JAMDA 18 (2017) 564–575

JAMDA

journal homepage: www.jamda.com

Special Article

The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty

Elsa Dent PhD [a,*], Christopher Lien MBBS, MPA [b], Wee Shiong Lim MBBS, MRCP, MHPEd [c], Wei Chin Wong MBBS [c], Chek Hooi Wong MBBS, MPH [d], Tze Pin Ng MD [e], Jean Woo MD [f], Birong Dong MD [g], Shelley de la Vega MD, MSc [h], Philip Jun Hua Poi MB, ChB [i], Shahrul Bahyah Binti Kamaruzzaman MD [i], Chang Won MD, PhD [j], Liang-Kung Chen MD, PhD [k], Kenneth Rockwood MD [l], Hidenori Arai MD, PhD [m], Leocadio Rodriguez-Mañas MD, PhD [n], Li Cao MD [o], Matteo Cesari MD, PhD [p], Piu Chan MD, PhD [q], Edward Leung FRCP [r], Francesco Landi MD [s], Linda P. Fried MD [t], John E. Morley MB, MCh [u], Bruno Vellas MD, PhD [p], Leon Flicker PhD, MBBS [v]

[a] *Center for Research in Geriatric Medicine, School of Medicine, The University of Queensland, Brisbane, Australia*
[b] *Department of Geriatric Medicine, Changi General Hospital, Singapore, Singapore*
[c] *Department of Geriatric Medicine, Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Singapore, Singapore*
[d] *Geriatric Education and Research Institute, Singapore, Singapore*
[e] *Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore*
[f] *The S H Ho Center for Gerontology and Geriatrics, The Chinese University of Hong Kong, Hong Kong, China*
[g] *Geriatrics Center Huaxi Hospital, Sichuan University, Chengdu, China*
[h] *University of the Philippines College of Medicine, Manila, Philippines; Institute on Aging, National Institutes of Health, University of the Philippines, Manila, Philippines*
[i] *Division of Geriatrics, University of Malaya Medical Center, Kuala Lumpur, Malaysia*
[j] *Department of Family Medicine, Kyung Hee University School of Medicine, Seoul, South Korea*
[k] *Center for Geriatrics and Gerontology, Taipei Veterans General Hospital; Aging and Health Research Center, National Yang Ming University, Taipei, Taiwan*
[l] *Dalhousie University, Halifax, Nova Scotia, Canada*
[m] *National Center for Geriatrics and Gerontology, Obu, Japan*
[n] *Department of Geriatrics, Hospital Universitario de Getafe, Madrid, Spain*
[o] *Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China*
[p] *CHU Toulouse, Toulouse, France*
[q] *Department of Geriatrics, Neurology, and Neurobiology, Xuanwu Hospital, Capital Medical University, Beijing, China*
[r] *Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong*
[s] *Catholic University of Sacred Heart, Rome, Italy*
[t] *Mailman School of Public Health, Columbia University Medical Center, New York, NY*
[u] *Divisions of Geriatric Medicine and Endocrinology, Saint Louis University, St. Louis, MO*
[v] *Western Australia Center for Health and Aging, University of Western Australia, Perth, Australia*

Keywords (MesH):
Frail elderly
Practice Guidelines as Topic*
aged
evidence-based medicine/standards*
patient care management
disease management

A B S T R A C T

Objective: To develop Clinical Practice Guidelines for the screening, assessment and management of the geriatric condition of frailty.
Methods: An adapted Grading of Recommendations, Assessment, Development, and Evaluation approach was used to develop the guidelines. This process involved detailed evaluation of the current scientific evidence paired with expert panel interpretation. Three categories of Clinical Practice Guidelines recommendations were developed: strong, conditional, and no recommendation.
Recommendations: Strong recommendations were (1) use a validated measurement tool to identify frailty; (2) prescribe physical activity with a resistance training component; and (3) address polypharmacy by reducing or deprescribing any inappropriate/superfluous medications. Conditional

ED is supported by an Australian National Health and Medical Research Council (NHMRC) grant (Grant number: 1112672).

* Address correspondence to Elsa Dent, PhD, Center for Research in Geriatric Medicine, Princess Alexandra Hospital, The University of Queensland, Woolloongabba, Brisbane, Queensland 4102, Australia.
E-mail address: elsa.dent@adelaide.edu.au (E. Dent).

http://dx.doi.org/10.1016/j.jamda.2017.04.018

recommendations were (1) screen for, and address modifiable causes of fatigue; (2) for persons exhibiting unintentional weight loss, screen for reversible causes and consider food fortification and protein/caloric supplementation; and (3) prescribe vitamin D for individuals deficient in vitamin D. No recommendation was given regarding the provision of a patient support and education plan.
Conclusions: The recommendations provided herein are intended for use by healthcare providers in their management of older adults with frailty in the Asia Pacific region. It is proposed that regional guideline support committees be formed to help provide regular updates to these evidence-based guidelines.

Frailty is a modern geriatric giant, and a major public health problem in the older population.[1] It has been recently defined by the International Association of Gerontology and Geriatrics Frailty Consensus as a reduced strength and physiologic malfunctioning that increases an individual's susceptibility to increased dependency, vulnerability, and death.[1] Frailty can be used as a marker of adverse outcome risk in older adults[2–4] and is increasingly used to predict patient outcomes across specialties such as oncology, cardiology, and orthopedics.[5–8]

There are multiple etiologic factors leading to frailty, including physiological changes and/or diseases associated with aging, inflammation, sarcopenia, polypharmacy, endocrine disorders, protein energy malnutrition, social isolation, and poverty.[1,3,5,9] The prevalence of frailty in community-dwelling older adults in the Asia-Pacific region is approximately 3.5%-27%,[4,10–24] which is comparable to the prevalence across Europe and the Americas.[25–31] Socioeconomically disadvantaged and indigenous communities can have a frailty prevalence of over 50%.[32,33] This frailty prevalence may be underestimated in several studies because of the large number of nonresponses in population health surveys of older adults.[34]

Frailty is more common in females and increases in prevalence with age.[1,3,30] It overlaps with comorbidity, although it can and often does occur independently from the presence of any chronic disease.[3,32,35] Frailty is not synonymous with disability but is causally related.[35,36] The condition is also costly, with reported healthcare expenses around €3500 ($4000 USD) over 3 months for older adults with frailty, approximately 5 times the cost for nonfrail adults.[37] This expense is of particular concern in the Asia-Pacific region, where older adults with high healthcare needs are often those not able to access publicly funded healthcare services.[38]

Currently, no accepted reference standard exists to identify frailty, and extensive international efforts are underway to identify the means of optimal measurement. Three major approaches to defining frailty exist:

(1) The physical phenotype model of Fried et al[36] and its rapid screen: FRAIL[39]
(2) The deficit accumulation model of Rockwood and Mitnitski which captures multimorbidity[40]
(3) Mixed physical and psychosocial models, such as the Tilburg Frailty Indicator[41] and Edmonton Frailty Scale[42]

Although most of the published literature on frailty focuses on its identification, etiology, and risks, there remains a large knowledge gap: consolidating the evidence-base of scientific literature to develop Clinical Practice Guidelines (CPGs) for treating frailty once it has been identified. There is an urgent need to develop such guidelines for the Asia-Pacific region, which has the largest population of older adults worldwide combined with much heterogeneity regarding population socioeconomics, provision of healthcare services, and ethnic diversity.[11,43,44]

Developing Clinical Practice Guidelines for Frailty

Conventionally, clinicians use CPGs as the basis for their standard care.[45] CPGs are evidence-based recommendations systematically developed by expert panels who have a working clinical knowledge of respective medical conditions.[45] CPGs for frailty are urgently needed for a variety of reasons:

- For better recognition of frailty by healthcare professionals;
- For the delivery of the best available evidence for the identification and management of frailty;
- To improve health and quality of life outcomes for older individuals affected by frailty; and
- To encourage healthcare providers to focus on improving the functional ability of older adults with frailty.

Although best practice guidelines have been developed for frailty in community and outpatient settings by the British Geriatrics Society,[46] these guidelines fall short on providing specific clinical recommendations.

The aims of this article are to develop evidence-based, multidisciplinary CPGs for the identification and management of frailty, specifically targeting health practitioners in the Asia-Pacific region. These guidelines will incorporate principles from the World Health Organization, which has recently highlighted the need to focus on maximization of the functional independence of older adults, rather than simply using a traditional single-disease medical approach.[47] This report will also discuss the evidence-base behind the development of each CPG.

Methods

Throughout the remainder of this article, the term "guidelines" will be used when referring to CPGs. The guidelines were developed using an adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.[45,48–50] The GRADE approach involved evaluating the current scientific evidence and forming consensus recommendations by a clinical expert panel comprised of multidisciplinary experts on frailty from various countries. The guidelines arose out of presentations at the Asia-Pacific Geriatrics Conference on "Geriatrics Beyond Borders: Are We Frailty Ready?" held in Singapore in 2016. Utilizing the information presented and the discussions at this conference, combined with a comprehensive literature search and review, a basic document was developed. This document was distributed to the expert panel who were encouraged to rank the strength of the guidelines and to propose changes. A modified Delphi process was used until all members of the expert panel were satisfied with the final document.

The strength of a guideline refers to its supporting evidence base, as well as the extent that its benefits outweigh any potential risks.[45,51] A strong recommendation in our manuscript is conceptualized as "we strongly recommend," and reflects that in the expert panel's judgement, there are substantial clinical benefits to the patient that distinctly outweigh the risks of undesirable effects,[45,51,52] taking into consideration patient preference.[53] A statement of "we conditionally recommend" means that although the majority of clinicians and informed patients would choose this modality, many would not because the benefits of treatment could potentially be undermined by an adverse event occurring.[45] A statement of "no recommendation" specifies that there is a low level of evidence supporting the

recommendation.[51] Recommendations are based on potentially treatable causes of frailty.

Clinical Guidelines

Table 1 summarizes guidelines for frailty; key principles outlined in this report are summarized in Table 2. Current common definitions of frailty overlap considerably with sarcopenia in relation to both muscle strength and physical function,[54–56] with sarcopenia defined as the progressive loss of skeletal muscle mass and strength that occurs with aging.[57] Sarcopenia may even be a component of frailty.[58] Thus, the clinical management of both frailty and sarcopenia can follow along similar lines. This document does not cover the overlap of frailty with other major systems, for instance, cognitive frailty.

