PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2011) **366**, 113–119
doi:10.1098/rstb.2010.0287

Review

Drug discovery and development for ageing: opportunities and challenges

William J. Evans*

Muscle Metabolism DPU, Metabolic Pathways CEDD, GlaxoSmithKline, Research Triangle Park, 27709 NC, USA

The prevention and treatment of late-life dysfunction are the goals of most geriatricians and should be the primary target for discovery and development of new medicines for elderly people. However, the development of new medicines for elderly people will face a number of challenges that are not seen for other patient populations. The burdens of multiple chronic diseases, low physiological reserve and polypharmacy must result in new clinical trials in frail older people with a high expectation of safety and efficacy. The etiology of functional limitations in elderly people is complex and often ascribed to conditions that escape the traditional definition of disease. While our society urgently needs new treatments that can reduce the burden of physical decline among older persons, guidelines on how these treatments should be developed and tested are currently lacking, in part because a consensus has not yet been achieved regarding the identifiable target diseases. New potential indications included sarcopaenia, anorexia of ageing, frailty, mobility disability and reduced functional capacity secondary to hospitalization. The challenges to conducting clinical trials in the elderly should not offset the great opportunity for the development of new medicines to prevent or reverse age-associated changes in body composition and poor functional capacity in the elderly.

Keywords: sarcopaenia; functional capacity; elderly; geriatrics

The sixth age shifts
Into the lean and slipper'd pantaloon
With spectacles on nose and pouch on side,
His youthful hose well sav'd, a world too wide
For his shrunk shank; and his big manly voice,
Turning again toward childish treble, pipes
And whistles in his sound. Last scene of all,
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.
(Shakespeare, *As You Like It*, Act II, Scene VII, lines 157–166)

1. INTRODUCTION

Ageing is associated with an astonishing number of changes and adaptive responses. The challenge of scientists and clinicians has been to separate true biological ageing from genetic and environmental adaptations. For example, a reduction in lean body mass and an increase in fat mass are the most striking and consistent changes associated with advancing age, but the contribution of true biological ageing to these changes is small. Skeletal muscle [1] and bone mass are the principal (if not exclusive) components of lean body mass to decline with age. These changes in body composition appear to occur throughout life and have important functional and metabolic consequences. Loss of muscle and bone with age results from lifestyle, genetics and biological ageing, and an understanding of each of these components has allowed for new therapies to treat osteopaenia to prevent osteoporosis and will allow for the development of new medicines to treat the loss of skeletal muscle. Nathan Shock's [2,3] seminal studies describing age-related reductions in cardiac function, glomerular filtration rate, taste, smell and a wide variety of physiological functions confirmed what most scientists believed to be true about ageing. However, a closer examination of the data revealed that many, if not most, of the subjects in Shock's studies had a burden of chronic diseases and that much of the loss of function owing to age may have been the result of disease rather than age. Examination of elderly people who are free of chronic disease has allowed a better understanding of age-related changes in physiological function. The common view of ageing, reflected in Shakespeare's description, as an inevitable slide into oblivion is being replaced by a better understanding of those aspects of ageing that may be preventable. The prevention and treatment of late-life dysfunction are the goals of most geriatricians and should be the primary target for discovery and development of new medicines for elderly people. However, the development of these new medicines for elderly people will face a number of challenges that are not seen for other patient populations. The burdens of multiple

*william.j.evans@gsk.com

One contribution of 15 to a Discussion Meeting Issue 'The new science of ageing'.

chronic diseases, low physiological reserve and polypharmacy will, necessarily, result in design of new clinical trials in frail older people with a high expectation of safety and efficacy.

2. CHALLENGES

Declining functional capacity is common in older people and poor functional capacity is a powerful risk factor for a number of outcomes including hospitalization, nursing home admission, decreased cognitive function (including dementia and Alzheimer's disease), injurious falls and bone fracture. The aim of this manuscript is to discuss the opportunities and challenges for developing new medicines to treat geriatric patients or to prevent age-related changes that may result in late-life dysfunction and loss of independence.

