Age-related deficit accumulation and the diseases of ageing

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ABSTRACT

With ageing, the potency of individual risk factors traditionally associated with common illnesses declines. Instead, it is becoming clear that the impact of a wide range of age-related deficits not traditionally considered as risk factors for these illnesses increases. These age-related deficits chiefly confer risk as a group, not individually. The many effects of age-related changes can be demonstrated epidemiologically, and in preclinical models, using a frailty index to distinguish between the contributions of traditional and non-traditional risk factors. Quantifying the contribution of age-related deficit accumulation in clinical and preclinical samples offers a powerful new tool for understanding mechanisms of age-related disease. It appears that a range of common late-life illnesses might be targeted by drugs aimed at ageing processes.

1. Introduction

Given that same-strain animals raised in controlled environments acquire age-related diseases and die at variable rates, it is unsurprising that people age at varying rates (Kirkwood et al., 2005). In consequence, even though each day brings each person closer to their own death, the risk of dying varies between individuals. By extreme old age (well past one hundred years) the only people left alive are those who age slowly. As a result, the mortality risk appears to fall. In 1979, that observation, then somewhat novel, gave rise to the term "frailty" to summarize unmeasured variability in the risk of death of people of the same age (Vaupel et al., 1979). The term has now been generalized to mean unmeasured variability in the risk of an adverse outcome for people with the same degree of exposure, and serves as an extension of proportional hazards modelling of survival (Hougaard, 1995).

Several attempts to operationalize frailty clinically followed. In 2001, two influential approaches appeared, each of which saw frailty as multiply determined, and as compromising (a largely undefined) physiological reserve (Rockwood and Howlett, 2018). One saw frailty as a clinical syndrome (Fried et al., 2001). The other (from our group) saw frailty as a state (Mitnitski et al., 2001). Frailty-as-a-state is the focus of the current review.

Frailty as a state of accelerated deficit accumulation proposes that people of the same age have variable risks of death because they have varying numbers of things wrong with them. More specifically, we mean that variability in mortality risk is closely related to variability in

the extent to which people have accumulated health deficits (Mitnitski et al., 2001). Here, after having first rehearsed some details of understanding frailty as deficit accumulation, and then showing how broadly generalizable that understanding is – including in extending to animal models – we will explore the implications for understanding risks for common late-life illness. In particular, we will show examples of how age-related deficit accumulation alters disease risk and expression in dementia and in heart disease. These effects exist at clinical and molecular/subcellular levels, and in relation to tissue function. We will argue that it is no coincidence that as the well-known potency of individual risk factors traditionally associated with common illnesses declines, other age-related health deficits *combine* to grow in risk. For example, as hypertension, hypercholesterolemia and stroke each become less of a risk for cognitive decline (Legdeur et al., 2018), the risk from non-specific age-related deficit accumulation increases (Song et al., 2014). These accumulated health deficits – i.e. the degree of frailty – affect not just the risk of dementia, but also whether classic neuropathological lesions are expressed as cognitive and functional decline (Wallace et al., 2019). We will underscore that their importance can be understood not just as compromising so-called "physiological reserve" - as damage propagates through complex networks, increasing because damage begets damage (Mitnitski et al., 2017a) - but as also signaling fundamental age-related processes. In short, *the deficit accumulation that underlies ageing promotes frailty as a matter of course* (Mitnitski et al., 2017b). This understanding of the fundamental relationship between frailty and ageing – including across the life course -

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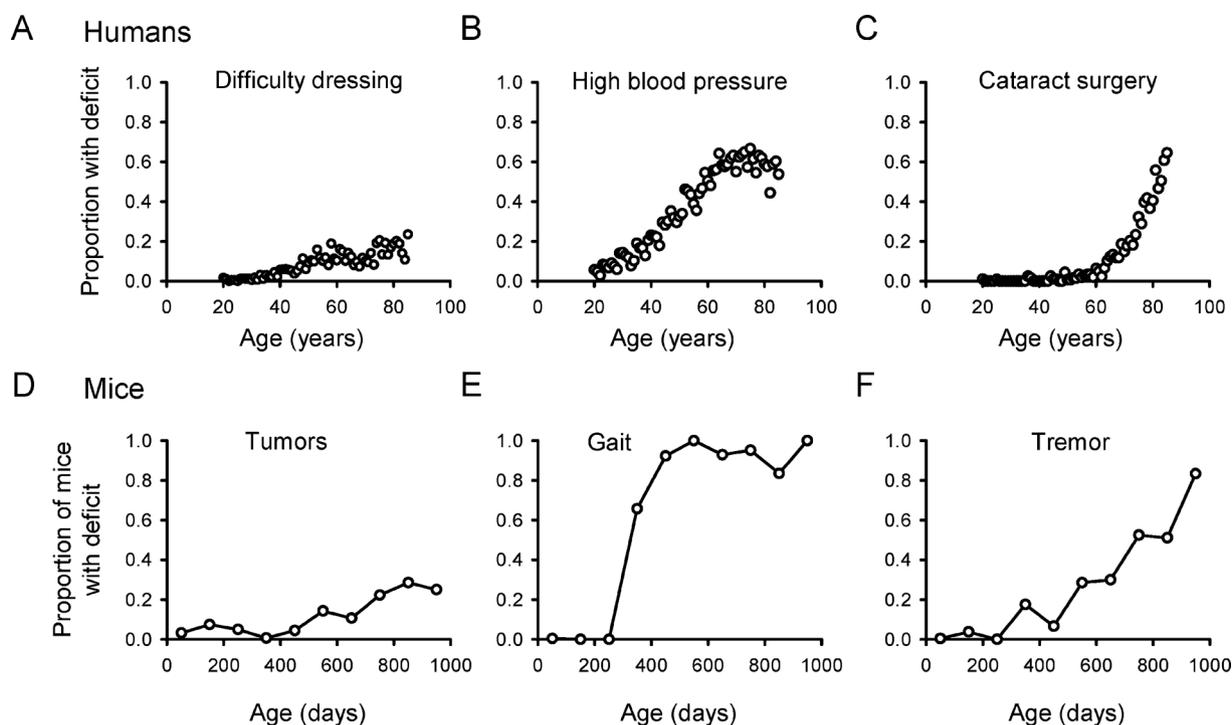*E-mail address:* kenneth.rockwood@dal.ca (K. Rockwood).

Fig. 1. Individual deficits that comprise the frailty index accumulate at varying rates in people and in mice. A,B,C. Individual deficits exhibit different patterns of accumulation with age in humans (n = 9,169). D,E,F. Similar results are observed when patterns of deficit accumulation are plotted as a function of age in C57BL/6 mice (n = 251 mice). Adapted and reprinted from Rockwood et al. (Rockwood et al. (2017)) with permission as outlined in the license (http://creativecommons.org/licenses/by/4.0/).

will have implications for how we understand frailty mechanisms and thereby potential treatments (Franceschi et al., 2018).

1.1. Frailty as deficit accumulation

Across the life course, as people age, they are more likely to accumulate health deficits (Rockwood and Mitnitski, 2007). These health deficits accumulate in varying patterns, from increasing slowly at a near-constant rate, to negative curvature, to upward curvature (Fig. 1, Panels A–C) (Rockwood et al., 2017). Similar patterns of deficit accumulation can be seen in naturally aging C57BL/6 mice (Fig. 1, Panels D–F) (Rockwood et al., 2017). When the varying deficits are combined in a frailty index however, they resolve into a typical pattern of slow, gradual accumulation across the life course (Fig. 2, Panel A) (Rockwood et al., 2017, 2011), as is also seen in mice (Fig. 2, Panel B) (Rockwood et al., 2017).

To calculate a frailty index, we first need a count of health deficits (Mitnitski et al., 2001). A health deficit can be any health variable in which the deficit / riskier state increases with age, and is associated with death (Searle et al., 2008) or other adverse outcomes of interest – such as time to nursing home admission. A deficit is coded as "0" when the health variable from which it is derived is not in the at-risk state (e.g. for a disease, if it absent; for a laboratory test value, if it is within the normal range; for an activity of daily living (ADL), if the person is independent in that task). Otherwise (disease present, lab value out of the normal range, dependence in a given ADL) the deficit is coded as "1". Deficits should cover many organ systems and consist in more than co-morbidities or function, though these should be included. For ease of interpretation, deficits should be calculated only when 80% or more of the variables contain valid data. Values in between 0 and 1 can also be scored (e.g. an ADL might be trichotomized as: 0 = independence; 0.5 = requires some assistance, and; 1 = complete dependence) or more finely graded. Even so, the impact of more graded scoring versus dichotomization of individual deficits appears to be negligible.

The frailty index score represents the proportion of deficits present from the proportion of deficits considered, i.e.

$$\text{Frailty Index score} = \frac{\text{Number of deficits in an individual}}{\text{Total number of deficits measured}}$$

For example, in a dataset with 50 health candidate deficits, a person with 10 things wrong (i.e. in whom 10 of the variables are deficits) has a frailty index score of 10/50 = 0.20. As long as at least thirty variables are included (in general, more is better) these results are remarkably robust, (Mitnitski et al., 2005) notably in predicting mortality (Rockwood et al., 2006; Kojima et al., 2018). Note too that there is no requirement that each variable individually be statistically significantly related to age or mortality. Instead, when combined in a single variable, small pieces of information are allowed to add up. (In short, instead of the traditional approach of reducing dimensionality by eliminating variables from the model, we collapse many dimensions into one variable.) Including many apparent dimensions into a single index variable of accumulated deficits yields a parsimonious model. Typically, we work with few variables beyond age, sex, frailty index and whatever other few key items might be of interest, such as social vulnerability or health protective factors. This strategy avoids specious associations, which is especially important in age-related conditions, inasmuch as "the problems of old age come as a package" (Fontana et al., 2014). In essence, the frailty index quantifies the size of that package (Howlett and Rockwood, 2014).