There is a spectrum of frailty ranging from fit to frail,[59] from which 3 categories are often distinguished: "frail," "prefrail," and "robust." It is possible for older adults to dynamically transition between these frailty categories.[10] For instance, individualized treatment or natural resolution of acute conditions in an older adult may result in an improvement of frailty status from a frail to prefrail state. The lower on the frailty spectrum an older adult is, the less likely they will move up the spectrum to the highest functioning levels.[60,61] An intervention that may benefit an older adult in the early stages of frailty might not be beneficial, or may even be harmful to, an older adult with severe frailty. Thus, frailty should be identified and managed as early as possible, with healthcare professionals advised to carefully weigh any benefits of treatments against harm to patients, particularly in those who are most frail and in whom treatments are less likely to show any benefit to the patient. Shared decision making between healthcare professionals, older adults, and their families is recommended when developing a management plan for an older adult with frailty.[62]

Recommendation 1: We Strongly Recommend that a Validated Measurement Tool Be Used to Identify Frailty

Frailty should be identified with a validated measurement tool. There are many such tools in existence (Table 3), with much heterogeneity in their classification and predictive abilities.[86–88] When choosing a frailty measurement to use, it is essential to select one, which not only accurately identifies frailty and predicts patient outcomes, but is also simple to use, well validated, and accounts for the priorities, resources, and objectives of the specific clinical setting.[3,5] The 2 most common frailty measurements are Fried's Frailty Phenotype[36] and Rockwood and Mitnitski's Frailty Index (FI).[40]

Table 1
Clinical Practice Guidelines for the Management of Frailty

Clinical Practice Guidelines for the Management of Frailty
Strong Recommendations
1. We strongly recommend that frailty be identified using a validated measurement tool.
2. We strongly recommend that older adults with frailty be referred to a progressive, individualized physical activity program that contains a resistance training component.
3. We strongly recommend that polypharmacy be addressed by reducing or deprescribing any inappropriate/superfluous medications.
Conditional Recommendations
4. We conditionally recommend that persons with frailty are screened for causes of fatigue.
5. We conditionally recommend that older adults with frailty who exhibit unintentional weight loss should be screened for reversible causes and considered for food fortification/protein and caloric supplementation.
6. We conditionally recommend that vitamin D be prescribed for persons found to be deficient in Vitamin D.
No Recommendation
7. We have no recommendation for the provision of an individualized support and education plan for older adults with frailty.

Table 2
Key Principles

1. Frailty is a defined as an age-related state characterized by a reduced strength and physiologic malfunctioning that increases an individual's susceptibility to increased dependency, vulnerability, and death.[1,3]
2. Frailty identification and management should be incorporated into a Comprehensive Geriatric Assessment (CGA) where possible.
3. Frailty should be identified with a validated frailty measurement tool, such as Fried's Frailty Phenotype, Rockwood and Mitnitski's Frailty Index, the Tilburg Frailty Index, or the FRAIL scale. The measurement tool should be chosen to match the clinical goal. Blood investigations are not required in the identification of frailty.
4. Frailty overlaps with sarcopenia, therefore, management principles may be similar between the 2 conditions.
5. Shared decision making between healthcare professionals, older adults, and their families should be facilitated when developing a management plan for older adults with frailty.
6. Practical recommendations for lifestyle modification should be provided for older persons with frailty, paying special attention to the incorporation of resistance training and adequate protein intake.
7. Identifying the treatable risk factors of frailty may prevent its progression— polypharmacy, weight loss, physical activity (resistance training), among others.
8. Education and support should be provided to older people and their caregivers. This training can be community based.

Frailty screening in the clinical setting

Frailty should be routinely screened for in adults aged 70 years and older, or those who have unintentionally lost >5% of their body weight in the previous year.[1] It is advised that frailty not be subjectively identified by superficial visual appearance of an older patient, because of large variations in clinical judgement across specialties, reproducibility of assessment, and the heterogeneity in frailty presentation.[89,90] Although there have been studies finding that initial clinical impression of frailty can predict patient outcomes,[91] a superficial visual inspection of an older adult is likely to only identify severe frailty.

Frailty identification as part of a Comprehensive Geriatric Assessment

Frailty can be measured as part of a Comprehensive Geriatric Assessment (CGA), which is the current reference standard for identifying and managing frailty,[46] or by practicing clinicians using the shorter-duration Rapid Geriatric Assessment.[78] A CGA determines the medical, functional, and psychosocial aspects of a frail older person using a thorough, multidimensional assessment process, and then uses this information to guide a person-centered support and care plan.[46,92] CGA and subsequent interventions have been demonstrated to be effective in reducing mortality and admission to higher level care in numerous randomized controlled trials (RCTs).[92] However, despite the many successes of CGAs, they can be labor-intensive and expensive to perform,[93] and in the Asia-Pacific region, the majority of practitioners may not have the resources to perform a full CGA. Thus, frailty screening should be performed in these cases to identify older adults for referral to full CGAs.

Frailty screening using Fried's Frailty Phenotype

Fried's phenotype classifies frailty as 3 or more physical setbacks out of a list of 5: slowness (slow walking speed), weakness (low grip strength), weight loss (≥4.5 kg in the previous year), exhaustion (self-reported), and low physical activity.[36] Conceptually, Fried's Frailty Phenotype captures the presence and severity of a distinct clinical syndrome of dysregulation in both energy and complex

Table 3
Frailty Measurements for Use in Clinical Practice

Frailty Measurements
Screening
Rapid screening
- FRAIL Scale[39]
- PRISMA-7[63]
- Tilburg Frailty Index (TFI)[41]
- Vulnerable Elders Survey (VES)[64]
- Self-Rated Health Deficits Index (HDI)[65]
- Sherbrooke Postal Questionnaire (SPQ)[66]
- The G8 Questionnaire[67]—for oncology patients
- Easy Care—short version[68]
- Study of Osteoporotic Fractures (SOF) Index[69]
- Identification of Seniors at Risk (ISAR)[70]
Detailed Screening
- Fried's Frailty Phenotype[36]
- Groningen Frailty Indicator (GFI)[71]
- Frailty Trait Scale (FTS)
Measurements (incorporates screening and assessment)
- Grip Strength[72–74]
- Gait Speed[75]
- Timed Up and Go (TUG)[76]
- Short Physical Performance Battery (SPPB)[77]
Assessment
Rapid Assessment
- Rapid Geriatric Assessment (RGA)[78]
- Edmonton Frailty Scale (EFS)[42]
Comprehensive Assessment
- Comprehensive Geriatric Assessment (CGA)[79]
- Easy-Care[80]
Metrics-Computed Assessment
- Frailty Index (FI)[40]
- Kihon Checklist[81]
- Multidimensional Prognostic Index (MPI)[82]
- Frailty Risk Score (FRS)[83]
Synthesis Assessment
- Clinical Frailty Scale (CFS)[84]
- Gérontopôle Frailty Screening Tool (GFST)[85]

PRISMA-7, The Program of Research to Integrate Services for the Maintenance of Autonomy. The categorization of frailty measurements is subject to change, and frailty measurements can belong in more than 1 category

adaptive systems essential to homeostasis, which in turn, offers a physiological basis for sarcopenia and fatigue.[36,94] Because of this physiological basis, Fried's Frailty Phenotype is well suited for identifying frailty in the clinical setting,[3,95] although it can sometimes be time-consuming to measure patient grip strength and walking speed in clinical settings.[96] Fried's Frailty Phenotype is regularly used in clinical settings in the Asia-Pacific region, where it is predictive of mortality, disability, falls, hospitalization, and risk of surgery.[17,18,20,21,87,97–100]

Frailty Index (FI) of cumulative deficits

The FI considers frailty as an age-related, dynamic state. It is expressed as a ratio between the number of health deficits an older person has from a predetermined list of 30 or more variables.[40,101,102] FI scores range from 0 to 1, with an upper limit of around 0.67.[103] For example, in a list of 50 health deficits, if an individual scores "yes" to 10 of these deficits, then their FI score is 0.2 (=10/50).

The FI has a multidimensional nature, incorporating domains such as physical function, multimorbidities, cognition, and psychosocial factors. Interventions to manage frailty can focus on these domains, thereby adding to the utility of the FI in clinical practice. Like Fried's Frailty Phenotype, the FI is frequently applied in the Asia-Pacific region.[11,12,19,100,104–112] The FI is also indicative of an older adult's biological age,[104] captures risk of mortality,[3] and is predictive of disability, admission to nursing homes, functional decline, surgery risk, and hospitalization.[98,113,114]

Despite the advantages of the FI, it can be time-consuming to undertake if collecting the data at the clinical level from scratch.[79] However, a major advantage of the FI is that it can be obtained from data already collected from a CGA.[115] Moreover, an electronic FI can be automatically derived from routinely collected electronic medical records, which was recently demonstrated by Clegg et al[115] in their study of 900,000 older adults using primary care records.

Other frailty measurements and screening tools

Recently, a hybrid measure containing elements from both the Frailty Index and Fried's Frailty Phenotype was developed: the FRAIL scale.[39] The FRAIL scale shows similar predictive accuracy to both the FI and Fried's Frailty Phenotype,[116] and is recommended by the International Academy on Nutrition and Aging (IANA) for use in clinical practice.[117] The FRAIL scale is being increasingly used in the Asia-Pacific region.[15,33,99,116,118–120]

Also emerging in the Asia-Pacific region is the Clinical Frailty Scale (CFS),[121,122] which is a well-validated 9-point global assessment tool[84] that predicts adverse outcomes in older adults.[121–123] The CFS allows frailty to be defined and graded using simple clinical descriptors available from routine clinical assessment.[122] However, the tool requires some clinical judgement and trained assessors are required for accurate classification.[124]

Other frailty measurements regularly applied in the Asia-Pacific region include the Study of Osteoporotic Fractures (SOF) index,[16,87] the Reported Edmonton Frailty Scale,[6,21,86] the Timed-Up-and-Go (TUG),[125–127] the Short Physical Performance Battery (SPPB),[128–131] and the Kihon checklist.[81]

For frailty measurement tools requiring physical assessments, using locally defined cut-off points is advised. For instance, populations in the Asia-Pacific region may have lower grip strength,[72,73] with Wu et al[74] reporting a ≥25% lower grip strength in Taiwanese older adults than in European adults. It is, thus, suggested that for Asian populations, the lowest 20th quintile of grip strength be used to define low muscle strength, or <26 kg for men and <18 kg for women.[43]

Recommendation 2: We Strongly Recommend that Older Adults with Frailty be Referred to a Progressive, Individualized Physical Activity Program that Contains a Resistance Training Component