It is generally recognized that geriatric patients have multiple co-morbid conditions and, as a result, interventions that target single diseases may have limited efficacy in this population. For example, a hypertensive older patient may have diminished renal function, insulin resistance and low levels of physical activity. Treating increased blood pressure has clear benefits but may have a limited (to no) effect on renal function, risk of diabetes, functional capacity or reduced physical activity. Thus, conducting a clinical trial in older individuals is intrinsically more difficult than in younger adults and may lead to disease-specific improvements that have little relevance for the life and well being of the individual. For this reason, it is crucial to consider the value of adding assessment of functional outcomes in randomized controlled trials (RCTs) involving older persons.

A substantial proportion of older persons with co-morbidity and frailty are often 'excluded' from clinical trials and effectiveness of most new treatments for chronic diseases that typically affect older persons is established in individuals who are substantially healthier than average age-matched individuals in the general population. As a consequence, when these new drugs are used in frail persons, those who most need new therapeutic options, unknown side effects are likely to emerge and the benefits evidenced in the original trials may not occur or may be not relevant in this population. In these complex patients, it is critical to know if the intervention has improved, or at least slowed decline, in functioning.

Functional and mobility limitations increase with advancing ageing. Many older people have difficulty in simple activities such as walking or standing from a chair, and cannot tolerate even light physical activity. The etiology of these functional limitations is complex and often ascribed to conditions that escape the traditional definition of disease, which is at the core of clinical medicine. While our society urgently needs new treatments that can reduce the burden of physical decline among older persons, guidelines on how these treatments should be developed and tested are currently lacking, in part because a consensus has not yet been achieved regarding the identifiable target diseases. The demographic imperative and resulting burgeoning in population morbidity can no longer be ignored and requires a substantial adaptation of the system of drug development. In simple words, while functional and mobility limitations are increasingly prevalent in older people, only a handful of clinical trials is underway to treat these problems.

The obvious challenge for many problems of ageing is that they do not fit well into the view of the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) for a treatable indication or condition. Almost all categories require that a disease, condition or syndrome, hereafter referred to simply as condition, be 'recognized' before an indication can be approved. According to the FDA, criteria to determine if a condition is recognized may come from professional organizations, from guidelines (like DSM IV), from Centers for Medicare and Medicaid Services (CMS) codes, Clinical Modification (i.e. ICD-9 CM) diagnostic codes or Current Procedural Terminology (CPT) codes. There are strong expectations that an extensive evidence base and a consensus of the clinical or scientific community support the existence of the condition, and that clear objective measures to document the presence of the condition are available and accessible to prescribers. To the extent that many problems of ageing have not been formally recognized by any of these processes, the FDA has no clear guidance on how to determine if a proposed indication would be acceptable. A number of conditions common in geriatric patients are both highly prevalent and treatable with the appropriate medicine or combination of medicine and lifestyle modification.

3. INVOLUNTARY WEIGHT LOSS, MALNUTRITION AND ANOREXIA

This may be the most clear potential indication for a common geriatric condition. Involuntary weight loss, poor appetite and poor nutritional status have been linked to increased morbidity and mortality among older people and particularly among institutionalized elderly people [4,5]. Involuntary weight loss and malnutrition are recognized as a treatable phenomenon by the CMS with a specific 'trigger' for when an intervention is appropriate [6]. A number of potentially correctable and treatable causes for this condition have been identified, such as swallowing problems, poor food quality and use of drugs that suppress appetite. However, ageing has been associated with a dysregulation in appetite and a number of elderly individuals suffering from involuntary weight loss may benefit from the use of an orexigenic agent [7]. Unfortunately, at the present time, no orexigenic agent is approved by the FDA to treat involuntary weight loss that is secondary to anorexia associated with ageing. Because poor appetite rather than food availability is the potential 'condition' for an FDA approved indication, providing nutritional supplements may be ineffective in the treatment of involuntary weight loss. The appetite stimulants that are currently available (although used 'off label') are either not very effective [7] or may stimulate appetite but not the accretion of lean body mass [8], which is the true desirable outcome, likely to have a positive effect on mobility, health and quality of life. Interestingly, although these two orexigenic medicines are approved to treat weight loss in patients with AIDS, their use is reimbursed by CMS, a strong indication on an unmet medical need.

In this case, there is a clear indication (anorexia leading to involuntary weight loss) that is associated with increased morbidity and mortality. This indication is well recognized by national professional organizations (American Dietetic Association, Gerontological Society of America and the American Medical Directors Association) with specific criteria for intervention. However, because there is no approved indication for anorexia of ageing, new potential agents that may stimulate appetite in this population of older patients may, at the discretion of the FDA, also need to demonstrate efficacy beyond increased appetite, food intake or body weight. This may include decreased mortality and/or improved functional capacity depending on the target population with this condition.

