Introduction

Worldwide, the number of people age 60 and older is expected to grow from nearly 900 million in 2015 to over 1.3 trillion in 2030 (1). Increased age is associated with gradual increases in molecular and cellular damage; impairment of bodily functions; decreased muscle mass and strength; loss of bone density; declining vision, hearing and cognition; multimorbidity; and frailty (2). Frailty has been conceptualized as a physiological syndrome of decreased reserve and resilience, resulting in progressive functional decline, increased vulnerability to many stressors, and an increase in negative health outcomes and dependence (3, 4). It has been recognized by the World Health Organization (2) and the U.S. National Academy of Sciences (5) as a major public health concern among the elderly, although consensus on a definition of frailty remains elusive (6). Nonetheless, research suggests that disability and dependence in the elderly may be preventable by targeting frail and pre-frail older adults (3, 7, 8).

Defining Frailty

In 2001, Linda Fried and colleagues proposed that the frailty phenotype is characterized by a constellation of symptoms including weakness, low energy, slow walking speed, low physical activity, and weight loss (9). Using this definition, older adults may be categorized into three groups along the disablement pathway (10): robust, frail or pre-frail, and dependent (Figure 1). Prevalence studies in several different populations have concluded that among those older than 65 years, approximately 50% are robust, 35-40% are frail or pre-frail, and 5-10% are dependent (11-13). Further studies have demonstrated that frailty and comorbidity are associated with increased hospital healthcare resource use and related costs (14).

The frailty syndrome results in a decline in many physiological systems, leading to increased vulnerability to loss of function following relatively minor illnesses such as urinary tract infections (4). The age-related loss of muscle mass and strength, known as sarcopenia, contributes to frailty (15), and loss of muscle mass has been shown to correlate with the risk of mortality in prefrail and frail older adults (16). Chronic inflammation has also been associated with both sarcopenia and frailty (17, 18). Physical frailty is also often associated with cognitive impairment, leading to the concept of “cognitive frailty” (19-22), which is associated with a high risk for developing dementia (23). Each of these physiologic contributors to frailty represents a potential therapeutic target.

Identifying frailty

Preventing frailty begins with identifying older persons at risk of becoming frail. In 2013, the Gérontopôle of Toulouse developed a screening tool to be implemented in primary care settings, the Gérontopôle Frailty Screening Tool (GFST) (24). This clinician-reported questionnaire asks six simple questions about whether the patient lives alone and has experienced weight loss, fatigue, mobility difficulties, memory problems, and gait speed. If any of these conditions are present, the questionnaire asks whether the clinician thinks the patient is frail and whether he or she is willing to be assessed at a frailty clinic. Other instruments developed to identify frail individuals include the Tilburg Frailty Indicator (TFI) (25), the Clinical Frailty Scale (CFS) (26), and the FiND (Frail, non-disabled) instrument, a self-reported questionnaire (27). In the future, biomarkers may also prove useful in the identification of frailty (28).

Also at the Gérontopôle in Toulouse, a Geriatric Frailty Clinic (GFC) was established in association with the University Department of General Medicine and the Midi-Pyrenees Regional Health Authority to support comprehensive and multidisciplinary assessment and management of frail older persons at an earlier stage of disability when it is still reversible. Among the first 1108 patients referred to the
GFC following screening by their primary care physician, 93.6% were determined to be frail or pre-frail and in need of intervention (29).

**Preventing frailty**

Prevention of frailty encompasses three overlapping approaches across the lifespan: First, increasing intrinsic capacity reserves in early aging; second, preserving function in late aging, and third, restoring function in frail older adults. These approaches reflect WHO’s concept of healthy aging as an interaction of intrinsic capacity and functional ability, with intrinsic capacity defined as the combination of an individual’s physical and mental capacity (2). In the first wave of the WHO Study on global AGEing and adult health (SAGE), they combined data from physical and cognitive assessments and biometric measures to document a gradual decline in intrinsic capacity across the adult lifespan (30).