The adage "move it, or lose it" is of fundamental importance for frailty management and prevention. Several recent systematic reviews and meta-analyses have concluded that physical activity is a crucial way to maintain and improve the physical strength, function and mobility of older adults with frailty.[55,132–135] Physical activity programs for older adults with frailty and/or the oldest old should contain targeted exercises to address sarcopenia-related muscle wastage and mobility loss.[55,136] Resistance training (strength training) is strongly recommended, with multiple RCTs demonstrating benefits for even the oldest old.[137–144] Benefits of resistance training include enhanced strength and power,[135,143,145,146] reductions in disability,[135,142,144] reduced fatigue,[147,148] and a decreased likelihood of admission to a hospital or nursing home.[144]

Multijoint resistance exercises should be performed in the first few weeks of physical activity prescription, with the gradual progression to more single-joint exercises.[149] Exercises mimicking daily activities are encouraged.[143,150] Higher intensities of resistance training appear to have more benefits than low intensity exercise for older adults,[55,135,145,151] although the optimal volume (number of sets and repetitions) of resistance training is not yet clear.[55,134] From a physiological point of view, muscle cells adapt the same way to physical activity regardless of age,[146] even though older adults may take longer to improve to the same level as younger adults.[136]

Balance and aerobic training are also recommended for older adults with frailty, even if these modes of exercise may not directly influence muscle strength.[55] Ongoing participation in a balance program can reduce fear of falling, and improve mobility and balance, according to a recent meta-analysis of 88 trials in older adults.[55] Balance training can also reduce falls risk[55,152] and major mobility disability[153] when combined with a resistance training program. It is, therefore, proposed that balance exercises accompany resistance training once an older adult with frailty is able to stand.[55] Prescription of walking for older adults with frailty is also advocated, ideally when an individual's balance, strength, and cognition are adequate to perform walking safely[55] given the close association between unstable walking and falls risk.[154] Reducing sedentary time may also be a first step in promoting older adults with frailty to be more physically active.[155]

Multimodal physical activity programs may also be beneficial for older adults with frailty. For instance, the recent large-scale Lifestyle Interventions and Independence for Elders (LIFE) Phase III RCT[153,156,157] found that multimodal exercise (resistance training, aerobic exercise (walking), balance, and flexibility exercises) reduced major mobility disability in older adults.[153] Most surprising was that the effects of this multimodal training on preventing mobility disability were highest among those who were frail (SPPB <8).[153] In the Asia-Pacific region, the recent Steps to Avoid Falls in the Elderly (SAFE) Study demonstrated that a combination of resistance, balance, and gait training reduced falls risk in older adults (with and without frailty) discharged from an emergency department[131]; however, this finding was only observed in those with low comorbidity. Future large-scale intervention studies should investigate the impact of multimodal exercise programs in older adults with frailty in the Asia-Pacific region.

Health practitioners should be aware that community-based programs for older people with frailty often fall very short of evidence-based recommendations.[55] Furthermore, adherence to physical activity programs is poor in older adults for a variety of reasons, including a fear of falling[158]; a lack of self-belief and coping strategies[142,159,160]; attitude[160,161]; and adverse social and environmental influences.[142] Essentially, older adults are more likely to adhere to a physical activity program if the program is supervised,[151] individually tailored,[55,131] contains self-efficacy training,[142] and the referring clinician encourages patient participation.[161]

Recommendation 3: We Strongly Recommend that Polypharmacy Be Addressed by Reducing or De-prescribing Any Inappropriate/Superfluous Medications

Much research has linked frailty development with polypharmacy.[1,162–166] We recommend that medications prescribed by frail older people be reviewed regularly. Medications, which are no longer needed can be deprescribed, regulating the dose in accordance with kidney function.[167,168] Withdrawal of inappropriate medications should be conducted under the supervision of a healthcare professional, with the aim to improve the outcomes of patients.[168] A recent systematic review reported that deprescription is most effective when implemented earlier, and that older adults can tolerate the withdrawal of certain medications without harmful circumstances.[169] Deprescribing is unlikely to lead to any significant adverse clinical outcomes, at least based on a recent RCT of older adults residing in residential aged care facilities.[170]

Regrettably, there exists a distinct lack of well-designed clinical trials on reducing inappropriate/superfluous medications in older adults with frailty, based on the findings of a systematic review by Tija et al.[171] In general, it is advised that deprescribing of inappropriate medications for older adults with frailty should occur using guidelines provided by: the Screening Tool of Older Person's Prescriptions (STOPP) criteria and Screening Tool to Alert doctors to Right Treatment (START) criteria[172–174]; the Beers criteria; and the McLeod criteria.[175] These deprescription guidelines focus on specific medications that should not be prescribed. General deprescription guidelines also exist, which do not solely focus on specific medications, and instead rely on evidence-based medicine and the older adult themselves: the Medication Appropriateness Index (MAI),[176] and the Inappropriate Medication Use and Prescribing Indicators tool.[177]

To implement a deprescription program for older adults with frailty, it is recommended that clinicians and pharmacists openly discuss the projected benefits of deprescription against potential harms with both the patient and their carer.[178] Health practitioners should also be aware of barriers to deprescription for older adults with frailty, including: incentives to over-prescribe[178]; a lack of agreement as to what medications to deprescribe[179]; and a lack of awareness of deprescription benefits.[178] Of note, in rural and/or lower socioeconomic areas, there may be the opposite problem: older adults with frailty may have unknown and untreated diseases.

Recommendation 4: We Conditionally Recommend that Persons with Frailty Are Screened for Reversible Causes of Fatigue

There are a number of treatable causes of fatigue including sleep apnea,[180,181] depression,[182,183] anemia,[182] hypotension,[183] hypothyroidism,[184] and B_{12} deficiency.[185] Fatigue is a key component of both Fried's Frailty Phenotype and the FRAIL scale.[36,39] Research reports have indicated that screening for reversible causes of fatigue, combined with targeted interventions, can improve the outcomes of older adults with frailty.[1,186] Nevertheless, very little rigorous research has addressed modifiable causes of fatigue in older adults with frailty. Although there are clinical trials showing that fatigue can be treated by addressing sleep apnea[180,187] and depression,[183] good quality clinical trials on other reversible causes of fatigue are required. Of note, Selective Serotonin Reuptake Inhibitors (SSRIs), which are widely prescribed to treat depression, may actually worsen frailty.[188]

Recommendation 5: We Conditionally Recommend that Older Adults with Frailty Who Exhibit Unintentional Weight Loss Should Be Screened for Reversible Causes and Considered for Protein and Caloric Supplementation/Food Fortification

Weight loss is a key feature of frailty[36,189,190] and should be managed by screening for and addressing identified reversible causes. Potentially reversible causes of weight loss can be identified using the comprehensive Meals on Wheels mnemonic[191] (Table 4) and include illness, dementia, medications, swallowing problems, and other such factors that contribute to weight loss and malnutrition.

Protein and caloric supplementation

Caloric and protein supplementation in frail persons with weight loss is conditionally recommended.[192–195] Food fortification (energy dense meals) is recommended foremost, with supplements as a complementary aspect.[196] Notwithstanding this, previous meta-analyses have been unable to ascribe benefits to protein calorie supplementation un-confounded with other treatments.[193,195,197] If nutritional supplementation does improve nutritional status, this improvement may not translate into functional improvement or mortality reduction.[197,198] Unfortunately a major concern of protein supplementation trials in older adults with frailty is that the control group is either nonexistent or significantly more nourished at baseline than the intervention group.[193,195,197,198] Future intervention studies should devise methodology to address this limitation to increase the evidence base behind protein supplementation in older adults with frailty.

Table 4
The Meals on Wheels Mnemonic of Reversible Causes of Weight Loss

Medications
Emotional (depression)
Alcoholism, anorexia tardive, abuse (elder)
Late life paranoia
Swallowing problems
Oral problems
Nosocomial infections, no money (poverty)
Wandering/dementia
Hyperthyroidism, hypercalcemia, hypoadrenalism
Enteric problems (malabsorption)
Eating problems (eg, tremor)
Low salt, low cholesterol diet
Shopping and meal preparation problems, stones (cholecystitis)

Supplementation with Essential Amino Acids (EAAs) is suggested for older people with frailty. EAAs are proteins the body cannot manufacture itself and are, therefore, essential to obtain from dietary intake. They include valine, leucine, isoleucine, lysine, threonine, tryptophan, methionine, phenylalanine, and histidine.[199] Several studies have found that older adults improve in their physical function when supplemented with leucine enriched EAAs.[199,200] For instance, Bauer et al reported that leucine-enriched whey protein increased muscle mass and leg function in older adults with sarcopenia.[200] Leucine is metabolized to β-hydroxy-β-methyl butyrate (HMB) in cells, and it appears that an HMB enriched protein mixture enhances muscle mass and function.[201]

Recommended daily intake for protein

Older adults are likely to need more protein intake than younger adults.[202,203] Current Recommended Daily Intakes (RDIs) for protein intake in older adults varies from 0.8 g/kg body weight (BW) per day[199,203] to 1.0 to 1.2 g/kg BW/day by the Protein needs with Ageing (PROT-AGE) study group,[204] and up to at least 1.2 g/kg BW/d as proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN).[196] ESPEN also recommend that protein intake be increased to 1.2 to 1.5 g/kg BW/d for those with malnutrition. The current upper limit of protein supplementation for older adults is not yet clear due to insufficient studies.[199] When supplementing older adults with high levels of protein, renal function should be monitored,[196,203] and the ESPEN suggest that a protein intake of 0.8 to 1 g/kg body weight per day for patients with acute or chronic kidney failure who are not receiving renal replacement therapy.[196] Also of consideration is that Asia-Pacific populations may show differing responses to protein supplementation compared with European or North American populations, thus, additional clinical trials in this region are encouraged.

Multicomponent interventions

In the Asia-Pacific region, there are emerging clinical trials showing the benefit of combining interventions (physical, nutritional, and cognitive interventions)[205] to manage frailty, although larger scale studies are needed. For example, the benefits of protein supplementation may be enhanced when combined with resistance training.[199] A recent study by Tieland et al[206] found that protein supplementation increased the physical function in older adults with frailty undergoing resistance training. Similarly, physical function and strength improved in older women with sarcopenia after they were supplemented with 3 g protein combined with physical activity (with physical activity alone not affecting strength in this cohort).[207] It is not yet clear whether a combination of physical activity/protein supplementation impacts on muscle mass, with studies reporting different results.[199,206,207]

In Europe, the Sarcopenia and Physical fRailty IN older people multicomponenT Treatment strategies (SPRINTT) project is currently investigating the effect of a multicomponent intervention including structured physical activity, nutritional counselling/dietary intervention, and an information and communication technology intervention. The SPRINTT study is a multicenter, Phase III RCT designed to prevent mobility disability in 1500 older adults with frailty and sarcopenia for 36 months.[208,209] In the Asia-Pacific region, there are very few clinical trials investigating multicomponent interventions in older adults with frailty.