4. FRAILTY

Although there is broad consensus, even outside the geriatric community, that frailty is a true clinical entity, the precise definition of this complex geriatric condition remains elusive. The Fried definition [9] provides a much needed operationalized construct for frailty and has been an invaluable stimulus for research in this important area. This definition of frailty uses five criteria that include: weight loss (or loss of muscle), slow walking speed, exhaustion (or fatigue), muscle weakness and low level of physical activity. Some of the frailty criteria can be easily and objectively assessed by a healthcare professional, while others, such as exhaustion (or fatigue) and level of physical activity are more difficult to quantify. However well recognized the condition or syndrome of frailty may be, it is clear that the etiology and potential treatment are multi-factorial and complex [10,11]. Deficiencies in skeletal muscle defined on the basis of quantity (sarcopaenia), quality (force production/cross sectional area) and/or strength are important and validated components of frailty [12]. However, reduced food intake [13], inflammation, anaemia [14], vitamin D deficiency [15] and hormonal status [16] have also been suggested to play an important role in the etiology of frailty.

Although it is generally hypothesized that frailty is a final pathway with multiple etiologies, evidence is emerging that dysfunction of one or more of the critical mechanisms that maintain biological homeostasis and allow adaptation to stress underlies frailty. Thus, it is conceivable that new pharmacological targets for the treatment of frailty will emerge sometime in the future. However, the FDA considers frailty a problematic indication for a number of reasons, including the lack of clear consensus among clinicians and investigators on the definition of frailty, uncertainty about whether it is a treatable condition, and the absence of clear treatment goals. Primary endpoints for any clinical trial must be considered to be components of the condition or disease; however, the current operational definition by Fried *et al*. includes criteria that are difficult to measure or not well defined. For this reason, until the geriatric community provides a consensus on clearly defined and easily measured criteria, the condition of frailty will probably not be considered for an indication by the FDA.

5. SARCOPAENIA

Sarcopaenia has been defined as the age-related loss of skeletal muscle mass [17]. Sarcopaenia appears to be a universal phenomenon and has been linked to a number of conditions including weakness, mobility limitations [18], disability, low bone density [19,20] and increased mortality. Like osteopaenia, which is strongly associated with bone fracture risk, sarcopaenia was initially considered a putative risk factor of specific distal outcomes such as falls, disability, fatigue and low levels of physical activity. However, the influence of muscle on many of these factors is complex. While muscle mass is related to strength, it is by no means the only determinant of force production. Increased and decreased levels of physical activity have powerful effects on strength and functional capacity in older people that are not explained by changes in muscle mass alone. In older people, increased body fatness has been more strongly linked to low functional capacity than muscle mass [21]. Nonetheless, although several factors may play a role, muscle weakness [22] and sarcopaenia remain as extremely important determinants of low functional capacity in older people [23].

As with many conditions associated with advancing age, sarcopaenia results from a number of factors, each of which may affect the trajectory of loss of skeletal muscle mass. Low testosterone, oestrogen and growth hormone levels in elderly people have an effect on muscle mass. Protein intake [24], vitamin D status [25], physical activity [26] and inflammation [27] also have been demonstrated to influence muscle mass in elderly people. Older people with type 2 diabetes are weaker, have lower muscle mass and quality than age-matched controls [28]. These patients also lose muscle at almost twice the rate of elderly people without diabetes [29].

A specific criterion to better define sarcopaenia has been described [30] and used by a number of investigators examining prevalence and impact of sarcopaenia. This criterion of a muscle mass that is two standard deviations lower that the average for a 30 year old man or woman has high specificity and can be measured with some degree of precision in most clinical settings in the United States. Among men and women aged 65 years or older, the prevalence of sarcopaenia according to this definition is high and shows a striking increase with advancing age [31]. Using this criterion, Janssen *et al*. [32] estimated that sarcopaenia resulted in an estimated direct healthcare cost in the United States in 2000 of $18.5 billion ($10.8 billion in men, $7.7 billion in women), which represented about 1.5 per cent of total healthcare expenditures for that year. The widespread use of dual x-ray absorptiometry to measure bone density as a diagnostic criterion for risk of osteoporosis has provided an opportunity to use this instrument for the purpose of identifying individuals with sarcopaenia. Because skeletal muscle mass is a prominent determinant of lower functional capacity, perhaps, diagnostic criteria for sarcopaenia will employ the Baumgartner criterion coupled with an easy to measure functional tool associated with morbidity and mortality such as gait speed or chair stand time.