Although the frailty index was originally focused on old age, its relationship to ageing itself (Figs. 1 and 2) has long been a focus of studies of age-related deficit accumulation (Rockwood and Mitnitski, 2007; Rockwood et al., 2004). This is likely to remain a useful area of inquiry, including in relation to diseases in which notions of accelerated aging are common, such as people who are socially vulnerable, or who have intellectual disability, or live with HIV/AIDS (Andrew et al., 2008; Brothers et al., 2014; Schoufour et al., 2015; McKenzie et al., 2015; Franconi et al., 2018). The challenge of how frailty relates to ageing is likely to benefit from studies of how frailty propagates through networks, as discussed below.
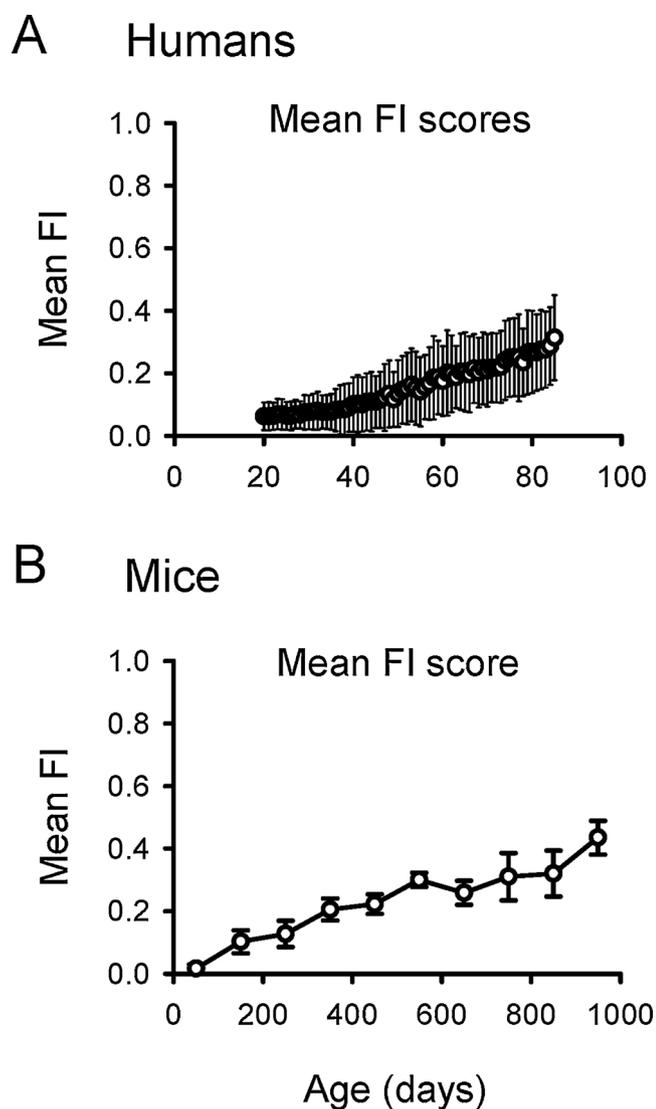
A Humans

B Mice

Fig. 2. Frailty index scores increase with age at similar rates in people and in mice. A. Frailty scores derived from 46 individual deficits were used to calculate clinical frailty index scores for 9169 people. Data were binned and averaged each year. B. Frailty scores were calculated from 31 individual mouse deficits for 251 mice. Data were binned and averaged in 100 day increments. The mean (± SD) values are illustrated. Adapted and reprinted from Rockwood et al. (Rockwood et al. (2017)) with permission as outlined in the license (http://creativecommons.org/licenses/by/4.0/).

More recent work shows that, as might be expected, when the rate of deficit accumulation is estimated from longitudinal data it is higher (Mitnitski and Rockwood, 2016; Hoogendijk et al., 2018) than the 3.0 to 3.5% rate estimated from sequential cross-sectional studies (Mitnitski et al., 2005). These longitudinal analyses suggest rates between 4.5–6%, which correspond to doubling times of about 12–15 years. Given the well-replicated relationship between frailty and mortality (Kojima et al., 2018), an analogy might be made to compound interest. Just as the numerical effect of a constant doubling that matters most to pensioners is that whichn occurs when they retire, so the most important doubling of mortality risk in relation to the degree of deficit accumulation is that experienced between 75–90 years, which for most people constitute the last years of life.

Rates of deficit accumulation also have been estimated in animal models. These studies have examined the relationship between the frailty index and age across the life course in naturally aging C57BL/6 mice (Parks et al., 2012; Whitehead et al., 2014; Feridooni et al., 2015a;

Rockwood et al., 2017). A cross-sectional study showed that the rate of deficit accumulation was 3.8% in mice, which is similar to the rates of between 3.0 and 3.5% estimated in cross-sectional studies in people (Mitnitski et al., 2005). However unlike the human studies, rates of deficit accumulation are similar in cross-sectional and longitudinal studies. For example, a rate of deficit accumulation of 3.6% has been reported in a large cohort of mice followed from 3 weeks of age until extinction (Rockwood et al., 2017). It is not yet clear why the rates of murine deficit accumulation are similar in longitudinal and cross-sectional studies, but it is possible that this reflects, at least in part, the lack of external repair in mice versus people.

1.2. Frailty and mortality

The relationship between frailty and mortality arises because, as we have seen, the higher the frailty index score, the greater the risk of death (Kojima et al., 2018). This allows us to address the question implicit in the idea that frailty represents unmeasured variability in the risk of death for people of the same age (Vaupel et al., 1979) – what is it measuring? Quantified as deficit accumulation, the frailty construct suggests that the reason that some people have a greater risk of death than do others of the same age is that, as a first approximation, they have more things wrong with them than do those with a lower risk of death. A few differences between the statistical and clinical conceptualizations are worth mentioning. First, the frailty index shows how the condition of increased age-associated risk is assayed for each individual; it also has a range that signals when risk is lower than is typical for a given age, which itself is a measure of relative fitness (Rockwood et al., 2011). Similarly, it is a dynamic measure; frailty index scores change over the life course to reflect individual changes in health, in contrast to the static value of frailty in the Vaupel et al. model (Vaupel et al., 1979). Interestingly, one aspect of the relationship between mortality and the degree of frailty is that at very high values (frailty scores of about 0.67) the risk of death becomes so high that less than 1% of people can survive accumulating an additional deficit (Rockwood and Mitnitski, 2006; Bennett et al., 2013; Shi et al., 2014; Armstrong et al., 2015a; Dent et al., 2017). Depending on how the frailty index is constructed - chiefly which items are used (e.g. how prevalent, with what information value (Farrell et al., 2018b)) - the result is sometimes lower (e.g. with an electronic frailty index (eFI) composed of 35 items, although the maximum value was 0.67, the 99% upper limit value was 0.49) (Clegg et al., 2016).

The eFI – validated further as a screening test in subsequent studies (Stow et al., 2018a; Brundle et al., 2019) and evaluated for use elsewhere (Ambagtsheer et al., 2018) - is also of interest in showing the stochasticity of the relationship between frailty and mortality in relation to age. Portrayed as a heat map generated from several hundred thousand cases enrolled using GP records in England and Wales, the relationship between mortality and frailty is consistent across age groups, even as survival not unexpectedly decreases with age (Fig. 3). Still, individual results vary (Stow et al., 2018a), as would be expected of a screening measure. In consequence, those who screen positive require assessment to develop care plans – including plans that might impact the lethality of deficit accumulation. Four points about frailty and mortality can be highlighted. First is that the degree of frailty matters; a single cutpoint such as 0.25 will inevitably show important variability in mortality: frailty is not all or none. On many grounds other than the risk of death – including the extent of disability, or co-morbidity or even mobility impairment, the degree of frailty matters to both risk and to care planning (Davis et al., 2011; Theou et al., 2012). Second, the chance of survival with high degrees of frailty is low enough that even in a large database, there are gaps in the record for people with very high frailty index scores (here eFI > 0.6; Fig. 3). Third, even when the degree of frailty is important, so too can age remain important in prognosis. Fourth, across the age spectrum, many people with low eFI scores outlived younger people with higher eFI
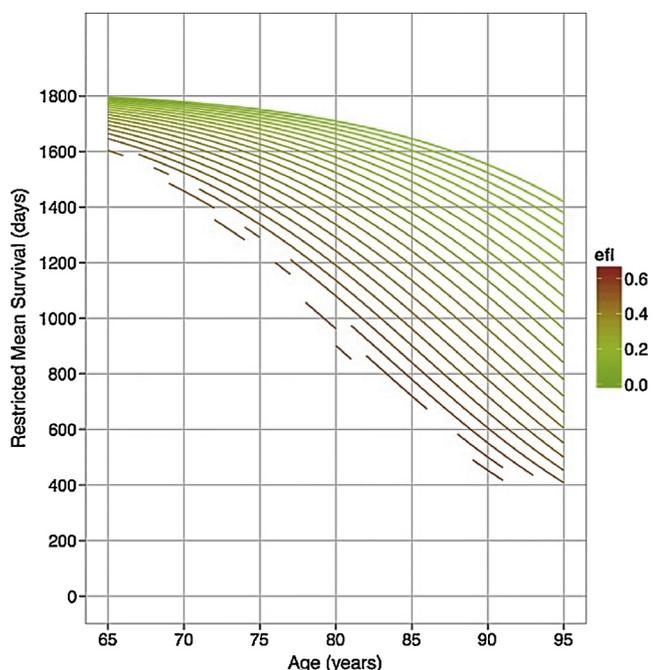
Fig. 3. The relationship between mortality and frailty is consistent across age groups. Heat map of survival (y-axis) in relation to age (x-axis) and eFI scores, using general practitioner records in England and Wales. Although mean survival falls with age at all ages, people with higher frailty index scores survive less that do fitter people of the same age. Reprinted from Clegg et al. (Clegg et al. (2016)) with permission as outlined in the license (http://creativecommons.org/licenses/by/4.0/).

scores, suggesting that the degree of deficit accumulation has the potential to be a marker of so-called "biological age". The importance of this point is that in contrast to a search for a single biomarker of age – or frailty for that matter – there is likely to be more information from combining candidate biomarkers, as the frailty index does (Farrell et al., 2018b). That appears to be borne out when comparing frailty biomarkers examined individually (Collerton et al., 2012), versus in combination, in a frailty index of biomarkers (Mitnitski et al., 2015).