Screening for unintentional weight loss and malnutrition

An adjunct conditional recommendation is that weight loss and malnutrition should be screened for using an accepted nutritional screening tool, such as the Mini Nutritional Assessment (MNA),[210] its short form version (MNA-SF),[211] or the Malnutrition Universal Screening Tool (MUST),[212] among others. These nutritional screening tools are regularly used in the Asia-Pacific region, often with population-specific cut-off points for anthropometric measures.[213–217] Nutritional screening may also identify conditions that can contribute to frailty but which may be not be easily spotted; for instance, sarcopenic obesity (low muscle mass and high body fat). Screening for low appetite may also be beneficial in older adults with frailty.[218]

Recommendation 6: We Conditionally Recommend that Vitamin D Be Prescribed for Older Adults Found to Be Deficient in Vitamin D

Vitamin D is a fat-soluble vitamin crucial for muscle and bone function, among many other physiological roles such as inflammation, metabolism, and blood glucose regulation.[219–222] It is predominantly synthesized in the skin from cholesterol, although dietary sources such as oily fish can contribute up to 10% of vitamin D intake.[220,223] Deficiencies in vitamin D are linked with reduced physical functioning[224,225] frailty development,[226–228] as well as falls and mortality.[226–228] Vitamin D deficiencies are common both in older adults with frailty[226,229–233] and in older populations residing in the Asia Pacific region,[221,228,234–238] although not all studies have found high rates of deficiencies.[239,240]

Sun exposure and vitamin D

Although it is possible to obtain an adequate vitamin D intake via sun exposure alone, this may not occur in older adults because of sun avoidance,[221] disability that limits outdoor exposure (such as residing in residential care),[227] and an ~75% reduced ability to synthesize vitamin D in the skin.[241] To optimize vitamin D intake without being burnt by the sun's harmful ultra violet (UV) rays, it is advised that in winter, older adults go outside in the middle of the day when the UV index is low (UV index l < 3); and in summer, to uncover arms and hands to the sunlight for only a few minutes in the morning or afternoon when the UV index is lower.[242,243] Importantly, vitamin D is bound to a vitamin D binding protein which is lower in darker skinned individuals,[244,245] so sunlight exposure may need to be higher in these individuals to gain adequate levels of vitamin D.[222]

Vitamin D supplementation for older adults with frailty

There are several clinical trials finding that vitamin D supplementation in older adults with vitamin D deficiency reduces likelihood of mortality, falls, and fractures.[1] However, these trials tend to focus on older adults without frailty.[233] Vitamin D supplementation for older adults with frailty remains a topic of much debate in the literature.[3,246,247] If supplements are prescribed, the suggested dosage is between 800 and 1000 IU of vitamin D daily,[248] although this dosage does also depend on an individual's condition, diet, and sunlight exposure.[247] However, there is concern regarding high dosages of vitamin D supplementation, especially in people without vitamin D deficiency, as this may *increase* the risk of falls and fractures.[249–251]

Vitamin D supplementation for older adults in general

When considering older adults in general, there are many meta-analyses and systematic reviews regarding the effectiveness of vitamin D supplementation, with contrasting findings.[246,248,252–254] For instance, Rosendahl-Riise et al[252] and Rejnmark et al[253] both reported that vitamin D supplementation in older adults did not improve muscle strength or mortality risk, respectively, although Rejnmark et al (2012) did observe a mortality reduction effect when vitamin D was combined with calcium supplementation.[253] On the other hand, Muir et al[248] found that supplementation with 800 to 1000 IU vitamin D daily did improve strength and balance in older adults. In addition, a recent Cochrane review reported that vitamin D supplementation decreased the risk of falls in older adults residing in care facilities.[255] There remains a paucity of clinical trials particularly in specific ethnic groups, although one recent trial from China found that long- term vitamin D supplementation did not improve muscle mass or function, at least in older men not deficient in vitamin D at baseline.[256]

Screening for vitamin D

Routine measurement of 25(OH) vitamin D levels cannot be recommended for all populations of older adults with frailty. Darker skinned individuals have lower vitamin D binding protein,[244,245] and, thus, the ability to determine normal vitamin D levels is questionable in persons of Asian or African descent.

Recommendation 7: We Have No Recommendation for the Provision of an Individualized Support and Education Plan for Older Adults with Frailty

Currently, there exists only a limited evidence-base regarding the provision of an individualized support and education plan for older adults with frailty and their caregivers. Although anecdotally and in small-scale studies such programs appear effective,[229] there is a definite need for large-scale, well-designed RCTs to support this recommendation. Notwithstanding this, there are several recent reports highlighting the importance of support and educational plans.[257,258] This support/training can come from communities, home care restorative services, allied health professionals, nursing staff, general practitioners, and geriatricians,[259–261] and should aim to maximize physical function.[260] The specific needs of the older person themselves should also be included in order to promote independence and person-centered care.[258,261]

A healthcare worker can be employed as a health system navigator to facilitate effective integration among healthcare services.[262] Healthcare integration is valuable given the higher need for healthcare services by older adults with frailty, and the barriers they face accessing these healthcare services.[259,262] Multidisciplinary intervention planning involving case management/case conferencing by managing physicians, nurses, and allied health professionals may improve the coordination of care delivery for older adults with frailty, which in turn, may assist in successfully treating frailty.[263] In spite of this positive finding, recent research has reported that compliance to multidisciplinary intervention is low for older people with frailty; although those that do adhere to the intervention may experience improved frailty status and mobility.[264] There is currently little evidence that integrating care services for older adults with frailty does improve individual outcomes,[265–268] although this may be true only in countries with already well-resourced primary care services.[268]

Discussion

This report provides clinical guidelines for the management of frailty in older adults and is based on current scientific evidence combined with an appraisal by international clinical experts in frailty. These guidelines are intended for use by healthcare providers to support their everyday management of older adults with frailty. They are not intended for use in isolation. Rather, it is advised that health professionals discuss with patients and their carers as to the best decisions regarding individualized treatment. It is also imperative for the health professional to recognize that the perceived benefit of any intervention should outweigh any potential harm for the older patient with frailty.

This guidelines document has deliberately been designed to be concise and condensed to ensure uptake and adherence by healthcare providers.[269] In addition, it may not be feasible, practical, or even beneficial for a frail patient to be referred to all treatment strategies outlined in this report. That is, an intervention that may benefit an older adult in the early stages of frailty might not beneficial, or may even be harmful to, an older adult with severe frailty.

Individual practitioners should select the most appropriate interventions consistent with patient preference, accessible resources, and minimization of patient harm.[58,270] The guidelines will also need to be adapted to the local context. For instance, in the Asia-Pacific region, the majority of practitioners may not have the resources to perform a full CGA, and, thus, use of a Rapid Geriatric Assessment may be beneficial.[78]

As a whole, there exists a lack of well-designed clinical trials addressing treatment modalities for frailty. Older adults with frailty are often excluded from clinical trials,[258] which limits the evidence base that clinical guidelines can be developed from. More robust clinical trials of adequate quality for older people with frailty are needed, particularly those focusing on outcomes that are valuable to the older adult themselves, such as functional independence, quality of life, and remaining at home.[260] Such trials are especially needed in the Asia-Pacific region given that most of the evidence-base underpinning frailty management comes from Europe and North America, which may not directly extrapolate to Asia-Pacific populations.

A major limitation of this report is that full systematic reviews were not undertaken for each recommendation. Standardized methods for synthesizing evidence into guidelines were also not adopted by expert panel members. Furthermore, because of the limited-evidence base of clinical trials involving older adults with frailty, caution is advised when developing clinical quality indicators for frailty management processes from the guidelines provided in this article.

Importantly, knowledge in geriatric medicine is constantly progressing, with new assessment techniques, treatment modalities, and technologies developed regularly. As such, evidence-based clinical guidelines for frailty need to be kept regularly updated and revised. It is proposed that regional guideline support committees be formed to help provide regular updates to evidence-based guidelines. These regional committees can also devise setting-specific guidelines for frailty management, including for emergency departments, primary care, oncology, cardiology, and orthopedics. Regular updating of clinical guidelines will ensure that practitioners have the latest evidence-base to guide the management of older adults with frailty. In addition, guidelines for frailty should be linked with clinical case scenarios to disseminate knowledge of its management.

Overall, with the rapid rise in the number of older people globally, it is imperative that frailty be identified and appropriately managed. It is anticipated that these clinical guidelines will improve the recognition of frailty by healthcare professionals and improve the quality of care and outcomes for older persons with frailty.

References

1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: A call to action. J Am Med Dir Assoc 2013;14:392–397.
2. Hartley P, Adamson J, Cunningham C, et al. Clinical frailty and functional trajectories in hospitalized older adults: A retrospective observational study. Geriatr Gerontol Int 2016; http://dx.doi.org/10.1111/ggi.12827.

3. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381:752–762.
4. Lee Y, Kim J, Han ES, et al. Frailty and body mass index as predictors of 3-year mortality in older adults living in the community. Gerontology 2014;60:475–482.
5. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. Eur J Intern Med 2016;31:3–10.
6. Kua J, Ramason R, Rajamoney G, Chong MS. Which frailty measure is a good predictor of early post-operative complications in elderly hip fracture patients? Archives of orthopaedic and trauma surgery 2016;136:639–647.
7. von Haehling S, Anker SD, Doehner W, et al. Frailty and heart disease. International journal of cardiology 2013;168:1745–1747.
8. Hamaker ME, Jonker JM, de Rooij SE, et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: A systematic review. Lancet Oncol 2012;13:e437–e444.
9. Lu Y, Tan CT, Nyunt MS, et al. Inflammatory and immune markers associated with physical frailty syndrome: Findings from Singapore longitudinal aging studies. Oncotarget 2016;7:28783–28795.
10. Lee JS, Auyeung TW, Leung J, et al. Transitions in frailty states among community-living older adults and their associated factors. J Am Med Dir Assoc 2014;15:281–286.
11. Woo J, Zheng Z, Leung J, Chan P. Prevalence of frailty and contributory factors in three Chinese populations with different socioeconomic and healthcare characteristics. BMC Geriatr 2015;15:163.
12. Noguchi N, Blyth FM, Waite LM, et al. Prevalence of the geriatric syndromes and frailty in older men living in the community: The Concord Health and Ageing in Men Project. Australas J Ageing 2016;35:255–261.
13. Zeng P, Wu S, Han Y, et al. Differences in body composition and physical functions associated with sarcopenia in Chinese elderly: Reference values and prevalence. Arch Gerontol Geriat 2015;60:118–123.
14. Vaingankar JA, Chong SA, Abdin E, et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int 2016 Aug 31 [Epub ahead of print].
15. Woo J, Yu R, Wong M, et al. Frailty Screening in the Community Using the FRAIL Scale. J Am Med Dir Assoc 2015;16:412–419.
16. Jung HW, Kim SW, Ahn S, et al. Prevalence and outcomes of frailty in Korean elderly population: Comparisons of a multidimensional frailty index with two phenotype models. PLoS One 2014;9:e87958.
17. Liu LK, Lee WJ, Chen LY, et al. Association between Frailty, Osteoporosis, Falls and Hip Fractures among Community-Dwelling People Aged 50 Years and Older in Taiwan: Results from I-Lan Longitudinal Aging Study. PLoS One 2015;10:e0136968.
18. Makizako H, Shimada H, Doi T, et al. Impact of physical frailty on disability in community-dwelling older adults: A prospective cohort study. BMJ open 2015;5:e008462.
19. Sathasivam J, Kamaruzzaman SB, Hairi F, et al. Frail Elders in an Urban District Setting in Malaysia: Multidimensional Frailty and Its Correlates. Asia-Pacific journal of public health 2015;27:52s–61s.
20. Chen S, Honda T, Chen T, et al. Screening for frailty phenotype with objectively-measured physical activity in a west Japanese suburban community: Evidence from the Sasaguri Genkimon Study. BMC Geriatr 2015;15:36.
21. Chang CI, Chan DC, Kuo KN, et al. Prevalence and correlates of geriatric frailty in a northern Taiwan community. J Formos Med Assoc 2011;110:247–257.
22. Ng TP, Feng L, Nyunt MS, et al. Frailty in older persons: Multisystem risk factors and the Frailty Risk Index (FRI). J Am Med Dir Assoc 2014;15:635–642.
23. Chong MS, Tay L, Ismail NH, et al. The case for stage-specific frailty interventions spanning community aging to cognitive impairment. J Am Med Dir Assoc 2015;16:1003.e13–1003.e19.
24. Zheng Z, Guan S, Ding H, et al. Prevalence and incidence of frailty in community-dwelling older people: Beijing Longitudinal Study of Aging II. J Am Geriatr Soc 2016;64:1281–1286.
25. Moreira VG, Lourenco RA. Prevalence and factors associated with frailty in an older population from the city of Rio de Janeiro, Brazil: The FIBRA-RJ Study. Clinics (Sao Paulo, Brazil) 2013;68:979–985.
26. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc 2010;58:681–687.
27. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 2009;64:675–681.
28. Garcia-Pena C, Avila-Funes JA, Dent E, et al. Frailty prevalence and associated factors in the Mexican health and aging study: A comparison of the frailty index and the phenotype. Exp Gerontol 2016;79:55–60.
29. Cawthon PM, Marshall LM, Michael Y, et al. Frailty in older men: Prevalence, progression, and relationship with mortality. J Am Geriatr Soc 2007;55:1216–1223.
30. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. J Am Geriatr Soc 2012;60:1487–1492.
31. Xue QL, Bandeen-Roche K, Varadhan R, et al. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 2008;63:984–990.
32. Biritwum RB, Minicuci N, Yawson AE, et al. Prevalence of and factors associated with frailty and disability in older adults from China, Ghana, India, Mexico, Russia and South Africa. Maturitas 2016;91:8–18.
33. Hyde Z, Flicker L, Smith K, et al. Prevalence and incidence of frailty in Aboriginal Australians, and associations with mortality and disability. Maturitas 2016;87:89–94.
34. McCaul KA, Almeida OP, Norman PE, et al. How many older people are frail? Using multiple imputation to investigate frailty in the population. J Am Med Dir Assoc 2015;16:439.e1–439.e7.
35. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and comorbidity in relation to frailty: How much do they overlap? Arch Gerontol Geriatr 2012;55:e1–e8.
36. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
37. Bock JO, Konig HH, Brenner H, et al. Associations of frailty with healthcare costs—Results of the ESTHER cohort study. BMC Health Serv Res 2016;16:128.
38. Reddy SR, Ross-Degnan D, Zaslavsky AM, et al. Health care payments in the Asia Pacific: Validation of five survey measures of economic burden. Int J Equity Health 2013;12:49.
39. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601–608.
40. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. Sci World J 2001;1:323–336.
41. Gobbens RJ, van Assen MA, Luijkx KG, et al. The Tilburg Frailty Indicator: Psychometric properties. J Am Med Dir Assoc 2010;11:344–355.
42. Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526–529.
43. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: Consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
44. Chen L-K, Rockwood K. Planning for frailty. J Clin Gerontol Geriatr 2012;3:3–4.
45. Woolf S, Schunemann HJ, Eccles MP, et al. Developing clinical practice guidelines: Types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. IS 2012;7:61.
46. Turner G, Clegg A. Best practice guidelines for the management of frailty: A British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age Ageing 2014;43:744–747.
47. Maurice J. WHO puts healthy ageing on the front burner. Lancet 2016;387:109–110.
48. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009;64:669–677.
49. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2004;328:1490.
50. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–735.
51. Cruz JE, Fahim G, Moore K. Practice Guideline Development, Grading, and Assessment. P T 2015;40:854–857.
52. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:465–474.
53. Dirksen CD. The use of research evidence on patient preferences in healthcare decision-making: Issues, controversies and moving forward. Exp Rev Pharmacoeconomics Outcomes Res 2014;14:785–794.
54. Landi F, Calvani R, Cesari M, et al. Sarcopenia as the Biological Substrate of Physical Frailty. Clin Geriat Med 2015;31:367–374.
55. Bauman A, Merom D, Bull FC, et al. Updating the evidence for physical activity: Summative reviews of the epidemiological evidence, prevalence, and interventions to promote "active aging". Gerontologist 2016;56:S268–S280.
56. Cesari M, Landi F, Vellas B, et al. Sarcopenia and physical frailty: Two sides of the same coin. Frontiers Aging Neurosci 2014;6:192.
57. Morley JE. Sarcopenia in the elderly. Fam Pract 2012;29:i44–i48.
58. Cesari M, Nobili A, Vitale G. Frailty and sarcopenia: From theory to clinical implementation and public health relevance. Eur J Intern Med 2016;35:1–9.
59. Romero-Ortuno R, O'Shea D. Fitness and frailty: Opposite ends of a challenging continuum! Will the end of age discrimination make frailty assessments an imperative? Age Ageing 2013;42:279–280.
60. Espinoza SE, Jung I, Hazuda H. Frailty transitions in the San Antonio Longitudinal Study of Aging. J Am Geriatr Soc 2012;60:652–660.
61. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med 2006;166:418–423.
62. van de Pol MH, Fluit CR, Lagro J, et al. Expert and patient consensus on a dynamic model for shared decision-making in frail older patients. Patient Educ Counsel 2016;99:1069–1077.
63. Raiche M, Hebert R, Dubois MF. PRISMA-7: A case-finding tool to identify older adults with moderate to severe disabilities. Arch Gerontol Geriatr 2008;47:9–18.