Sarcopaenia may be an indication that is particularly responsive to an anabolic stimulus. Bhasin *et al*. [33] have demonstrated that testosterone administration in men with low testosterone levels results in a significant increase in muscle size and a proportionate increase in strength in both young and elderly men.

Although condition, etiology, prevalence and consequences of sarcopaenia have been well described, there is little consensus on its prevention or treatment. Resistance exercise can stimulate large changes in muscle mass and strength in healthy [34], and frail older people [35]; however, no consensus exists on pharmacological or nutritional treatment for this condition. The FDA or EMEA may not consider sarcopaenia itself as an indication at this time. First, its direct association with functional status and quality of life outcomes is complex and still being researched. Second, no professional organization has issued a position statement concerning sarcopaenia as a treatable condition. Because of this apparent lack of interest, concern, or consensus from professional organizations dealing with geriatric syndromes or conditions, the FDA and EMEA have little evidence that the medical or geriatric community has a cohesive view of sarcopaenia as a treatable geriatric condition. Recently, a consensus panel arrived at a definition for the diagnosis of sarcopaenia.

6. SARCOPENIC OBESITY

As stated, sarcopaenia is an important predictor of a number of outcomes in geriatrics, however, sarcopaenia and increased body fatness are an even more powerful risk factor for late-life disability [36,37]. Age and obesity are associated with increased levels of intra-myocellular lipid, which decreases muscle force production [38] and insulin sensitivity [39]. In addition, body fatness is an independent predictor of disability in elderly people. Zoico *et al*. [37] showed that older people with a BMI over 30 and low muscle mass had a three to four times increased risk of functional limitations as those with a lower BMI. They concluded that obesity was strongly associated with self-reported physical functional health, equivalent to being 11 years older for men and 16 years for women. However powerful a risk factor obesity may be in older people, weight loss is associated with an increased mortality risk [40]. Weight loss, whether intentional or unintentional results in accelerated loss of bone density and muscle mass resulting in increased fall and fracture risk [41]. There is a need for development of medicines to preserve bone and muscle mass during weight loss in elderly people. This represents both a challenge and an opportunity to meet an unmet medical need.

7. MOBILITY LIMITATION SECONDARY TO MUSCLE WEAKNESS

Limited mobility is perhaps the strongest predictor of morbidity and mortality in older persons, and one of the most important contributors to quality of life. Measurements of functional capacity have been employed to examine this condition and the proceedings of a previous meeting with the FDA [42] outlined the importance of these measures for the examination of indication for any drug that targets muscle mass, weakness or low functional capacity. Mobility limitations and weakness are easy to measure in geriatric patients, and both clinicians and patients understand their importance. Mobility limitation could potentially be accepted by the FDA and EMEA because it is widely recognized as an important geriatric condition, is measured with instruments that have good validity, reliability and sensitivity to change, has been well documented as to its relation to multiple adverse outcomes in older persons, and has been studied as to how it relates to clinically meaningful change. As for other potential indications described, the etiology for limited mobility is generally considered multi-factorial, including sarcopaenia and/or increased body fatness, balance disorders, joint pain and arthritis, cognitive impairment, anaemia and poor vision. However, there is increasing evidence that these risk factors tend to be related and to occur jointly in the same individuals and that they are all related to a common pathophysiological mechanism. Again, signalling molecules that contribute to the stability of the homeostatic network are the most probable candidates and may soon become targets for the treatment of mobility problems in older persons.