1.3. The regularity of age-related deficit accumulation

The relationship between mean survival times, frailty and mortality (Fig. 3) reflects notable regularity in how age-related deficits accumulate, at least when combined in a frailty index (Mitnitski et al., 2001, 2017b; Mitnitski et al., 2005; Rockwood et al., 2004; Mitnitski and Rockwood, 2016; Hoogendijk et al., 2018; Whitehead et al., 2014; Bennett et al., 2013; Clegg et al., 2016). This regularity is also reflected in how deficits accumulate across the life course (Fig. 4). At younger ages (here 45–50) many people have very few clinically evident deficits, as counted in particular in a self-reported study (Rockwood et al., 2004). In consequence, about 40% of people have a frailty index score of zero (Rockwood et al., 2004). By age 80, this proportion has fallen to about 5%. Notably too, the mode shifts, reflecting increased level of deficit accumulation with age (Rockwood et al., 2004).

Survival data on very old people (aged 80+ at baseline) from China (Bennett et al., 2013) also illustrate the remarkable regularity of the behaviour of the frailty index (Fig. 5). Across successive waves of the Chinese Longitudinal Health and Longevity Study, although survival diminished greatly at successive two-year follow-up re-evaluations (as shown by a decrease in the areas under the curve in Fig. 5A), neither the mode nor the limit changed perceptibly.

The orderliness of deficit accumulation is not always readily apparent. For example, individuals show many trajectories in the degree of health deficit accumulation (Mitnitski et al., 2012) (Fig. 6). The
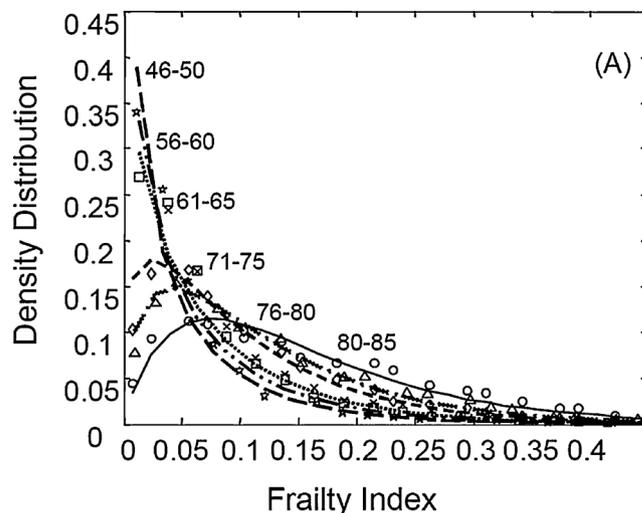

Fig. 4. Deficit accumulation across the life course. The proportionate distribution (y-axis) of frailty index scores (x-axis) changes across the life course. At younger ages (here 46–50) about 42% of people have frailty index scores equal to 0. This proportion declines with age, and the mode increases, as does the area under a long right-hand tail, which nevertheless falls well short of a frailty index score of 1.0. Reprinted from Rockwood et al. (Rockwood et al. (2004)) with permission as outlined in Rightslink.
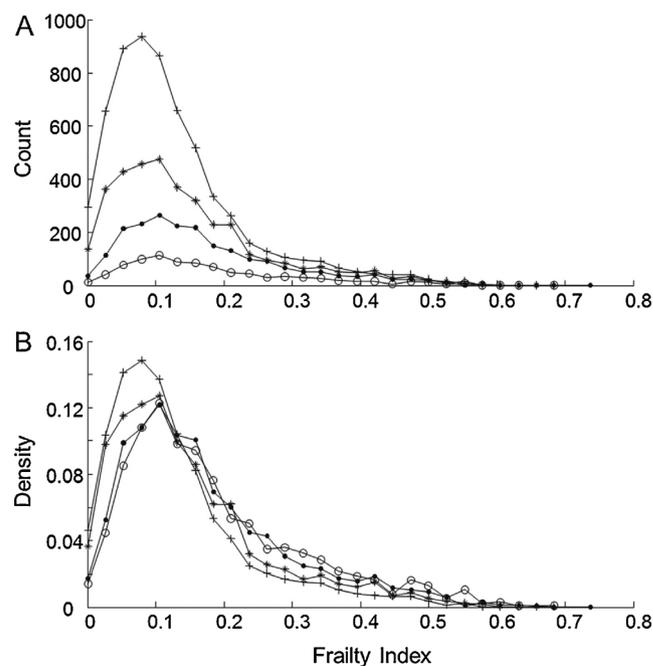

Fig. 5. Change in the absolute (Panel A) and proportionate (Panel B) distributions of the frailty index amongst very old (ages 80–99) people in China. Distribution of the frailty index as a function of the number of people in each wave. Data are expressed as the absolute number of individuals (A) and as a percentage (B). Despite the high mortality rate, the modes and limits are similar. Reprinted from Bennett et al. (Bennett et al. (2013)) with permission as outlined in Rightslink.

regularity hidden in such a "spaghetti plot" is revealed when the change in the number of deficits is presented as a function of the number of deficits at baseline (Fig. 7). A multistate stochastic model of transition in the frailty index score makes clear that the accumulation of deficits is orderly at the group level, even as individual results might suggest otherwise (Mitnitski et al., 2006). The output of the model first estimates the chance of an individual being alive at the end of a given follow-up interval. For those who are alive, the model's output is a
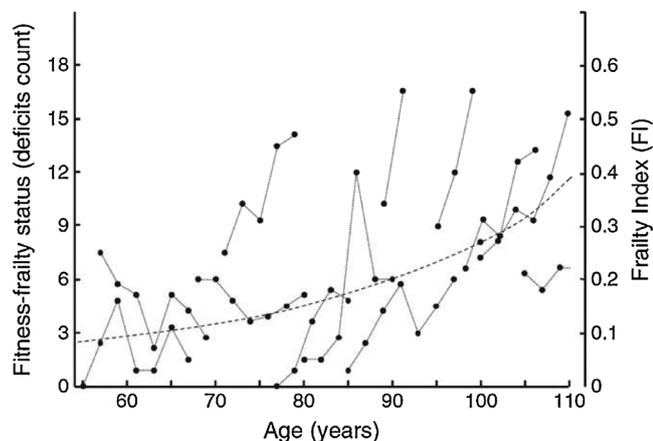
Fig. 6. The individual trajectories of deficit counts in twelve participants in the National Population Health Survey. Frailty, quantified with a deficit count (y-axis, left) and as the frailty index (y-axis, right), increases on average with age, but individual trajectories vary greatly. Reprinted from Mitnitski et al. (Mitnitski et al. (2012)) with permission as outlined in Rightslink.

probability distribution of their frailty index scores – many people stay at the same score, or within a score that represents one deficit (e.g. 0.03 in a 33-item index). For most people, as with aging, change is slow, and sudden "jumps" in the frailty index scores are uncommon (Mitnitski et al., 2017a).

The orderliness of changes in the frailty index, and its robust flexibility - in particular, its wide reproducibility that does not depend on which deficits are chosen – have stimulated a search for what mechanism might underlie such regularity. An initial proposal suggested that the occurrence of a deficit reflected a condition in which local

damage went unremoved or unrepaired (Mitnitski et al., 2013). This led initially to a proposal that queuing theory could offer a quantitative framework: the degree of deficit accumulation (as an example of the length of queue) was a function of the number of people who arrived to queue up (here, the rate of damage) and how long it took to process each one (the analogy for recovery time, reflecting repair processes) (Mitnitski et al., 2013). Later work in the same conceptual frame of damage and repair, with more damage impairing repair processes, suggested using the apparatus of an asymmetric double-well potential / Kramers equilibrium (Kramers, 1940). Borrowed from physical chemistry to calculate the energy states of electrons, Kramers equilibrium demonstrates how a higher damage rate can make greater deficit accumulation more likely. That is because damage begets damage, first by exceeding recovery time – so that damage from one insult is still not repaired when more damage arrives, and then by prolonging how long recovery time takes, as recovery processes themselves become damaged (Taneja et al., 2016). Subsequent work has further elaborated this model (Fig. 8) (Farrell et al., 2018a, 2016). This has allowed for an understanding of how deficits propagate through a scale-free network to give rise to the law-like relationship between age and mortality observed for people after about the age of 30, until about the age of 90 years (Kirkwood, 2015). It shows why frailty measures that integrate many items are likely to formally be more informative than those that aggregate just a few. Important too is that the model suggests that most frailty measures can be viewed as special cases of deficit accumulation, which is why they empirically have similar characteristics (Theou et al., 2013, 2014).