64. Chapman MD, Le BH, Gorelik A. The Vulnerable Elders Survey and its prognostic relationship to survival in an older community-based palliative population. BMJ Support Palliat Care 2013;3:335–342.
65. Lucicesare A, Hubbard RE, Searle SD, Rockwood K. An index of self-rated health deficits in relation to frailty and adverse outcomes in older adults. Aging Clin Exp Res 2010;22:255–260.
66. Hebert R, Bravo G, Korner-Bitensky N, Voyer L. Predictive validity of a postal questionnaire for screening community-dwelling elderly individuals at risk of functional decline. Age Ageing 1996;25:159–167.
67. Baitar A, Van Fraeyenhove F, Vandebroek A, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. J Geriatr Oncol 2013;4:32–38.
68. Melis RJ, van Eijken MI, Borm GF, et al. The design of the Dutch EASYcare study: A randomised controlled trial on the effectiveness of a problem-based community intervention model for frail elderly people [NCT00105378]. BMC Health Serv Res 2005;5:65.
69. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2007;62:744–751.
70. McCusker J, Bellavance F, Cardin S, et al. Detection of older people at increased risk of adverse health outcomes after an emergency visit: The ISAR screening tool. J Am Geriatr Soc 1999;47:1229–1237.
71. Steverink N, Slaets JP, Schuurmans H, van Lis M. Measuring Frailty: Developing and testing of the Groningen Frailty Indicator (GFI). Gerontologist 2001; 41:236–237.
72. Lam NW, Goh HT, Kamaruzzaman SB, et al. Normative data for hand grip strength and key pinch strength, stratified by age and gender for a multiethnic Asian population. Singapore Med J 2016;57:578–584.
73. Malhotra R, Ang S, Allen JC, et al. Normative Values of Hand Grip Strength for Elderly Singaporeans Aged 60 to 89 Years: A Cross-Sectional Study. J Am Med Dir Assoc 2016;17:864.e1–864.e7.
74. Wu SW, Wu SF, Liang HW, et al. Measuring factors affecting grip strength in a Taiwan Chinese population and a comparison with consolidated norms. Appl Ergonomics 2009;40:811–815.
75. Stanaway FF, Gnjidic D, Blyth FM, et al. How fast does the Grim Reaper walk? Receiver operating characteristics curve analysis in healthy men aged 70 and over. BMJ (Clinical research ed) 2011;343:d7679.
76. Podsiadlo D, Richardson S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–148.
77. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94.
78. Morley JE, Adams EV. Rapid Geriatric Assessment. J Am Med Dir Assoc 2015; 16:808–812.
79. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: Different instruments for different purposes. Age Ageing 2014; 43:10–12.
80. Craig C, Chadborn N, Sands G, et al. Systematic review of EASY-care needs assessment for community-dwelling older people. Age Ageing 2015;44: 559–565.
81. Satake S, Senda K, Hong YJ, et al. Validity of the Kihon Checklist for assessing frailty status. Geriatr Gerontol Int 2016;16:709–715.
82. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res 2008;11:151–161.
83. Pijpers E, Ferreira I, van de Laar RJ, et al. Predicting mortality of psychogeriatric patients: A simple prognostic frailty risk score. Postgraduate Med J 2009; 85:464–469.
84. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.
85. Vellas B, Balardy L, Gillette-Guyonnet S, et al. Looking for frailty in community-dwelling older persons: The Gerontopole Frailty Screening Tool (GFST). J Nutri Health Aging 2013;17:629–631.
86. Hii TB, Lainchbury JG, Bridgman PG. Frailty in acute cardiology: Comparison of a quick clinical assessment against a validated frailty assessment tool. Heart Lung Circ 2015;24:551–556.
87. Dent E, Chapman I, Howell S, et al. Frailty and functional decline indices predict poor outcomes in hospitalised older people. Age Ageing 2014;43: 477–484.
88. Hoogendijk EO, van der Horst HE, Deeg DJ, et al. The identification of frail older adults in primary care: Comparing the accuracy of five simple instruments. Age Ageing 2013;42:262–265.
89. Mack M. Frailty and aortic valve disease. J Thorac Cardiovasc Surg 2013;145: S7–S10.
90. Rodes-Cabau J, Mok M. Working toward a frailty index in transcatheter aortic valve replacement: A major move away from the "eyeball test". JACC Cardiovasc Intervent 2012;5:982–983.
91. O'Neill BR, Batterham AM, Hollingsworth AC, et al. Do first impressions count? Frailty judged by initial clinical impression predicts medium-term mortality in vascular surgical patients. Anaesthesia 2016;71:684–691.
92. Ellis G, Whitehead MA, Robinson D, et al. Comprehensive geriatric assessment for older adults admitted to hospital: Meta-analysis of randomised controlled trials. BMJ (Clinical research ed) 2011;343:d6553.
93. Romero-Ortuno R. Frailty in primary care. Interdisciplinary topics in gerontology and geriatrics 2015;41:85–94.
94. Fried LP. Interventions for human frailty: Physical activity as a model. Cold Spring Harbor Perspect Med 2016;6:6.
95. Chen X, Mao G, Leng SX. Frailty syndrome: An overview. Clin InterventAging 2014;9:433–441.
96. Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: A systematic review. Age Ageing 2015;44:148–152.
97. Dent E, Hoogendijk EO. Psychosocial factors modify the association of frailty with adverse outcomes: A prospective study of hospitalised older people. BMC Geriatr 2014;14:108.
98. Ensrud KE, Ewing SK, Cawthon PM, et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc 2009;57:492–498.
99. Jung HW, Jang IY, Lee YS, et al. Prevalence of frailty and aging-related health conditions in older Koreans in rural communities: A cross-sectional analysis of the aging Study of Pyeongchang Rural Area. J Korean Med Sci 2016;31: 345–352.
100. Zhu Y, Liu Z, Wang Y, et al. Agreement between the frailty index and phenotype and their associations with falls and overnight hospitalizations. Arch Gerontol Geriatr 2016;66:161–165.
101. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
102. Cesari M, Costa N, Hoogendijk EO, et al. How the Frailty Index may support the allocation of health care resources: An example from the INCUR Study. J Am Med Dir Assoc 2016;17:448–450.
103. Bennett S, Song X, Mitnitski A, Rockwood K. A limit to frailty in very old, community-dwelling people: A secondary analysis of the Chinese longitudinal health and longevity study. Age Ageing 2013;42:372–377.
104. Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. J Gerontol A Biol Sci Med Sci 2005;60: 1046–1051.
105. Yu P, Song X, Shi J, et al. Frailty and survival of older Chinese adults in urban and rural areas: Results from the Beijing Longitudinal Study of Aging. Arch Gerontol Geriatr 2012;54:3–8.
106. Ma L, Zhang L, Tang Z, et al. Use of the frailty index in evaluating the prognosis of older people in Beijing: A cohort study with an 8-year follow-up. Arch Gerontol Geriatr 2016;64:172–177.
107. Yang F, Gu D. Predictability of frailty index and its components on mortality in older adults in China. BMC Geriatr 2016;16:145.
108. Hao Q, Song X, Yang M, et al. Understanding risk in the oldest old: Frailty and the metabolic syndrome in a Chinese community sample aged 90+ years. J Nutri Health Aging 2016;20:82–88.
109. Liu Z, Wang Q, Zhi T, et al. Frailty Index and its relation to falls and overnight hospitalizations in elderly Chinese people: A population-based study. J Nutri Health Aging 2016;20:561–568.
110. Zeng A, Song X, Dong J, et al. Mortality in relation to frailty in patients admitted to a specialized geriatric intensive care unit. J Gerontol A Biol Sci Med Sci 2015;70:1586–1594.
111. Armstrong JJ, Mitnitski A, Launer LJ, et al. Frailty in the Honolulu-Asia Aging Study: Deficit accumulation in a male cohort followed to 90% mortality. J Gerontol A Biol Sci Med Sci 2015;70:125–131.
112. Almeida OP, Hankey GJ, Yeap BB, et al. Depression, frailty, and all-cause mortality: A cohort study of men older than 75 years. J Am Med Dir Assoc 2015;16:296–300.
113. Dent E, Hoon E, Karnon J, et al. Frailty and health service use in rural South Australia. Arch Gerontol Geriatr 2016;62:53–58.
114. Rochat S, Cumming RG, Blyth F, et al. Frailty and use of health and community services by community-dwelling older men: The Concord Health and Ageing in Men Project. Age Ageing 2010;39:228–233.
115. Rockwood K, Rockwood MR, Mitnitski A. Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. J Am Geriatr Soc 2010;58:318–323.
116. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. J Am Geriatr Soc 2012;60:1478–1486.
117. Abellan van Kan G, Rolland Y, Bergman H, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12:29–37.
118. Chao CT, Hsu YH, Chang PY, et al. Simple self-report FRAIL scale might be more closely associated with dialysis complications than other frailty screening instruments in rural chronic dialysis patients. Nephrology (Carlton, Vic) 2015;20:321–328.
119. Lopez D, Flicker L, Dobson A. Validation of the frail scale in a cohort of older Australian women. J Am Geriatr Soc 2012;60:171–173.
120. Li Y, Zou Y, Wang S, et al. A Pilot Study of the FRAIL Scale on Predicting Outcomes in Chinese Elderly People With Type 2 Diabetes. J Am Med Dir Assoc 2015;16:714.e7–714.e12.
121. Basic D, Shanley C. Frailty in an older inpatient population: Using the clinical frailty scale to predict patient outcomes. J Aging Health 2015;27: 670–685.
122. Gregorevic KJ, Hubbard RE, Lim WK, Katz B. The clinical frailty scale predicts functional decline and mortality when used by junior medical staff: A prospective cohort study. BMC Geriatr 2016;16:117.

123. Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: A multicentre prospective cohort study. CMAJ 2014;186:E95–E102.
124. Rockwood K, Abeysundera MJ, Mitnitski A. How should we grade frailty in nursing home patients? J Am Med Dir Assoc 2007;8:595–603.
125. Fang WH, Huang GS, Chang HF, et al. Gender differences between WOMAC index scores, health-related quality of life and physical performance in an elderly Taiwanese population with knee osteoarthritis. BMJ Open 2015;5: e008542.
126. Li CI, Li TC, Lin WY, et al. Combined association of chronic disease and low skeletal muscle mass with physical performance in older adults in the Sarcopenia and Translational Aging Research in Taiwan (START) study. BMC Geriatr 2015;15:11.
127. Kim H, Suzuki T, Kim M, et al. Incidence and predictors of sarcopenia onset in community-dwelling elderly Japanese women: 4-year follow-up study. J Am Med Dir Assoc 2015;16:85.e1–85.e8.
128. Fukui S, Kawakami M, Otaka Y, et al. Physical frailty in older people with severe aortic stenosis. Aging Clin Exp Res 2016;28:1081–1087.
129. Kim YH, Kim KI, Paik NJ, et al. Muscle strength: A better index of low physical performance than muscle mass in older adults. Geriatr Gerontol Int 2016;16: 577–585.
130. Oh B, Cho B, Choi HC, et al. The influence of lower-extremity function in elderly individuals' quality of life (QOL): An analysis of the correlation between SPPB and EQ-5D. Arch Gerontol Geriatr 2014;58:278–282.
131. Matchar DB, Duncan PW, Lien CT, et al. Randomized Controlled Trial of Screening, Risk Modification, and Physical Therapy to Prevent Falls Among the Elderly Recently Discharged From the Emergency Department to the Community: The Steps to Avoid Falls in the Elderly Study. Arch Phys Med Rehabil 2017;98:1086–1096.
132. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for the management of frailty: A systematic review. J Aging Res 2011;2011:569194.
133. Chou CH, Hwang CL, Wu YT. Effect of exercise on physical function, daily living activities, and quality of life in the frail older adults: A meta-analysis. Arch Phys Med Rehabil 2012;93:237–244.
134. de Labra C, Guimaraes-Pinheiro C, Maseda A, et al. Effects of physical exercise interventions in frail older adults: A systematic review of randomized controlled trials. BMC Geriatr 2015;15:154.
135. Raymond MJ, Bramley-Tzerefos RE, Jeffs KJ, et al. Systematic review of high-intensity progressive resistance strength training of the lower limb compared with other intensities of strength training in older adults. Arch Phy Med Rehabil 2013;94:1458–1472.
136. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exer 2009;41:1510–1530.
137. Schreier MM, Bauer U, Osterbrink J, et al. Fitness training for the old and frail. Effectiveness and impact on daily life coping and self-care abilities. Zeitschrift fur Gerontologie und Geriatrie 2016;49:107–114.
138. Oh SL, Kim HJ, Woo S, et al. Effects of an integrated health education and elastic band resistance training program on physical function and muscle strength in community-dwelling elderly women–Healthy Aging and Happy Aging II. study. Geriatr Gerontol Int 2017;17:825–833.
139. Forti LN, Van Roie E, Njemini R, et al. Load-specific inflammation mediating effects of resistance training in older persons. J Am Med Dir Assoc 2016;17: 547–552.
140. Chung CL, Thilarajah S, Tan D. Effectiveness of resistance training on muscle strength and physical function in people with Parkinson's disease: A systematic review and meta-analysis. Clin Rehabil 2016;30:11–23.
141. Fiatarone Singh MA, Gates N, Saigal N, et al. The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: A randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc 2014;15:873–880.
142. Liu CJ, Latham N. Can progressive resistance strength training reduce physical disability in older adults? A meta-analysis study. Disabil Rehabil 2011;33: 87–97.
143. Cadore EL, Moneo AB, Mensat MM, et al. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. Age (Dordrecht, Netherlands) 2014;36:801–811.
144. Singh NA, Quine S, Clemson LM, et al. Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: A randomized controlled trial. J Am Med Dir Assoc 2012;13:24–30.
145. Steib S, Schoene D, Pfeifer K. Dose-response relationship of resistance training in older adults: A meta-analysis. Med Sci Sports Exer 2010;42: 902–914.
146. Landi F, Marzetti E, Martone AM, et al. Exercise as a remedy for sarcopenia. Curr Opin Clin Nutri Metab Care 2014;17:25–31.
147. Hagstrom AD, Marshall PW, Lonsdale C, et al. Resistance training improves fatigue and quality of life in previously sedentary breast cancer survivors: A randomised controlled trial. Eur J Cancer Care 2016;25:784–794.
148. Liu JY, Lai CK, Siu PM, et al. An individualized exercise programme with and without behavioural change enhancement strategies for managing fatigue among frail older people: A quasi-experimental pilot study. Clin Rehabil 2016;31:521–531.
149. Franklin BA, Whaley MH, Howley ET, Balady GJ. ACSM's Guidelines for Exercise Testing and Prescription. 9th ed. 2013. Philadelphia, Pa: Lippincott Williams & Wilkins.
150. Bray NW, Smart RR, Jakobi JM, Jones GR. Exercise prescription to reverse frailty. Appl Physiol Nutri Metab 2016;41:1112–1116.
151. Thiebaud RS, Funk MD, Abe T. Home-based resistance training for older adults: A systematic review. Geriatr Gerontol Int 2014;14:750–757.
152. Thomas S, Mackintosh S, Halbert J. Does the 'Otago exercise programme' reduce mortality and falls in older adults?: A systematic review and meta-analysis. Age Ageing 2010;39:681–687.
153. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. JAMA 2014;311:2387–2396.
154. Jefferis BJ, Merom D, Sartini C, et al. Physical activity and falls in older men: The critical role of mobility limitations. Med Sci Sports Exercise 2015;47: 2119–2128.
155. Izquierdo M, Rodriguez-Manas L, Casas-Herrero A, et al. Is it ethical not to precribe physical activity for the elderly frail? J Am Med Dir Assoc 2016;17: 779–781.
156. Santanasto AJ, Glynn NW, Lovato LC, et al; LIFE Study Group. Effect of physical activity versus health education on physical function, grip strength and mobility. J Am Geriatr Soc 2017 Feb 21 [Epub ahead of print].
157. Manini TM, Beavers DP, Pahor M, et al; LIFE study investigators. Effect of physical activity on self-reported disability in older adults: Results from the LIFE Study. J Am Geriatr Soc 2017;65:980–988.
158. Freiberger E, Blank WA, Salb J, et al. Effects of a complex intervention on fall risk in the general practitioner setting: A cluster randomized controlled trial. Clin Intervent Aging 2013;8:1079–1088.
159. Freiberger E, Kemmler W, Siegrist M, Sieber C. Frailty and exercise interventions: Evidence and barriers for exercise programs. Zeitschrift fur Gerontologie und Geriatrie 2016;49:606–611.
160. de Souto Barreto P, Morley JE, Chodzko-Zajko W, et al. Recommendations on physical activity and exercise for older adults living in long-term care facilities: A taskforce report. J Am Med Dir Assoc 2016;17:381–392.
161. Hawley-Hague H, Horne M, Campbell M, et al. Multiple levels of influence on older adults' attendance and adherence to community exercise classes. Gerontologist 2014;54:599–610.
162. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 2012;65:989–995.
163. Rolland Y, Morley JE. Editorial: Frailty and polypharmacy. J Nutr Health Aging 2016;20:645–646.
164. Flaherty JH, Perry HM III, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. J Gerontol A Biol Sci Med Sci 2000; 55:M554–M559.
165. Bronskill SE, Gill SS, Paterson JM, et al. Exploring variation in rates of polypharmacy across long term care homes. J Am Med Dir Assoc 2012;13:309. e15–309.e21.
166. Moulis F, Moulis G, Balardy L, et al. Searching for a polypharmacy threshold associated with frailty. J Am Med Dir Assoc 2015;16:259–261.
167. Resnick B, Pacala JT. 2012 Beers Criteria. J Am Geriatr Soc 2012;60:612–613.
168. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging de fi nition of 'deprescribing' with network analysis: Implications for future research and clinical practice. Br J Clin Pharmacol 2015;80:1254–1268.
169. Frank C, Weir E. Deprescribing for older patients. CMAJ 2014;186:1369–1376.
170. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in frail older people: A randomised controlled trial. PLoS One 2016;11:e0149984.
171. Tjia J, Velten SJ, Parsons C, et al. Studies to reduce unnecessary medication use in frail older adults: A systematic review. Drugs Aging 2013;30:285–307.
172. Hamilton H, Gallagher P, Ryan C, et al. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med 2011;171:1013–1019.
173. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age Ageing 2015;44: 213–218.
174. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Therapeut 2008;46:72–83.
175. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: A national consensus panel. CMAJ 1997;156:385–391.
176. Lund BC, Carnahan RM, Egge JA, et al. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother 2010;44:957–963.
177. Basger BJ, Chen TF, Moles RJ. Inappropriate medication use and prescribing indicators in elderly Australians: Development of a prescribing indicators tool. Drugs Aging 2008;25:777–793.
178. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: A real need to deprescribe in older patients. Med J Australia 2014;201:390–392.
179. Page AT, Etherton-Beer CD, Clifford RM, et al. Deprescribing in frail older people—Do doctors and pharmacists agree? RSAP 2016;12:438–449.
180. Tang NKY, Lereya ST, Boulton H, et al. Nonpharmacological treatments of insomnia for long-term painful conditions: A systematic review and meta-analysis of patient-reported outcomes in randomized controlled trials. Sleep 2015;38:1751–1764.