8. HOSPITALIZATION AND/OR INSTITUTIONALIZATION

Going to bed is a common response to an illness, but one that can cause other unwanted side effects. A patient admitted to a hospital is assigned a bed where almost all of his or her time is spent. As Harper & Lyles [43] point out, 'Staying in bed legitimizes an illness, and for many ill patients, bed is the most comfortable place. Consequently, adverse effects of bed rest remain common clinical problems.' Bed rest amplifies degenerative responses that are common to ageing. Thus, bed rest causes loss of skeletal muscle mass and strength, increased loss of nitrogen and calcium, increased insulin resistance and loss of balance even in young healthy volunteers. The consequences of bed rest on individuals with a decreased physiological reserve, such as the elderly, are neither well studied nor understood. There are a number of reasons why a patient may need to remain in bed during illness or as part of recovery from trauma or surgery; however, bed rest will always result in adverse metabolic and functional consequences. Hospitalized elderly patients show a significant and substantial decrease in activities of daily living (ADL) [44] and the percentage of patients showing this decrease in ADL increase with advancing age. Elderly people are the most likely to be placed in bed because of illness, trauma, loss of balance or increasingly because of a greatly diminished functional capacity. Very often, the most frail and medically compromised individual is placed in bed for extremely long periods of time. US national statistics show that increasing age is associated with a longer average length of stay in a hospital, and patients above the age of 65 years account for more than 35 per cent of

all hospital discharges [45]. Equally important, almost half of elderly patients are not discharged to go to their homes; rather, they are sent to another institution for what is termed 'rehabilitation', but often is a short or a long stay at a nursing home. The US national average length of stay in a hospital increases dramatically with advancing age, by an average of more than 6 days for those between 65 and 80 years old when compared with those aged 20–50 years. There are regional differences; for example, average length of stay in the northeastern US is approximately 40 per cent greater than that of the western US. These data also differ by diagnosis. Diabetes as a co-morbid disease increases the length of stay by about 30 per cent [45]. A recent report titled 'Loss of independence in activities of daily living in older adults hospitalized with medical illness: increased vulnerability with age' by Convinsky *et al.* [44] showed that 35 per cent of patients over the age of 70 years had a decline in ADL function as a result of hospitalization. While age was not strongly related with ADL prior to admission, it was strongly associated with ADL decline as a result of a hospital stay. The investigators concluded that the oldest patients are at 'particularly high risk of poor functional outcomes' because they are very likely to develop new functional deficits as a direct result of hospitalization.

Kortebein *et al.* [46] examined the effect of 10 days bed rest in elderly people. This study showed that prolonged bed rest resulted in a substantial loss of muscle from the legs (approx. 1 kg) that was associated with a 30 per cent decrease in the rate of muscle protein synthesis, increased hepatic and peripheral insulin resistance, and profoundly negative nitrogen balance. These subjects also showed an average 15 per cent loss of maximal aerobic capacity, decreased strength and a large decrease in levels of physical activity [47]. This study represents the 'best case' in that the older people in this study were uncompromised by disease or trauma and were provided (and consumed) a diet containing the recommended dietary allowance for macro and micronutrients. Young, healthy subjects respond to 28 days of bed rest with an average loss of about 400 g of muscle from the legs. The health and vitality of elders are too often severely compromised by hospitalization and prolonged inactivity and, even though the medical condition may have been resolved, they leave the hospital severely deconditioned, weak, orthostatically intolerant and diabetic. The care and treatment of elderly hospitalized patients represent an important challenge for the clinician to maintain nutritional status and prevent loss of function because poor nutritional and functional statuses are such powerful predictors of rehospitalization, admissions to long-term care facilities, and mortality [13,48,49].

9. NEED FOR BIOMARKERS

Biomarkers for disease progression among geriatric patients are few. However, recognition by clinicians of the extreme vulnerability of elderly patients may be a critical first step. For instance, Sullivan *et al.* [48] reported that 21 per cent of patients over the age of 65 years were provided with less than 50 per cent of their energy requirements. These patient lost weight and their risk of pre-mature mortality and rehospitalization was substantially greater than those patients with similar age and nutritional status at admission who were fed an adequate amount of calories. The principal reason for this lack of food provided to these patients was that physicians simply forgot to remove 'NPO' (nothing by mouth) from their admission orders. Functional capacity is easy to measure and should be considered to be a vital sign for geriatric patients. This will allow healthcare professionals to more closely monitor small changes that may be an early signal of a long-term problem.

10. CONCLUSIONS

The list of potential indications that might be considered by regulators for geriatric patients is by no means exhaustive. However, reliance on current regulations related to approval of medicines for conditions commonly seen in geriatric patients would mean that none can be considered as fully acceptable as an indication for drug approval. Continued discussions with regulators about the issues related to geriatrics with an emphasis on preservation of functional capacity are critical. At the same time, geriatrics researchers must become fully aware of the evidence needed by the regulators to develop a new approach to drug indications and begin to work towards these new indications.