The network modeling has advanced an interesting question about how deficits accumulate, including how they scale up. Obviously, whatever happens in ageing happens at molecular or subcellular levels – quirks and quarks don't age, so this matter is one of failure of broadly
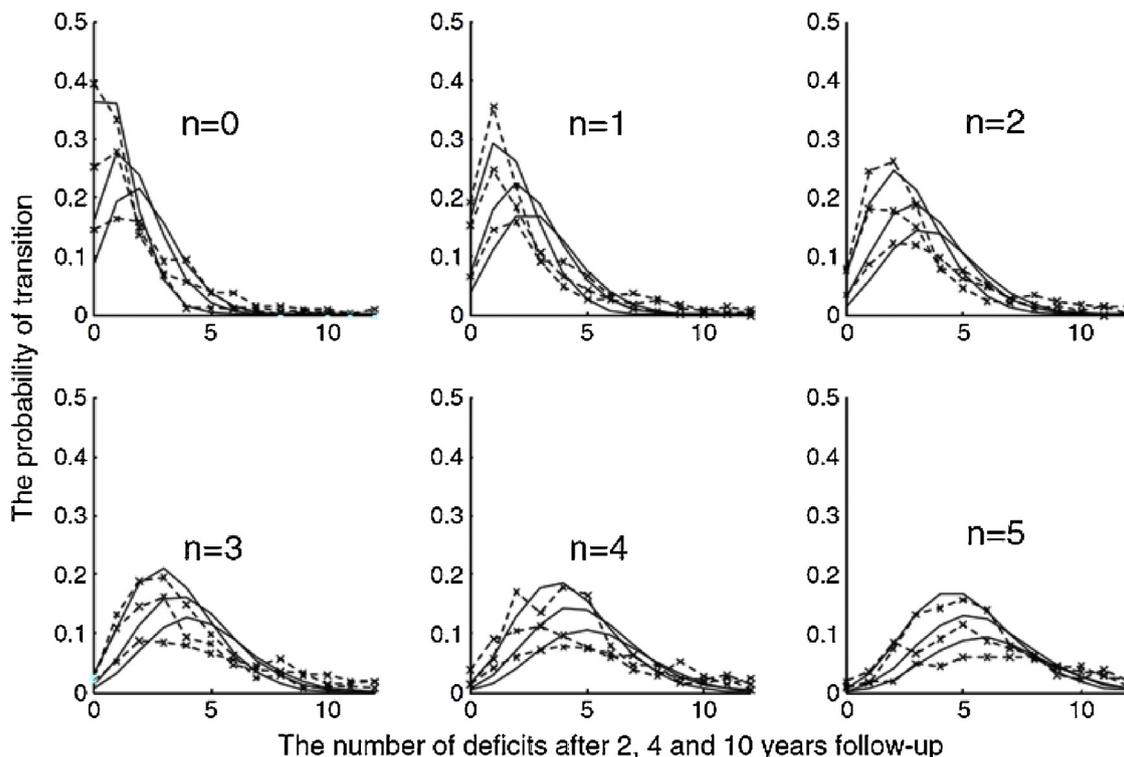

Fig. 7. The probability of transitioning from a baseline deficit count, denoted as "n" in each graph, to a higher or lower deficit count as a function of years follow-up. Compared with the variability shown in Fig. 6, the overall pattern of transition probabilities is orderly, and is conditional on the starting state. Note that, with time, the area under the curve diminishes, as survival decreases. Lower areas under the curve are also evident as the number of deficits at baseline increases. Overall the pattern is to transition to a higher deficit count, although transitions to a lower count are also possible at each baseline state. In each panel, the x axis is the number of deficits at follow up and the y axis is the probability of transition to the follow up state. In all cases n refers to the number of deficits at baseline. Reprinted from Mitnitski et al. (Mitnitski et al. (2012)) with permission as outlined in Rightslink.
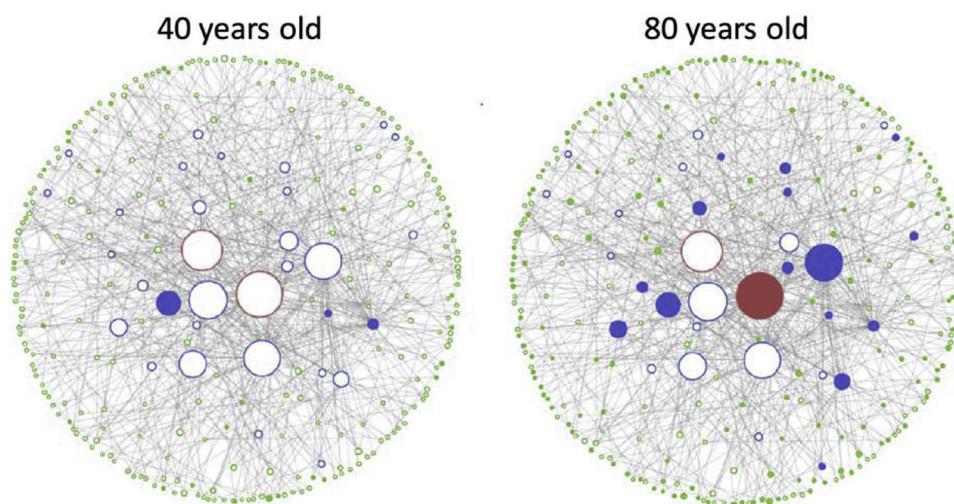
Fig. 8. Connectivity networks of an individual at 40 years of age (left) and again at 80 years of age (right). Larger nodes denote higher levels of connectivity and damaged nodes are filled while undamaged nodes are empty. The red circles denote mortality nodes and the blue circles are 30 frailty nodes. With age there is an increase in damage at the mortality and frailty nodes. Reprinted from Mitnitski et al. (Rutenberg et al., 2018) with permissions outlined in Rightslink (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

construed systems (Gavrilov et al., 2002). How such deficits become clinically visible suggests that there is first subclinical deficit accumulation (Howlett and Rockwood, 2013), the characteristics of which are now becoming more apparent.

1.4. The FI-lab

As noted, not all individual deficits accumulate in the same way [Fig. 1]. Despite the notable regularity of the increase in the frailty index, it turns out that a single pattern does not hold in all classes of deficits. In particular, as we discovered in 2014, the behavior of a frailty index composed entirely of common laboratory measures (e.g. routine blood work, blood pressure etc.) is not identical to a frailty index composed of clinical measures (Howlett et al., 2014). In other words, not all types of deficits accumulate in the same way. The FI-Lab has a higher y-intercept. With a fixed upper limit, it thereby has a lower slope, leading to a longer doubling time – approximately 24 years versus the doubling time (by the same method of calculation) of about 18 years for a clinical frailty index. The FI-Lab has been replicated in a variety of settings (Blodgett et al., 2016; King et al., 2017; Ma et al., 2018; Hao et al., 2019), including institutional long term care (Rockwood et al., 2015; Yang et al., 2018), clinical series (Klausen et al., 2017; Ritt et al., 2017; Cheung et al., 2017), and clinical trials (Theou et al., 2016; Justice et al., 2019).

A frailty index based on abnormalities in standard laboratory test results, analogous to the FI-Lab used in humans, has been developed for use in mice (Parks et al., 2012; Feridooni et al., 2015a; Kane et al., 2019). The frailty index data obtained with this tool shows similar characteristics to FI-Lab used in people. Specifically, there is a submaximal limit of ˜0.67, a normal distribution and deficits that occur across a range of items in different mice (Kane et al., 2019). As in humans, FI-Lab scores are higher than frailty scores based on physical assessment. This supports the idea that frailty results from the accumulation of subcellular/cellular deficits that appear as abnormal laboratory test results and ultimately "scale up" to become expressed as clinical deficits.

Studies in mouse models have shown that frailty scores based on clinical assessment are higher in females than in males (Kane et al., 2019), as also seen in people (Gordon et al., 2017). This observation has given rise to the idea of the morbidity-mortality paradox, where women have higher frailty index scores than men at all ages, but they live longer than men (Gordon et al., 2017). Reasons for this health-survival paradox are not yet clear. Studies that explore male-female differences in the ability to respond to adverse events, a characteristic that incorporates the idea of "resilience" (Schosserer et al., 2019), would be of considerable interest.

1.5. Frailty and social vulnerability

Proposing damage/repair mechanisms as the basis for deficit accumulation obviously gives rise to the question of how variability in these rates might be quantified. Candidate mechanisms reflect what are felt to be primary manifestations of ageing, such as damage induced through the course of metabolism, or by genomic instability, telomere attrition, loss of proteostasis, or epigenetic alterations together with the rest of the so-called "hallmarks" (López-Otín et al., 2013) or "pillars" (Kennedy et al., 2014) of ageing. Systematic sources of variability in addition to sex include a host of factors that can be grouped as social vulnerability (Andrew et al., 2008). Interestingly, it appears that the many components of social vulnerability, such as social support, engagement, living situations and contextual socio-economic status accumulate in a way that is akin to health deficits, although accumulating at a lower rate. In contrast to health deficits, almost no person has zero items of social vulnerability, at least when the items included as deficits extend to self-esteem, sense of control and relations with others (Andrew and Keefe, 2014).