Intrinsic capacity can be explained by a combination of genetic factors, behavior, environmental exposures, and social determinants such as availability of resources (31, 32). The fact that many of these factors are modifiable implies that intrinsic capacity may be improved. Indeed, abundant evidence suggests that increasing physical activity and improving nutrition offers protection against age-related physical and cognitive decline across the lifespan (2, 33, 34). One study suggested that a diet high in protein and anti-oxidants could prevent frailty (35). However, additional studies are needed to show that nutrition can postpone frailty in older persons (36). Recent technological improvements including the accelerometers, voice analysis, and other technologies built into smart phones and other devices now offer the means to monitor physical activity, diet, sleeping patterns, and mental states across the lifespan, thus encouraging self-management (37-39).

The third pillar of frailty prevention involves restoring function in persons identified as frail. Treatments range from non-pharmacological (40) to pharmacologic approaches (41) aimed at ameliorating the loss of skeletal mass and strength associated with sarcopenia and frailty and improving function, cognition, and well-being.

Non-pharmacologic interventions typically combined physical exercise with nutritional approaches. These interventions build on studies showing, for example, that in older populations, physical activity intervention programs improve health quality and function, reduce major mobility disability, and may delay frailty onset (42-44); and that adherence to the Mediterranean diet is associated with higher physical performance (45). Other studies have suggested benefits from specific nutrients. For example, vitamin D (46) and essential amino acid (EAA) supplementation (47) have been shown to improve function; and the leucine metabolite, beta-hydroxy-beta-methylbutyrate may increase muscle mass and strength (48). Prebiotics that alter the composition of the microbiota have also been shown to improve some frailty criteria (49). And another study showed that long-term tea consumption was associated with improved mental health in older persons (50). A number of multi-modal prevention programs have been built upon these and other observations. These include:

- The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) trial. This randomized controlled trial is testing a combined intervention of physical activity, nutritional counseling, and an information and communication technology intervention versus an educational program in older adults with physical frailty and sarcopenia (51).
- The Vitality, Independence, and Vigor 2 (VIVE2). This randomized controlled study demonstrated that a physical activity program improved mobility, with no additional benefit when combined with a nutritional supplement (52).
- The Vitamin D3, Omega-3, Home Exercise – HeALTHy Aging and Longevity Trial (DO-HEALTH) is a large healthy aging study of whether the combination of nutritional supplements and a home exercise program will promote healthy aging (http://do-health.eu).
- The Multi-domain Alzheimer’s Prevention Trial (MAPT). This randomized controlled study tested a multi-domain intervention combining nutrition, physical exercise, cognitive and social activities, and omega-3 polyunsaturated fatty acids in frail older adults at risk of cognitive decline (54).
- The Nolan trial is testing a Brain Protector Blend of nutritional supplements in older adults with memory complaints to see if it can improve cognition.

An improved understanding of the biological underpinnings of frailty and sarcopenia indicating changes in many physiologic systems including energy metabolism, muscle development, and hormonal and inflammatory functions (55) suggests several possible pharmacological approaches to treatment that are currently in development (41). These include a class of agents called myostatin inhibitors that promote muscle growth (56), androgens including testosterone (57), compounds called selective androgen receptor modulators (SARMs) that increase androgenic signaling (58), and anti-inflammatory compounds (59). Infusions of mesenchymal stem cells, which have potent anti-inflammatory properties, have also shown promise as a treatment for frailty (60).

**Conclusions**

There is an emerging consensus that preventing frailty in older adults could dramatically improve health outcomes and
quality of life, and enable a longer period of independent living. Integrated care offers perhaps the greatest opportunity for encouraging healthy aging across the lifecourse and preserving function in late aging. However, healthcare systems not currently not organized to deliver integrated care over the lifecourse, but rather to identify and treat acute illness. Change is needed at both the healthcare delivery and policy levels to emphasize integrated care across the lifecourse and to encourage health aging.

Conflict of Interests: None

References

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