While mortality may be an important endpoint for a number of diseases and conditions, most geriatricians consider improved functional capacity and independence as preferred endpoints for their elderly patients. A number of potential treatments for weakness and low functional capacity in elderly people are currently in development. These new treatments must be coupled with indications that are specific to the mechanism of action and conditions that are also specific to geriatric patients. Clearly, the important and daunting task of evaluating effectiveness and safety for any new indication (and its treatment) fall on the FDA and the EMEA. However, there is also an important task that must be addressed by the community of clinicians and scientists who are involved in the treatment and investigation of factors associated with frailty and poor function: coming to a consensus of what constitutes an indication and the specific criteria for the identification of any treatable condition and developing appropriate outcome measures. Consideration of drug–drug interactions will also be of critical importance in advancing new medicines targeted towards geriatric patients.

In the past, changes in the approach to diagnosis and treatment of traditional diseases has opened the door for new therapies for the treatment and prevention of osteopaenia (bone density), heart disease (cholesterol lowering), type 2 diabetes (insulin sensitizing agents) and many others. As new therapeutic targets are identified and new agents are developed that specifically address functional problems in older persons, new approaches to drug testing and approval will be needed. A close partnership between the FDA, EMEA and the 'geriatric' community is essential for this transformation to take place.

Finally, while Shakespeare was able to describe the prevailing notions of ageing, he also expressed what our goals should be for the development of new medicines to treat elderly people:

> Though I look old, yet I am strong and lusty;
> For in my youth I never did apply
> Hot and rebellious liquors in my blood
> Nor did not with unbashful forehead woo
> The means of weakness and debility;
> Therefore my age is as a lusty winter,
> Frosty, but kindly. Let me go with you;
> I'll do the service of a younger man
> In all your business and necessities.
> (Shakespeare, *As you like it*, Act II, Scene III, lines 46–55)