Social vulnerability, sometimes referred to as "social frailty" (Bessa et al., 2018), is powerfully linked to adverse health outcomes (Andrew et al., 2018). For example, in the Canadian Study of Health and Aging, the degree of social vulnerability was considered in relation to five-year mortality in the fittest ten per cent of people aged 70 years and older (Andrew et al., 2012). Even in the Canadian context of universal health care and extensive social services, mortality varied considerably: the mortality rate for the least vulnerable tertile was 10.8%, compared to 32.5% for the most vulnerable tertile. This 22% absolute mortality difference in the fittest corresponded to a significant hazard rate of 2.5 (1.4–4.3) in a model adjusted for age and sex.

The question has arisen as to whether social factors should be included in a frailty measure. Undoubtedly, social factors should be considered in understanding the risk of adverse outcomes (Rockwood et al., 1994). Whether they should be included at the level of the variable (Panza et al., 2019) or at the level of the model (Andrew, 2015; Armstrong et al., 2015b) is not yet clear.

1.6. Relation between late life illness, ageing and frailty

Alzheimer disease is a compelling and increasingly concerning example of how large is the gap between understanding ageing as simply more than the passage of time, thereby permitting single protein abnormalities to wreak havoc on cognition, versus seeing ageing as intrinsic to disease risk and dementia expression (Brayne and Calloway, 1988; Hunter et al., 2018). Abnormal processing of the beta-amyloid precursor protein to give rise to all the toxic effects of Alzheimer disease

remains a central dogma, despite longstanding (Rockwood, 1997) and mounting criticism of viewing it as a "stand alone" disease (Canevelli et al., 2017). Given that age remains the single most potent risk for dementia, and that frailty quantifies variability in the risk for dementia with age, a 2011 report unsurprisingly showed that frailty was a potent risk for late-life dementia (Song et al., 2011). Perhaps more surprising was that this held even when the frailty index was composed of items not otherwise known to be risks for dementia. Further, when modelled with traditional dementia risk factors, the frailty index reduced the strength of their association with dementia; the greatest predictive value was achieved when all health deficits, whether known as dementia risks or not, and whether individually statistically significantly associated with dementia or not were combined in a single frailty index (Song et al., 2014, 2011). This work has been multiply replicated in many settings (Wang et al., 2017; Trebbastoni et al., 2017; Rogers et al., 2017) and has been extended more generally to include cognitive decline (Kelaiditi et al., 2016; Sterniczuk et al., 2013). This relationship holds even when the degree of social vulnerability – including years of education – is taken into account (Godin et al., 2017; Armstrong et al., 2015c).

A 2019 report, noting that the association between Alzheimer disease neuropathology and cognitive impairment is weak (Scheltens and Rockwood, 2011; Boyle et al., 2019), investigated how this relationship might be moderated by frailty. Using data from the celebrated Rush Memory and Aging Project (Bennett et al., 2018) Wallace et al. (Wallace et al. (2019) found that the degree of frailty modified the relationship between neuropathology and cognition. In particular, people with little neuropathology but clinical disease expression were more likely to be frail than those with little neuropathology who did not have dementia; likewise the degree of frailty was significantly lower in people who met neuropathological criteria for dementia but did not express it than those who did. These relationships held even when items associated with dementia risk were excluded from the frailty index. In short, considering age-related deficit accumulation gave a more complete account of dementia risk than did an approach that considered risks arising from other diseases, or even in the classic understanding of Alzheimer disease as the main driver of dementia.

1.7. Heart disease in old age

A similar weakening of the relationship between traditional risk factors for heart disease and its expression has been reported using data from the Nova Scotia Heart Health Survey. There a frailty index made up of age-related deficits not known to be associated with heart disease was found to drive incident coronary heart disease hospitalization and death (Wallace et al., 2014). Studies in rodent models that have begun to explore the effects of age and frailty on the cardiovascular system offer some insights into how this arises (Fares and Howlett, 2010; Feridooni et al., 2015b). For example, the extent of age-related left ventricular hypertrophy and contractile dysfunction is closely graded by the level of frailty in ageing mice (Feridooni et al., 2017). This suggests that frailty promotes conditions that facilitate the development of diseases such as heart failure. Other work has shown that age-related atrial dysfunction is closely graded by overall health status, as measured by frailty index scores in aging mice (Moghtadaei et al., 2016). These frailty-dependent changes in the atria are associated with longer lasting atrial fibrillation in aging mice (Jansen et al., 2017). Clinically the evaluation of frailty adds to prognostication and care planning in a variety of cardiovascular conditions (Shi et al., 2018; Yanagawa et al., 2019; Drudi et al., 2018; Hornsby et al., 2019).

Together, as detailed elsewhere in this volume (Banga et al., 2019) the results of these pre-clinical studies suggest that frailty sets the stage for the development of late life cardiovascular diseases. Related to heart disease, the frailty index can also help predict mortality risk in people suffering from chronic diseases such as the metabolic syndrome (a cluster of risk factors for poor cardiovascular outcomes including central obesity plus two or more of: elevated triglycerides, low high-density lipoprotein cholesterol, hypertension or type 2 diabetes). Interestingly, while there is an association between frailty and the metabolic syndrome, but this association weakens dramatically with age and the frailty index is a better predictor of mortality than the metabolic syndrome at all ages (Kane et al., 2017). Likewise, even in very old people (aged 90+ years) in age-adjusted models, frailty more than the metabolic syndrome explained the risk of death including in age-adjusted models (Hao et al., 2016).

2. Discussion

Here we have considered the current state of play of understanding frailty as deficit accumulation. A few points about how deficits accumulate are striking. The first is how robust is the simple expedient of counting health deficits and dividing them by the number of deficits counted. The resulting "frailty index' gives approximately the same results independently of the number of items counted, or, for the most part, their nature – as long as a few rules about which items should count as deficits are followed. Early on, it was recognized that the setting matters: in the community, the typical distribution has a mode on the left of the distribution, and fits a gamma model, with a long right tale (Mitnitski et al., 2001). The mean value of the frailty index increases with age, and with age the distribution broadens. In contrast, in clinical series, the increase in the mean value of the frailty index with age is attenuated, and the distribution typically approximates the normal (Mitnitski et al., 2005). Still a more recent discovery has been that the nature of items does matter: in particular, a frailty index based on laboratory deficits has a higher intercept and lower slope in relation to age. This appears to reflect that preclinical deficits precede clinical ones (Howlett and Rockwood, 2013; Howlett et al., 2014). Whether they also resolve more slowly (as the recent report of a senolytic trial might suggest (Justice et al., 2019) is also of interest. More work on the frailty index distribution will be essential to address whether – or to what extent – preclinical frailty markers might resolve in the face of better functional performance.

Understanding what represents a meaningful difference in a change in a frailty index score is another important area of inquiry. Likewise how a frailty index might summarize biomarkers across the life course – or whether it might in fact meet the definition for a biomarker itself requires evaluation. Change in relation to the frailty index and the question of how the past trajectory of a frailty index score influences its future prediction value is of interest. It is hard for most clinicians to believe that how a patient arrived at a particular frailty index value is not important to where their next frailty index score will land. Although that has been difficult to demonstrate, a 2018 report suggest that rapidly rising frailty is more lethal that arriving at the same FI value more slowly (Stow et al., 2018b).

Increasingly it appears both that the problems of old age come as a package (Fontana et al., 2014) and that the frailty index quantified that package both clinically and in basic science models (Howlett and Rockwood, 2014). Frailty means the "end of the disease era" (Cesari et al., 2016). This has consequences for understanding late-life illnesses (e.g. "To tackle HFpEF [heart failure with preserved ejection fraction] as an isolated disease is inevitably an exercise in disappointing results; the heart of the forest is still only a tree. Patients with HFpEF still bear the burden of multimorbidity, frailty, and aging) (Kim and Shi, 2019).

These are just a few examples of the important consequences that can arise from a quantitative understanding of multiply determined variability in the risk of adverse health outcomes with age. We close with a few caveats. First, although frailty is rooted in understanding differences in the risk of death of people of the same age (Vaupel et al., 1979), the goal is wider than that, and it is to understand risk more broadly. An important part of that is to extend to the risk of other adverse outcomes; if frailty evaluation were simply a matter of mortality prediction, we would include age in the definition. Instead, frailty

evaluation couples prognosis with care plans, including plans to pre-vent worse frailty, and to achieve better health. This requires that we recognize the depth of understanding that can be achieved from a quantitative account of deficit accumulation. The ongoing lack of re-solution between the frailty as a syndrome and frailty as a state (the subject of recurring debate in both general (Walston and Bandeen-Roche, 2015) and disease-specific (Afilalo, 2016; Rockwood, 2016) contexts) can lead to nihilism, and to the creation of new ad hoc frailty measures, or a demand to settle on one, ignore the other and move on. Into this comes advocacy for new ideas such as resilience and intrinsic capacity. The former is largely on unsettled ground of its own (Schosserer et al., 2019; Rockwood and Mitnitski, 2015; Rudzinski et al., 2017; Schorr et al., 2017; Stainton et al., 2018; Dulin et al., 2019), as is the latter, and for the most part still rooted in a conceptual more than a quantitative understanding.

Presumably the way forward is not to celebrate one view and de-nigrate the others. Instead, we must be realistic about what we know, and use that understanding of our ignorance to search for an over-arching understanding that can explain the varying concepts that are now in play (many other examples include complex system dysregu-lation, homeostenosis, or loss of any of physiological reserve, functional reserve, homeostasis or vitality). However we go about it, we are un-likely to simply set aside what is known about age-related deficit ac-cumulation so that it can seem more acceptable by camouflaging the reality with pleasing words. Instead, our goal is to better understanding late-life health so that we can better serve those at greatest risk.

