenosis” OR “carotid artery stenting” OR “carotid revascularization” OR “carotid surgery”) AND (“frail*” OR “geriatric assessment” OR “sarcopenia” OR “low muscle mass” OR “muscle loss” OR “muscle atrophy” OR “cognit*” OR “physical fitness” OR “physical activity” OR “walking speed” OR “gait speed” OR “slowness” OR “weakness” OR “nutrition*” OR “unintentional weight loss” OR “oldest patient*” OR “oldest old” OR “vulnerable elder*” OR “hand grip” OR “grip strength”))

OVIDSP/Medline

(“carotid endarterectomy” OR “carotid stenosis” OR “carotid artery stenting” OR “carotid revascularization” OR “carotid surgery”) AND (“frail*” OR “geriatric assessment” OR “sarcopenia” OR “low muscle mass” OR “muscle loss” OR “muscle atrophy” OR “cognit*” OR “physical fitness” OR “physical activity” OR “walking speed” OR “gait speed” OR “slowness” OR “weakness” OR “nutrition*” OR “unintentional weight loss” OR “oldest patient*” OR “oldest old” OR “vulnerable elder*” OR “hand grip” OR “grip strength”)

Cochrane

ID	Search
#1	MeSH descriptor: [Endarterectomy, Carotid] explode all trees
#2	MeSH descriptor: [Carotid Stenosis] explode all trees
#3	(carotid endarterectomy):ti,ab,kw OR (carotid stenosis):ti,ab,kw OR (carotid artery stenting):ti,ab,kw OR (carotid revascularization):ti,ab,kw OR (carotid surgery):ti,ab,kw
#4	MeSH descriptor: [Frailty] explode all trees
#5	MeSH descriptor: [Frail Elderly] explode all trees
#6	MeSH descriptor: [Geriatric Assessment] explode all trees
#7	MeSH descriptor: [Sarcopenia] explode all trees
#8	MeSH descriptor: [Cognition] explode all trees
#9	MeSH descriptor: [Physical Fitness] explode all trees
#10	MeSH descriptor: [Walking Speed] explode all trees
#11	MeSH descriptor: [Nutritional Status] explode all trees
#12	MeSH descriptor: [Hand Strength] explode all trees
#13	(frail*):ti,ab,kw OR (geriatric assessment):ti,ab,kw OR (sarcopenia):ti,ab,kw OR (low muscle mass):ti,ab,kw OR (muscle loss):ti,ab,kw
#14	(muscle atrophy):ti,ab,kw OR (physical fitness):ti,ab,kw OR (physical activity):ti,ab,kw OR (walking speed):ti,ab,kw OR (cognit*):ti,ab,kw
#15	(gait speed):ti,ab,kw OR (slowness):ti,ab,kw OR (weakness):ti,ab,kw OR (nutrition):ti,ab,kw OR (unintentional weight loss):ti,ab,kw
#16	(oldest patient*):ti,ab,kw OR (oldest old):ti,ab,kw OR (vulnerable elder*):ti,ab,kw OR (hand grip):ti,ab,kw OR (grip strength):ti,ab,kw
#17	(#1 OR #2 OR #3) AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 #13 #15 OR #16)

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