REFERENCES

1 Tzankoff, S. P. & Norris, A. H. 1978 Longitudinal changes in basal metabolic rate in man. *J Appl Physiol.* **33**, 536–539.
2 Falzone Jr, J. A. & Shock, N. W. 1956 Physiological limitations and age. *Public Health Rep.* **71**, 1185–1193.
3 Brandfonbrener, M., Landowne, M. & Shock, N. W. 1955 Changes in cardiac output with age. *Circulation* **12**, 557–566.
4 Morley, J. E. 2003 Anorexia and weight loss in older persons. *J. Gerontol. A Biol. Sci. Med. Sci.* **58**, M131–M137. (doi:10.1093/gerona/58.2.M131)
5 Thomas, D. R., Verdery, R. B., Gardner, L., Kant, A. & Lindsay, J. 1991 A prospective study of outcome from protein-energy malnutrition in nursing home residents. *J. Parenter. Enter. Nutr.* **15**, 400–404. (doi:10.1177/0148607191015004400)
6 Thomas, D. R., Ashmen, W., Morley, J. E. & Evans, W. J. 2000 Nutritional management in long-term care: development of a clinical guideline. *J. Gerontol. Med. Sci.* **55A**, M725–M734. (doi:10.1093/gerona/55.12.M725)
7 Morley, J. E. 2002 Orexigenic and anabolic agents. *Clin. Geriatr. Med.* **18**, 853–866. (doi:10.1016/S0749-0690(02)00036-8)
8 Evans, W. J. 2007 Editorial: megestrol acetate use for weight gain should be carefully considered. *J. Clin. Endocrinol. Metabol.* **92**, 420–421. (doi:10.1210/jc.2006-2734)
9 Fried, L. P. *et al.* 2001 Frailty in older adults: evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **56**, M146–M157. (doi:10.1093/gerona/56.3.M146)
10 Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D. & Anderson, G. 2004 Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J. Gerontol. A Biol. Sci. Med. Sci.* **59**, M255–M263. (doi:10.1093/gerona/56.3.M255)
11 Walston, J. 2004 Frailty–the search for underlying causes. *Sci. Aging Knowl. Environ.* **2004**, e4. (doi:10.1126/sageke.2004.4.pe4)
12 Cesari, M., Leeuwenburgh, C., Lauretani, F., Onder, G., Bandinelli, S., Maraldi, C., Guralnik, J. M., Pahor, M. & Ferrucci, L. 2006 Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *Am. J. Clin. Nutr.* **83**, 1142–1148.
13 Bartali, B., Frongillo, E. A., Bandinelli, S., Lauretani, F., Semba, R. D., Fried, L. P. & Ferrucci, L. 2006 Low nutrient intake is an essential component of frailty in older persons. *J. Gerontol. A Biol. Sci. Med. Sci.* **61**, 589–593.
14 Leng, S., Chaves, P., Koenig, K. & Walston, J. 2002 Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J. Am. Geriatr. Soc.* **50**, 1268–1271. (doi:10.1046/j.1532-5415.2002.50315.x)
15 Montero-Odasso, M. & Duque, G. 2005 Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. *Mol. Aspects Med.* **26**, 203–219.
16 Morley, J. E., Kim, M. J. & Haren, M. T. 2005 Frailty and hormones. *Rev. Endocr. Metab. Disord.* **6**, 101–108. (doi:10.1007/s11154-005-6722-9)
17 Evans, W. 1995 What is sarcopenia? *J. Gerontol.* **50A**, 5–8.
18 Janssen, I., Heymsfield, S. B. & Ross, R. 2002 Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J. Am. Geriatr. Soc.* **50**, 889–896. (doi:10.1046/j.1532-5415.2002.50216.x)
19 Walsh, M. C., Hunter, G. R. & Livingstone, M. B. 2006 Sarcopenia in premenopausal and postmenopausal women with osteopenia, osteoporosis and normal bone mineral density. *Osteoporosis Int.* **17**, 61–67. (doi:10.1007/s00198-005-1900-x)
20 Ferrucci, L., Russo, C. R., Lauretani, F., Bandinelli, S. & Guralnik, J. M. 2002 A role for sarcopenia in late-life osteoporosis. *Aging Clin. Exp. Res.* **14**, 1–4.
21 Lebrun, C. E., van der Schouw, Y. T., de Jong, F. H., Grobbee, D. E. & Lamberts, S. W. 2006 Fat mass rather than muscle strength is the major determinant of physical function and disability in postmenopausal women younger than 75 years of age. *Menopause* **13**, 474–481. (doi:10.1097/01.gme.0000222331.23478.ec)
22 Newman, A. B., Kupelian, V., Visser, M., Simonsick, E. M., Goodpaster, B. H., Kritchevsky, S. B., Tylavsky, F. A., Rubin, S. M. & Harris, T. B. 2006 Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J. Gerontol. A Biol. Sci. Med. Sci.* **61**, 72–77.
23 Sowers, M. R., Crutchfield, M., Richards, K., Wilkin, M. K., Furniss, A., Jannausch, M., Zhang, D. & Gross, M. 2005 Sarcopenia is related to physical functioning and leg strength in middle-aged women. *J. Gerontol. A Biol. Sci. Med. Sci.* **60**, 486–490.
24 Campbell, W. W., Trappe, T. A., Wolfe, R. R. & Evans, W. J. 2001 The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. *J. Gerontol. A Biol. Sci. Med. Sci.* **56**, M373–M380.
25 Visser, M., Deeg, D. J. & Lips, P. 2003 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.* **88**, 5766–5772. (doi:10.1210/jc.2003-030604)
26 Hughes, V. A., Frontera, W. R., Roubenoff, R., Evans, W. J. & Singh, M. A. 2002 Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. *Am. J. Clin. Nutr.* **76**, 473–481.
27 Schaap, L. A., Pluijm, S. M., Deeg, D. J. & Visser, M. 2006 Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am. J. Med.* **119**, e9–e17. (doi:10.1016/j.amjmed.2005.10.049)
28 Park, S. W., Goodpaster, B. H., Strotmeyer, E. S., de Rekeneire, N., Harris, T. B., Schwartz, A. V., Tylavsky, F. A. & Newman, A. B. 2006 Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes* **55**, 1813–1818. (doi:10.2337/db05-1183)
29 Park, S. W. *et al.* 2009 Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care* **32**, 2136–2137. (doi:10.2337/dc09-0264)