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References

Afilalo, J., 2016. Conceptual models of frailty: the sarcopenia phenotype. Can. J. Cardiol. 32 (9), 1051–1055. https://doi.org/10.1016/j.cjca.2016.05.017.

Ambagtsheer, R., Beilby, J., Dabravolskaj, J., Abbasi, M., Archibald, M., Dent, E., 2018. Application of an electronic Frailty Index in Australian primary care: data quality and feasibility assessment. Aging Clin. Exp. Res.(August). https://doi.org/10.1007/s40520-018-1023-9. [Epub ahead of print].

Andrew, M.K., 2015. Frailty and social vulnerability. Interdiscip. Top. Gerontol. Geriatr. 41, 186–195. https://doi.org/10.1159/000381236.

Andrew, M., Keefe, J., 2014. Social vulnerability from a social ecology perspective: a cohort study of older adults from the National Population Health Survey of Canada. BMC Geriatr. 14 (1). https://doi.org/10.1186/1471-2318-14-90.

Andrew, M.K., Mitnitski, A.B., Rockwood, K., 2008. Social vulnerability, frailty and mortality in elderly people. PLoS One 3 (5), e2232. https://doi.org/10.1371/journal.pone.0002232.

Andrew, M., Mitnitski, A., Kirkland, S., Rockwood, K., 2012. The impact of social vul-nerability on the survival of the fittest older adults. Age Ageing 41 (2), 161–165. https://doi.org/10.1093/ageing/afr176.

Andrew, M.K., Dupuis-Blanchard, S., Maxwell, C., et al., 2018. Social and societal im-plications of frailty, including impact on Canadian healthcare systems. J. Frailty Aging 7 (4), 217–223. https://doi.org/10.14283/jfa.2018.30.

Armstrong, J., Mitnitski, A., Launer, L., White, L., Rockwood, K., 2015a. Frailty in the Honolulu-Asia Aging Study: deficit accumulation in a male cohort followed to 90% mortality. J. Gerontol. A Biol. Sci. Med. Sci. 70 (1), 125–131. https://doi.org/10.1093/gerona/glu089.

Armstrong, J., Mitnitski, A., Andrew, M., Launer, L., White, L., Rockwood, K., 2015b. Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. Alzheimers Res. Ther. 7 (1). https://doi.org/10.1186/s13195-015-0120-7.

Armstrong, J., Mitnitski, A., Andrew, M., Launer, L., White, L., Rockwood, K., 2015c. Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. Alzheimers Res. Ther. 7 (1). https://doi.org/10.1186/s13195-015-0120-7.

Banga, S., Heinze-Milne, S.D., Howlett, S.E., 2019. Rodent models of frailty and their application in preclinical research. Mech. Ageing Dev. https://doi.org/10.1016/j.mad.2019.01.008. pii:S0047-6374(19)30002-8. [Epub ahead of print].

Bennett, S., Song, X., Mitnitski, A., Rockwood, K., 2013. A limit to frailty in very old, community-dwelling people: a secondary analysis of the Chinese longitudinal health and longevity study. Age Ageing 42 (3), 372–377. https://doi.org/10.1093/ageing/afs180.

Bennett, D., Buchman, A., Boyle, P., Barnes, L., Wilson, R., 2018. Schneider J. Religious orders study and Rush Memory and aging project. J. Alzheimers Dis. 64 (s1), S161–S189. https://doi.org/10.3233/jad-179939.

Bessa, B., Ribeiro, O., Coelho, T., 2018. Assessing the social dimension of frailty in old age: a systematic review. Arch. Gerontol. Geriatr. 78, 101–113. https://doi.org/10.1016/j.archger.2018.06.005.

Blodgett, J.M., Theou, O., Howlett, S.E., Wu, F.C., Rockwood, K., 2016. A frailty index based on laboratory deficits in community-dwelling men predicted their risk of ad-verse health outcomes. Age Ageing 45 (4), 463–468. https://doi.org/10.1093/ageing/afw054.

Boyle, P., Yu, L., Leurgans, S., et al., 2019. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Ann. Neurol. 85 (1), 114–124. https://doi.org/10.1002/ana.25380.

Brayne, C., Calloway, P., 1988. Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? Lancet 331 (8597), 1265–1267. https://doi.org/10.1016/s0140-6736(88)92081-8.

Brothers, T., Kirkland, S., Guaraldi, G., et al., 2014. Frailty in people aging with human immunodeficiency virus (HIV) infection. J. Infect. Dis. 210 (8), 1170–1179. https://doi.org/10.1093/infdis/jiu258.

Brundle, C., Heaven, A., Brown, L., et al., 2019. Convergent validity of the electronic frailty index. Age Ageing 48 (1), 152–156. https://doi.org/10.1093/ageing/afy162.

Canevelli, M., Cesari, M., Remiddi, F., et al., 2017. Promoting the assessment of frailty in the clinical approach to cognitive disorders. Front. Aging Neurosci. 9. https://doi.org/10.3389/fnagi.2017.00036.

Cesari, M., Marzetti, E., Thiem, U., et al., 2016. The geriatric management of frailty as paradigm of "The end of the disease era". Eur. J. Intern. Med. 31, 11–14. https://doi.org/10.1016/j.ejim.2016.03.005.

Cheung, A., Haas, B., Ringer, T.J., McFarlan, A., Wong, C., 2017. Canadian study of health and aging clinical frailty scale: Does it predict adverse outcomes among geriatric trauma patients? J. Am. Coll. Surg. 225 (5), 658–665. https://doi.org/10.1016/j.jamcollsurg.2017.08.008. e3.

Clegg, A., Bates, C., Young, J., et al., 2016. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 45 (3), 353–360. https://doi.org/10.1093/ageing/afw039.

Collerton, J., Martin-Ruiz, C., Davies, K., et al., 2012. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. Mech. Ageing Dev. 133 (6), 456–466. https://doi.org/10.1016/j.mad.2012.05.005.

Davis, D., Rockwood, M.R., Mitnitski, A., Rockwood, K., 2011. Impairments in mobility and balance in relation to frailty. Arch. Gerontol. Geriatr. 53 (1), 79–83. https://doi.org/10.1016/j.archger.2010.06.013.

Dent, E., Dal Grande, E., Price, K., Taylor, A., 2017. Frailty and usage of health care systems: results from the South Australian Monitoring and Surveillance System (SAMSS). Maturitas. 104, 36–43. https://doi.org/10.1016/j.maturitas.2017.07.003.

Drudi, L.M., Ades, M., Landry, T., et al., 2018. Scoping review of frailty in vascular surgery. J. Vasc. Surg. S0741-5214 (18), 32465–32470. https://doi.org/10.1016/j.jvs.2018.10.053. [Epub ahead of print].

Dulin, A.J., Dale, S.K., Earnshaw, V.A., et al., 2019. Resilience and HIV: a review of the definition and study of resilience. AIDS Care 30, S6–S17. https://doi.org/10.1080/09540121.2018.1515470.

Fares, E., Howlett, S.E., 2010. Effect of age on cardiac excitation-contraction coupling. Clin. Exp. Pharmacol. Physiol. 37 (1), 1–7. https://doi.org/10.1111/j.1440-1681.2009.05276.x.

Farrell, S., Mitnitski, A., Rockwood, K., Rutenberg, A., 2016. Network model of human aging: frailty limits and information measures. Phys. Rev. E 94 (5). https://doi.org/10.1103/physreve.94.052409.

Farrell, S., Mitnitski, A., Theou, O., Rockwood, K., Rutenberg, A., 2018a. Probing the network structure of health deficits in human aging. Phys. Rev. E 98 (3). https://doi.org/10.1103/physreve.98.032302.

Farrell, S.G., Mitnitski, A., Theou, O., Rockwood, K., Rutenberg, A., 2018b. Probing the network structure of health deficits in human aging. Phys. Rev. E 9893, 032302. https://doi.org/10.1103/PhysRevE.98.032302.

Feridooni, H., Sun, M., Rockwood, K., Howlett, S.E., 2015a. Reliability of a frailty index based on the clinical assessment of health deficits in male C57BL/6J mice. J. Gerontol. A Biol. Sci. Med. Sci. 70 (6), 686–693. https://doi.org/10.1093/gerona/glu161.

Feridooni, H.A., Dibb, K., Howlett, S.E., 2015b. How cardiomyocyte excitation, calcium release and contraction become altered with age. J. Mol. Cell. Cardiol. 83, 62–72. https://doi.org/10.1016/j.yjmcc.2014.12.004.

Feridooni, H.A., Kane, A.E., Ayaz, O., et al., 2017. The impact of age and frailty on ventricular structure and function in C57BL/6J mice. J Physiol. (Lond.) 595 (12), 3721–3742. https://doi.org/10.1113/jp274134.

Fontana, L., Kennedy, B., Longo, V., Seals, D., Melov, S., 2014. Medical research: treat ageing. Nature 511 (7510), 405–407. https://doi.org/10.1038/511405a.

Franceschi, C., Garagnani, P., Morsiani, C., et al., 2018. The continuum of aging and age-related diseases: common mechanisms but different rates. Front Med. (Lausanne) 5, 61. https://doi.org/10.3389/fmed.2018.00061.

Franconi, I., Theou, O., Wallace, L., et al., 2018. Construct validation of a frailty index, an HIV index and a protective index from a clinical HIV database. PLoS One 13 (10), e0201394. https://doi.org/10.1371/journal.pone.0201394.

Fried, L., Tangen, C., Walston, J., et al., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56 (3), M146–M157. https://doi.org/10.1093/gerona/56.3.m146.