181. Basunia M, Fahmy SA, Schmidt F, et al. Relationship of symptoms with sleep-stage abnormalities in obstructive sleep apnea-hypopnea syndrome. J Commun Hosp Intern Med Perspect 2016;6:32170.
182. Stadje R, Dornieden K, Baum E, et al. The differential diagnosis of tiredness: A systematic review. BMC Fam Pract 2016;17:147.
183. Taylor WD. Clinical practice. Depression in the elderly. N Engl J Med 2014; 371:1228–1236.
184. Dominguez LJ, Bevilacqua M, Dibella G, Barbagallo M. Diagnosing and managing thyroid disease in the nursing home. J Am Med Dir Assoc 2008;9:9–17.
185. Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: Clinical picture and radiological findings. Nutrients 2013;5:4521–4539.
186. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007;55:780–791.
187. Vitiello MV, McCurry SM, Shortreed SM, et al. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. Pain 2014; 155:1547–1554.
188. Lakey SL, LaCroix AZ, Gray SL, et al. Antidepressant use, depressive symptoms, and incident frailty in women aged 65 and older from the Women's Health Initiative Observational Study. J Am Geriatr Soc 2012;60:854–861.
189. Morley JE, Malmstrom TK, Rodriguez-Manas L, Sinclair AJ. Frailty, sarcopenia and diabetes. J Am Med Dir Assoc 2014;15:853–859.
190. Morley JE. Anorexia, weight loss, and frailty. J Am Med Dir Assoc 2010;11: 225–228.
191. Morley JE. Undernutrition in older adults. Fam Pract 2012;29:i89–i93.
192. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev 2009:Cd003288.
193. Milne AC, Avenell A, Potter J. Meta-analysis: Protein and energy supplementation in older people. Ann Intern Med 2006;144:37–48.
194. Wright OR, Connelly LB, Capra S, Hendrikz J. Determinants of foodservice satisfaction for patients in geriatrics/rehabilitation and residents in residential aged care. Health Expectations 2013;16:251–265.
195. Collins J, Porter J. The effect of interventions to prevent and treat malnutrition in patients admitted for rehabilitation: A systematic review with meta-analysis. J Human Nutri Dietetics 2015;28:1–15.
196. Bounoure L, Gomes F, Stanga Z, et al. Detection and treatment of medical inpatients with or at-risk of malnutrition: Suggested procedures based on validated guidelines. Nutrition 2016;32:790–798.
197. Beck AM, Dent E, Baldwin C. Nutritional intervention as part of functional rehabilitation in older people with reduced functional ability: A systematic review and meta-analysis of randomised controlled studies. J Hum Nutr Diet 2016;29:733–745.
198. Beck AM, Holst M, Rasmussen HH. Oral nutritional support of older (65 years+) medical and surgical patients after discharge from hospital: Systematic review and meta-analysis of randomized controlled trials. Clin Rehabil 2013;27:19–27.
199. Fukagawa NK. Protein and amino acid supplementation in older humans. Amino Acids 2013;44:1493–1509.
200. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: A randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2015;16:740–747.
201. Cramer JT, Cruz-Jentoft AJ, Landi F, et al. Impacts of high-protein oral nutritional supplements among malnourished men and women with sarcopenia: A multicenter, Randomized, Double-Blinded, Controlled Trial. J Am Med Dir Assoc 2016;17:1044–1055.
202. Morley JE, Argiles JM, Evans WJ, et al. Nutritional recommendations for the management of sarcopenia. J Am Med Dir Assoc 2010;11:391–396.
203. Paddon-Jones D, Short KR, Campbell WW, et al. Role of dietary protein in the sarcopenia of aging. Am J Clin Nutr 2008;87:1562s–1566s.
204. Bauer J, Biolo G, Cederholm T, et al. Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14:542–559.
205. Ng TP, Feng L, Nyunt MS, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. The American journal of medicine 2015;128: 1225–1236.e1.
206. Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: A randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2012;13:720–726.
207. Kim HK, Suzuki T, Saito K, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: A randomized controlled trial. J Am Geriatr Soc 2012;60:16–23.
208. Cesari M, Landi F, Calvani R, et al. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. Aging Clin Exp Res 2017;29:81–88.
209. Landi F, Cesari M, Calvani R, et al. The "Sarcopenia and Physical fRailty IN older people: Multicomponent Treatment strategies" (SPRINTT) randomized controlled trial: Design and methods. Aging Clin Exp Res 2017;29:89–100.
210. Bauer JM, Kaiser MJ, Anthony P, et al. The Mini Nutritional Assessment—Its history, today's practice, and future perspectives. Nutr Clin Pract 2008;23:388–396.
211. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): A practical tool for identification of nutritional status. J Nutr Health Aing 2009;13:782–788.
212. Stratton RJ, Hackston A, Longmore D, et al. Malnutrition in hospital outpatients and inpatients: Prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. Br J Nutr 2004;92: 799–808.
213. Chang HH, Tsai SL, Chen CY, Liu WJ. Outcomes of hospitalized elderly patients with geriatric syndrome: Report of a community hospital reform plan in Taiwan. Arch Gerontol Geriatr 2010;50:S30–S33.
214. Chan M, Lim YP, Ernest A, Tan TL. Nutritional assessment in an Asian nursing home and its association with mortality. J Nutr Health Aging 2010; 14:23–28.
215. Tsai AC, Yang SF, Wang JY. Validation of population-specific Mini-Nutritional Assessment with its long-term mortality-predicting ability: Results of a population-based longitudinal 4-year study in Taiwan. Br J Nutr 2010;104: 93–99.
216. Tsai AC, Chang TL, Wang JY. Short-form Mini-Nutritional Assessment with either BMI or calf circumference is effective in rating the nutritional status of elderly Taiwanese–Results of a national cohort study. Br J Nutr 2013;110: 1126–1132.
217. Chao PC, Chuang HJ, Tsao LY, et al. The Malnutrition Universal Screening Tool (MUST) and a nutrition education program for high risk cancer patients: Strategies to improve dietary intake in cancer patients. BioMedicine 2015;5: 17.
218. Wilson MM, Thomas DR, Rubenstein LZ, et al. Appetite assessment: Simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. Am J Clin Nutr 2005;82:1074–1081.
219. Leung RY, Cheung BM, Nguyen US, et al. Optimal vitamin D status and its relationship with bone and mineral metabolism in Hong Kong Chinese. Bone 2017;97:293–298.
220. Bolland MJ, Grey A, Cundy T. Vitamin D and health in adults in Australia and New Zealand: A position statement. Med J Australia 2012;197:553. author reply-4.
221. Wahlqvist ML. Vitamin D in North-East Asian clinical nutrition practice. Asia Pac J Clin Nutr 2013;22:166–169.
222. Nowson CA, McGrath JJ, Ebeling PR, et al. Vitamin D and health in adults in Australia and New Zealand: A position statement. Med J Australia 2012;196: 686–687.
223. Jayaratne N, Hughes MC, Ibiebele TI, et al. Vitamin D intake in Australian adults and the modeled effects of milk and breakfast cereal fortification. Nutrition 2013;29:1048–1053.
224. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88: 5766–5772.
225. Tieland M, Brouwer-Brolsma EM, Nienaber-Rousseau C, et al. Low vitamin D status is associated with reduced muscle mass and impaired physical performance in frail elderly people. Eur J Clin Nutr 2013;67:1050–1055.
226. Wong YY, McCaul KA, Yeap BB, et al. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: The Health in Men Study. J Clin Endocrinol Metab 2013;98:3821–3828.
227. Flicker L, Mead K, MacInnis RJ, et al. Serum vitamin D and falls in older women in residential care in Australia. J Am Geriatr Soc 2003;51: 1533–1538.
228. Shimizu Y, Kim H, Yoshida H, et al. Serum 25-hydroxyvitamin D level and risk of falls in Japanese community-dwelling elderly women: A 1-year follow-up study. Osteoporosis Int 2015;26:2185–2192.
229. Zhou J, Huang P, Liu P, et al. Association of vitamin D deficiency and frailty: A systematic review and meta-analysis. Maturitas 2016;94:70–76.
230. Artaza-Artabe I, Saez-Lopez P, Sanchez-Hernandez N, et al. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016;93:89–99.
231. Halfon M, Phan O, Teta D, Vitamin D. A review on its effects on muscle strength, the risk of fall, and frailty. BioMed Res Int 2015;2015:953241.
232. Wong YY, Flicker L. Hypovitaminosis D and frailty: Epiphenomenon or causal? Maturitas 2015;82:328–335.
233. Bruyere O, Cavalier E, Buckinx F, Reginster JY. Relevance of vitamin D in the pathogenesis and therapy of frailty. Curr Opin Clin Nutr Metab Care 2017;20: 26–29.
234. Song HR, Kweon SS, Choi JS, et al. High prevalence of vitamin D deficiency in adults aged 50 years and older in Gwangju, Korea: The Dong-gu Study. J Korean Med Sci 2014;29:149–152.
235. Zhen D, Liu L, Guan C, et al. High prevalence of vitamin D deficiency among middle-aged and elderly individuals in northwestern China: Its relationship to osteoporosis and lifestyle factors. Bone 2015;71:1–6.
236. van Schoor NM, Lips P. Worldwide vitamin D status. Best practice and research Clin Endocrinol Metab 2011;25:671–680.
237. Bacon CJ, Kerse N, Hayman KJ, et al. Vitamin D status of Maori and non-Maori octogenarians in New Zealand: A Cohort Study (LiLACS NZ). Asia Pac J Clin Nutr 2016;25:885–897.
238. G R, Gupta A. Vitamin D deficiency in India: Prevalence, causalities and interventions. Nutrients 2014;6:729–775.

239. Chan R, Chan CC, Woo J, et al. Serum 25-hydroxyvitamin D, bone mineral density, and non-vertebral fracture risk in community-dwelling older men: Results from Mr. Os, Hong Kong. Arch Osteoporosis 2011;6:21–30.
240. Chin KY, Ima-Nirwana S, Ibrahim S, et al. Vitamin D status in Malaysian men and its associated factors. Nutrients 2014;6:5419–5433.
241. Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080s–1086s.
242. Cancer Council of Australia. Position statement—Sun exposure and vitamin D - risks and benefits. Available at: http://wiki.cancer.org.au/policy/Position_statement_-_Risks_and_benefits_of_sun_exposure; 2017. Accessed January 16, 2017.
243. Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, Seibel MJ, Mason RS. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Australia 2012;196:686–687.
244. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991–2000.
245. Nair R, Maseeh A, Vitamin D. The "sunshine" vitamin. J Pharmacol Pharmacotherapeut 2012;3:118–126.
246. Annweiler C, Schott AM, Berrut G, et al. Vitamin D-related changes in physical performance: A systematic review. J Nutr Health Aging 2009;13:893–898.
247. Dix CF, Robinson A, Bauer JD, Wright ORL. Vitamin D: Australian dietitian's knowledge and practices. Nutr Diet 16 Jun 2016 [Epub ahead of print].
248. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: A systematic review and meta-analysis. J Am Geriatr Soc 2011;59:2291–2300.
249. Sanders KM, Seibel MJ. Therapy: New findings on vitamin D3 supplementation and falls—When more is perhaps not better. Nat Rev Endocrinol 2016;12:190–191.
250. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. JAMA 2010;303:1815–1822.
251. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: A randomized clinical trial. JAMA Intern Med 2016;176:175–183.
252. Rosendahl-Riise H, Spielau U, Ranhoff AH, et al. Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: A systematic review and meta-analysis. J Hum Nutri Diet 2016;30:3–15.
253. Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: Patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab 2012;97:2670–2681.
254. Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: A systematic review. J Am Geriatr Soc 2003;51:1219–1226.
255. Cameron ID, Gillespie LD, Robertson MC, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev 2012:Cd005465.
256. Chan R, Chan D, Woo J, et al. Not all elderly people benefit from vitamin D supplementation with respect to physical function: Results from the Osteoporotic Fractures in Men Study, Hong Kong. J Am Geriatr Soc 2012;60:290–295.
257. Beard JR, Officer A, de Carvalho IA, et al. The World report on ageing and health: A policy framework for healthy ageing. Lancet 2016;21:2145–2154.
258. Holroyd-Leduc J, Resin J, Ashley L, et al. Giving voice to older adults living with frailty and their family caregivers: Engagement of older adults living with frailty in research, healthcare decision making, and in health policy. Res Involvement Engagement 2016;2:23.
259. Baillie L, Gallini A, Corser R, et al. Care transitions for frail, older people from acute hospital wards within an integrated healthcare system in England: A qualitative case study. Int J Integrated Care 2014;14:e009.
260. Parsons JG, Sheridan N, Rouse P, et al. A randomized controlled trial to determine the effect of a model of restorative home care on physical function and social support among older people. Arch Phys Med Rehabil 2013;94:1015–1022.
261. Senior HE, Parsons M, Kerse N, et al. Promoting independence in frail older people: A randomised controlled trial of a restorative care service in New Zealand. Age Ageing 2014;43:418–424.
262. Manderson B, McMurray J, Piraino E, Stolee P. Navigation roles support chronically ill older adults through healthcare transitions: A systematic review of the literature. Health Soc Care Commun 2012;20:113–127.
263. Cameron ID, Fairhall N, Langron C, et al. A multifactorial interdisciplinary intervention reduces frailty in older people: Randomized trial. BMC Med 2013;11:65.
264. Fairhall N, Sherrington C, Cameron ID, et al. A multifactorial intervention for frail older people is more than twice as effective among those who are compliant: Complier average causal effect analysis of a randomised trial. J Physiother 2017;63:40–44.
265. Metzelthin SF, van Rossum E, de Witte LP, et al. The reduction of disability in community-dwelling frail older people: Design of a two-arm cluster randomized controlled trial. BMC Public Health 2010;10:511.
266. Muntinga ME, Hoogendijk EO, van Leeuwen KM, et al. Implementing the chronic care model for frail older adults in The Netherlands: Study protocol of ACT (frail older adults: Care in transition). BMC Geriatr 2012;12:19.
267. Bleijenberg N, Drubbel I, Ten Dam VH, et al. Proactive and integrated primary care for frail older people: Design and methodological challenges of the Utrecht primary care PROactive frailty intervention trial (U-PROFIT). BMC Geriatr 2012;12:16.
268. Hoogendijk EO. How effective is integrated care for community-dwelling frail older people? The case of The Netherlands. Age Ageing 2016;45:585–588.
269. Gagliardi AR, Alhabib S. Trends in guideline implementation: A scoping systematic review. Implement Sci 2015;10:54.
270. Cesari M, Prince M, Thiyagarajan JA, et al. Frailty: An emerging public health priority. J Am Med Dir Assoc 2016;17:188–192.