30 Baumgartner, R. N., Koehler, K. M., Gallagher, D., Romero, L., Heymsfield, S. B., Ross, R. R., Garry, P. J. & Lindeman, R. D. 1998 Epidemiology of sarcopenia among the elderly in New Mexico. *Am. J. Epidemiol.* **147**, 755–763.
31 Iannuzzi-Sucich, M., Prestwood, K. M. & Kenny, A. M. 2002 Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J. Gerontol. A Biol. Sci. Med. Sci.* **57**, M772–M777.
32 Janssen, I., Shepard, D. S., Katzmarzyk, P. T. & Roubenoff, R. 2004 The healthcare costs of sarcopenia in the United States. *J. Am. Geriatr. Soc.* **52**, 80–85. (doi:10.1111/j.1532-5415.2004.52014.x)
33 Bhasin, S. *et al.* 2005 Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J. Clin. Endocrinol. Metab.* **90**, 678–688. (doi:10.1210/jc.2004-1184)
34 Frontera, W. R., Meredith, C. N., O'Reilly, K. P., Knuttgen, H. G. & Evans, W. J. 1988 Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J. Appl. Physiol.* **64**, 1038–1044.
35 Fiatarone, M. A. *et al.* 1994 Exercise training and nutritional supplementation for physical frailty in very elderly people. *N. Engl. J. Med.* **330**, 1769–1775. (doi:10.1056/NEJM199406233302501)
36 Baumgartner, R. N., Wayne, S. J., Waters, D. L., Janssen, I., Gallagher, D. & Morley, J. E. 2004 Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes. Res.* **12**, 1995–2004. (doi:10.1038/oby.2004.250)
37 Zoico, E., Di Francesco, V., Guralnik, J. M., Mazzali, G., Bortolani, A., Guariento, S., Sergi, G., Bosello, O. & Zamboni, M. 2004 Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. *Int. J. Obes. Relat. Metab. Disord.* **28**, 234–241.
38 Goodpaster, B. H., Carlson, C. L., Visser, M., Kelley, D. E., Scherzinger, A., Harris, T. B., Stamm, E. & Newman, A. B. 2001 Attenuation of skeletal muscle and strength in the elderly: the Health ABC study. *J. Appl. Physiol.* **90**, 2157–2165.
39 Goodpaster, B. H. & Brown, N. F. 2005 Skeletal muscle lipid and its association with insulin resistance: what is the role for exercise? *Exerc. Sport Sci. Rev.* **33**, 150–154. (doi:10.1097/00003677-200507000-00008)
40 Miller, S. L. & Wolfe, R. R. 2008 The danger of weight loss in the elderly. *J. Nutr. Health Aging* **12**, 487–491. (doi:10.1007/BF02982710)
41 Ensrud, K. E., Ewing, S. K., Stone, K. L., Cauley, J. A., Bowman, P. J. & Cummings, S. R. 2003 Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J. Am. Geriatr. Soc.* **51**, 1740–1747.
42 Bhasin, S. *et al.* 2008 Functional outcomes for clinical trials in frail older persons: time to be moving. *J. Gerontol. A Biol. Sci. Med. Sci.* **63**, 160–164.
43 Harper, C. M. & Lyles, Y. M. 1988 Physiology and complications of bed rest. *J. Am. Geriatr. Soc.* **36**, 1047–1054.
44 Convinsky, K. E., Palmer, R. M., Fortinsky, R. H., Counsel, S. R., Stewart, A. L., Kresevic, D., Burant, D. & Landefeld, C. S. 2003 Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *J. Am. Geriatr. Soc.* **51**, 451–458.
45 Anonymous. 2003 *HCUPnet, healthcare cost and utilization project*. Rockville, MD: Agency for Healthcare Research and Quality. See http://www.ahrq.gov/data/acup/hcupnet.htm.
46 Kortebein, P., Ferrando, A., Lombeida, J., Wolfe, R. & Evans, W. J. 2007 Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* **297**, 1772–1774. (doi:10.1001/jama.297.16.1772-b)
47 Kortebein, P. *et al.* 2008 Functional impact of 10 days of bed rest in healthy older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **63**, 1076–1081.
48 Sullivan, D. H., Sun, S. & Walls, R. C. 1999 Protein-energy undernutrition among elderly hospitalized patients: a prospective study. *JAMA* **281**, 2013–2019. (doi:10.1001/jama.281.21.2013)
49 Guralnik, J. M., Ferrucci, L., Simonsick, E. M., Salive, M. E. & Wallace, R. B. 1995 Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N. Engl. J. Med.* **332**, 556–561. (doi:10.1056/NEJM199503023320902)