Gavrilov, L., Gavrilova, N., Olshansky, S., Carnes, B., 2002. Genealogical data and the biodemography of human longevity. Biodemogr, Soc. Biol. 49 (3-4), 160–173. https://doi.org/10.1080/19485565.2002.9989056.

Godin, J., Armstrong, J., Rockwood, K., Andrew, M., 2017. Dynamics of frailty and cognition after age 50: why it matters that cognitive decline is mostly seen in old age. J. Alzheimers Dis. 58 (1), 231–242. https://doi.org/10.3233/jad-161280.

Gordon, E., Peel, N., Samanta, M., Theou, O., Howlett, S.E., Hubbard, R., 2017. Sex differences in frailty: a systematic review and meta-analysis. Exp. Gerontol. 89, 30–40. https://doi.org/10.1016/j.exger.2016.12.021.

Hao, Q., Song, X., Yang, M., Dong, B., Rockwood, K., 2016. Understanding risk in the oldest old: frailty and the metabolic syndrome in a Chinese community sample aged 90+ years. J. Nutr. Health Aging. https://doi.org/10.1007/s12603-015-0553-5.

Hao, Q., Sun, X., Yang, M., Dong, B., Dong, B., Wei, Y., 2019. Prediction of mortality in Chinese very old people through the frailty index based on routine laboratory data. Sci. Rep. 9 (1). https://doi.org/10.1038/s41598-018-36569-9.

Hoogendijk, E., Rockwood, K., Theou, O., et al., 2018. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. Age Ageing 47 (5), 727–733. https://doi.org/10.1093/ageing/afy081.

Hornsby, W.E., Sareini, M.A., Golbus, J.R., et al., 2019. Lower extremity function is independently associated with hospitalization burden in heart failure with preserved ejection fraction. J. Card. Fail. 25 (1), 2–9. https://doi.org/10.1016/j.cardfail.2018.09.002.

Hougaard, P., 1995. Frailty models for survival data. Lifetime Data Anal. 1 (3), 255–273. https://doi.org/10.1007/bf00985760.

Howlett, S.E., Rockwood, K., 2013. New horizons in frailty: ageing and the deficit-scaling problem. Age Ageing 42 (4), 416–423. https://doi.org/10.1093/ageing/aft059.

Howlett, S.E., Rockwood, K., 2014. Ageing: develop models of frailty. Nature 512 (7514). https://doi.org/10.1038/512253d. 253-253.

Howlett, S.E., Rockwood, M., Mitnitski, A., Rockwood, K., 2014. Standard laboratory tests to identify older adults at increased risk of death. BMC Med. 12 (1). https://doi.org/10.1186/s12916-014-0171-9.

Hunter, S., Smailagic, N., Brayne, C., 2018. Dementia research: populations, progress, problems, and predictions. J. Alzheimers Dis. 64 (s1), S119–S143. https://doi.org/10.3233/JAD-179927.

Jansen, H., Moghtadaei, M., Mackasey, M., et al., 2017. Atrial structure, function and arrhythmogenesis in aged and frail mice. Sci. Rep. 7 (1). https://doi.org/10.1038/srep44336.

Justice, J.N., Nambiar, A.M., Tchkonia, T., et al., 2019. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine 40, 554–563. https://doi.org/10.1016/j.ebiom.2018.12.052.

Kane, A., Gregson, E., Theou, O., Rockwood, K., Howlett, S.E., 2017. The association between frailty, the metabolic syndrome, and mortality over the lifespan. Geroscience 39 (2), 221–229. https://doi.org/10.1007/s11357-017-9967-9.

Kane, A., Keller, K., Heinze-Milne, S., Grandy, S., Howlett, S.E., 2019. A murine frailty index based on clinical and laboratory measurements: links between frailty and proinflammatory cytokines differ in a sex-specific manner. J. Gerontol. A Biol. Sci. Med. Sci. 74 (3), 275–282. https://doi.org/10.1093/gerona/gly117.

Kelaiditi, E., Canevelli, M., Andrieu, S., et al., 2016. Frailty index and cognitive decline in Alzheimer's disease: data from the impact of cholinergic treatment use study. J. Am. Geriatr. Soc. 64 (6), 1165–1170. https://doi.org/10.1111/jgs.13956.

Kennedy, B.K., Berger, S.L., Brunet, A., et al., 2014. Geroscience: Linking aging to chronic disease. Cell 159 (4), 709–713. https://doi.org/10.1016/j.cell.2014.10.039.

Kim, D.H., Shi, S.M., 2019. Lower-extremity function as a marker of frailty and outcomes of heart failure with preserved ejection fraction in older adults. J. Card. Fail. 25 (1), 10–11. https://doi.org/10.1016/j.cardfail.2018.11.002.

King, K.E., Fillenbaum, G.G., Cohen, H.J., 2017. A cumulative deficit laboratory test-based Frailty Index: Personal and neighborhood associations. J. Am. Geriatr. Soc. 65 (9), 1981–1987. https://doi.org/10.1111/jgs.14983.

Kirkwood, T.B., 2015. Deciphering death: a commentary on Gompertz (1825)' On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies'. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 370 (1666). https://doi.org/10.1098/rstb.2014.0379. 20140379-20140379.

Kirkwood, T., Feder, M., Finch, C., et al., 2005. What accounts for the wide variation in life span of genetically identical organisms reared in a constant environment? Mech. Ageing Dev. 126 (3), 439–443. https://doi.org/10.1016/j.mad.2004.09.008.

Klausen, H.H., Petersen, J., Bandholm, T., et al., 2017. Association between routine laboratory tests and long-term mortality among acutely admitted older medical patients: a cohort study. BMC Geriatr. 1;17 (March 1), 62. https://doi.org/10.1186/s12877-017-0434-3. Erratum in: BMC Geriatr. 2017 Mar 15;17 (1):67.

Kojima, G., Iliffe, S., Walters, K., 2018. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing 47 (2), 193–200. https://doi.org/10.1093/ageing/afx162.

Kramers, H., 1940. Brownian motion in a field of force and the diffusion model of chemical reactions. Physica. 7 (4), 284–304. https://doi.org/10.1016/s0031-8914(40)90098-2.

Legdeur, N., Heymans, M.W., Comijs, H.C., Huisman, M., Maier, A.B., Visser, P.J., 2018. Age dependency of risk factors for cognitive decline. BMC Geriatr. 20;18 (August 1), 187. https://doi.org/10.1186/s12877-018-0876-2.

López-Otín, C., Blasco, M., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.

Ma, T., Lu, D., Zhu, Y.S., et al., 2018. ACTN3 genotype and physical function and frailty in an elderly Chinese population: the Rugao Longevity and Ageing Study. Age Ageing 47 (3), 416–422. https://doi.org/10.1093/ageing/afy007.

McKenzie, K., Ouellette-Kuntz, H., Martin, L., 2015. Using an accumulation of deficits approach to measure frailty in a population of home care users with intellectual and developmental disabilities: an analytical descriptive study. BMC Geriatr. 15, 170. https://doi.org/10.1186/s12877-015-0170-5.

Mitnitski, A., Rockwood, K., 2016. The rate of aging: the rate of deficit accumulation does not change over the adult life span. Biogerontology 17 (1), 199–204. https://doi.org/10.1007/s10522-015-9583-y.

Mitnitski, A., Mogilner, A., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. Transfus. Apher. Sci. 1, 323–336. https://doi.org/10.1100/tsw.2001.58.

Mitnitski, A., Song, X., Skoog, I., et al., 2005. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J. Am. Geriatr. Soc. 53 (12), 2184–2189. https://doi.org/10.1111/j.1532-5415.2005.00506.x.

Mitnitski, A., Bao, L., Rockwood, K., 2006. Going from bad to worse: a stochastic model of transitions in deficit accumulation, in relation to mortality. Mech. Ageing Dev. 127 (5), 490–493. https://doi.org/10.1016/j.mad.2006.01.007.

Mitnitski, A., Song, X., Rockwood, K., 2012. Trajectories of changes over twelve years in the health status of Canadians from late middle age. Exp. Gerontol. 47 (12), 893–899. https://doi.org/10.1016/j.exger.2012.06.015. Correction in Exp Gerontol. 2016;83:171. doi: 10.1016/j.exger.2016.07.009.

Mitnitski, A., Song, X., Rockwood, K., 2013. Assessing biological aging: the origin of deficit accumulation. Biogerontology 14 (6), 709–717. https://doi.org/10.1007/s10522-013-9446-3.

Mitnitski, A., Collerton, J., Martin-Ruiz, C., et al., 2015. Age-related frailty and its association with biological markers of ageing. BMC Med. 13 (1). https://doi.org/10.1186/s12916-015-0400-x.

Mitnitski, A., Rutenberg, A., Farrell, S., Rockwood, K., 2017a. Aging, frailty and complex networks. Biogerontology 18 (4), 433–446. https://doi.org/10.1007/s10522-017-9684-x.

Mitnitski, A., Howlett, S.E., Rockwood, K., 2017b. Heterogeneity of human aging and its assessment. J. Gerontol. A Biol. Sci. Med. Sci. 72 (7), 877–884. https://doi.org/10.1093/gerona/glw089.

Moghtadaei, M., Jansen, H., Mackasey, M., et al., 2016. The impacts of age and frailty on heart rate and sinoatrial node function. J Physiol. (Lond.) 594 (23), 7105–7126. https://doi.org/10.1113/jp272979.

Panza, F., Lozupone, M., Logroscino, G., 2019. Understanding frailty to predict and prevent dementia. Lancet Neurol. 18 (2), 133–134. https://doi.org/10.1016/S1474-4422(18)30446-0.

Parks, R., Fares, E., MacDonald, J., et al., 2012. A procedure for creating a Frailty Index based on deficit accumulation in aging mice. J. Gerontol. A Biol. Sci. Med. Sci. 67 (3), 217–227. https://doi.org/10.1093/gerona/glr193.

Ritt, M., Jäger, J., Ritt, J.I., Sieber, C.C., Gaßmann, K.G., 2017. Operationalizing a frailty index using routine blood and urine tests. Clin. Interv. Aging 12, 1029–1040. https://doi.org/10.2147/cia.s131987.

Rockwood, K., 1997. Lessons from mixed dementia. Int. Psychogeriatr. 9 (3), 245–249. https://doi.org/10.1017/s1041610297004407.

Rockwood, K., 2016. Conceptual models of frailty: accumulation of deficits. Can. J. Cardiol. 32 (9), 1046–1050. https://doi.org/10.1016/j.cjca.2016.03.020.

Rockwood, K., Howlett, S.E., 2018. Fifteen years of progress in understanding frailty and health in aging. BMC Med. 16 (1). https://doi.org/10.1186/s12916-018-1223-3.

Rockwood, K., Mitnitski, A., 2006. Limits to deficit accumulation in elderly people. Mech. Ageing Dev. 127 (5), 494–496. https://doi.org/10.1016/j.mad.2006.01.002.

Rockwood, K., Mitnitski, A., 2007. Frailty in relation to the accumulation of deficits. J. Gerontol. A Biol. Sci. Med. Sci. 62 (7), 722–727. https://doi.org/10.1093/gerona/62.7.722.

Rockwood, K., Mitnitski, A., 2015. Resilience and frailty: further steps, best taken together. Eur Ger Med. 6 (5), 405–407. https://doi.org/10.1016/j.eurger.2015.06.001.

Rockwood, K., Fox, R.A., Stolee, P., Robertson, D., Beattie, B.L., 1994. Frailty in elderly people: an evolving concept. Can. Med. Assoc. J. 150 (4), 489–495.

Rockwood, K., Mogilner, A., Mitnitski, A., 2004. Changes with age in the distribution of a frailty index. Mech. Ageing Dev. 125 (7), 517–519. https://doi.org/10.1016/j.mad.2004.05.003.

Rockwood, K., Mitnitski, A., Song, X., Steen, B., Skoog, I., 2006. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J. Am. Geriatr. Soc. 54 (6), 975–979. https://doi.org/10.1111/j.1532-5415.2006.00738.x.

Rockwood, K., Song, X., Mitnitski, A., 2011. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 183 (8), E487–E494. https://doi.org/10.1503/cmaj.101271.

Rockwood, K., McMillan, M., Mitnitski, A., Howlett, S.E., 2015. A Frailty Index based on common laboratory tests in comparison with a Clinical Frailty Index for older adults in long-term care facilities. J. Am. Med. Dir. Assoc. 16 (10), 842–847. https://doi.org/10.1016/j.jamda.2015.03.027.

Rockwood, K., Blodgett, J., Theou, O., et al., 2017. A frailty index based on deficit accumulation quantifies mortality risk in humans and in mice. Sci. Rep. 7 (1). https://doi.org/10.1038/srep43068.

Rogers, N.T., Steptoe, A., Cadar, D., 2017. Frailty is an independent predictor of incident dementia: evidence from the English longitudinal study of ageing. Sci. Rep. 7 (1). https://doi.org/10.1038/s41598-017-16104-y.

Rudzinski, K., McDonough, P., Gartner, R., Strike, C., 2017. Is there room for resilience? A scoping review and critique of substance use literature and its utilization of the concept of resilience. Subst. Abuse Treat. Prev. Policy 12 (1), 41. https://doi.org/10.1186/s13011-017-0125-2.

Rutenberg, A., Mitnitski, A., Farrell, S., Rockwood, K., 2018. Unifying aging and frailty through complex dynamical networks. Exp. Gerontol. 107, 126–129. https://doi.org/10.1016/j.exger.2017.08.027.

Scheltens, P., Rockwood, K., 2011. How golden is the gold standard of neuropathology in dementia? Alzheimers Dement. 7 (4), 486–489. https://doi.org/10.1016/j.jalz.2011.04.011.

Schorr, A., Carter, C., Ladiges, W., 2017. The potential use of physical resilience to predict healthy aging. Pathobiol. Aging Age Relat. Dis. 8 (1), 1403844. https://doi.org/10.

1080/20010001.2017.1403844.

Schosserer, M., Banks, G., Dogan, S., et al., 2019. Modelling physical resilience in ageing mice. Mech. Ageing Dev. 177, 91–102. https://doi.org/10.1016/j.mad.2018.10.001.

Schoufour, J.D., Mitnitski, A., Rockwood, K., Evenhuis, H.M., Echteld, M.A., 2015. Predicting 3-year survival in older people with intellectual disabilities using a Frailty Index. J. Am. Geriatr. Soc. 63 (3), 531–536. https://doi.org/10.1111/jgs.13239.

Searle, S., Mitnitski, A., Gahbauer, E., Gill, T., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8 (1). https://doi.org/10.1186/1471-2318-8-24.

Shi, J., Yang, Z., Song, X., et al., 2014. Sex differences in the limit to deficit accumulation in late middle-aged and older Chinese people: results from the Beijing Longitudinal Study of Aging. J. Gerontol. A Biol. Sci. Med. Sci. 69 (6), 702–709. https://doi.org/10.1093/gerona/glt143.

Shi, S., Afilalo, J., Lipsitz, L.A., et al., 2018. Frailty phenotype and deficit accumulation Frailty Index in predicting recovery after transcatheter and surgical aortic valve replacement. J. Gerontol. A Biol. Sci. Med. Sci.(August). https://doi.org/10.1093/gerona/gly196. [Epub ahead of print].

Song, X., Mitnitski, A., Rockwood, K., 2011. Nontraditional risk factors combine to predict Alzheimer disease and dementia. Neurology 77 (3), 227–234. https://doi.org/10.1212/wnl.0b013e318225c6bc.

Song, X., Mitnitski, A., Rockwood, K., 2014. Age-related deficit accumulation and the risk of late-life dementia. Alzheimers Res. Ther. 6 (5-8), 54. https://doi.org/10.1186/s13195-014-0054-5.

Stainton, A., Chisholm, K., Kaiser, N., et al., 2018. Resilience as a multimodal dynamic process. Early Interv. Psychiatry. https://doi.org/10.1111/eip.12726.

Sterniczuk, R., Theou, O., Rusak, B., Rockwood, K., 2013. Sleep disturbance is associated with incident dementia and mortality. Curr. Alzheimer Res. 10 (7), 767–775. https://doi.org/10.2174/15672050113109990134.

Stow, D., Matthews, F., Barclay, S., et al., 2018a. Evaluating frailty scores to predict mortality in older adults using data from population based electronic health records: case control study. Age Ageing 47 (4), 564–569. https://doi.org/10.1093/ageing/afy022.

Stow, D., Matthews, F.E., Hanratty, B., 2018b. Frailty trajectories to identify end of life: a longitudinal population-based study. BMC Med. 16 (September (1)), 171. https://doi.org/10.1186/s12916-018-1148-x.

Taneja, S., Mitnitski, A., Rockwood, K., Rutenberg, A., 2016. Dynamical network model for age-related health deficits and mortality. Phys. Rev. E 93 (2). https://doi.org/10.1103/physreve.93.022309.

Theou, O., Rockwood, M., Mitnitski, A., Rockwood, K., 2012. Disability and co-morbidity in relation to frailty: How much do they overlap? Arch. Gerontol. Geriatr. 55 (2), e1–e8. https://doi.org/10.1016/j.archger.2012.03.001.

Theou, O., Brothers, T., Mitnitski, A., Rockwood, K., 2013. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. J. Am. Geriatr. Soc. 61 (9), 1537–1551. https://doi.org/10.1111/jgs.12420.

Theou, O., Brothers, T., Peña, F., Mitnitski, A., Rockwood, K., 2014. Identifying common characteristics of frailty across seven scales. J. Am. Geriatr. Soc. 62 (5), 901–906. https://doi.org/10.1111/jgs.12773.

Theou, O., Chapman, I., Wijeyaratne, L., et al., 2016. Can an intervention with testosterone and nutritional supplement improve the frailty level of under-nourished older people? J. Frailty Aging 5 (4), 247–252. https://doi.org/10.14283/jfa.2016.108.

Trebbastoni, A., Canevelli, M., D'Antonio, F., et al., 2017. The impact of frailty on the risk of conversion from mild cognitive impairment to Alzheimer's Disease: Evidences from a 5-Year Observational Study. Front. Med. (Lausanne) 4. https://doi.org/10.3389/fmed.2017.00178.

Vaupel, J., Manton, K., Stallard, E., 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demogr. 16 (3), 439. https://doi.org/10.2307/2061224.

Wallace, L., Theou, O., Kirkland, S., et al., 2014. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. PLoS One 9 (3), e90475. https://doi.org/10.1371/journal.pone.0090475.

Wallace, L., Theou, O., Godin, J., Andrew, M., Bennett, D., Rockwood, K., 2019. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. Lancet Neurol. 18 (2), 177–184. https://doi.org/10.1016/s1474-4422(18)30371-5.

Walston, J.D., Bandeen-Roche, K., 2015. Frailty: a tale of two concepts. BMC Med. 13, 185. https://doi.org/10.1186/s12916-015-0420-6.

Wang, C., Ji, X., Wu, X., et al., 2017. Frailty in relation to the risk of Alzheimer's disease, dementia, and death in older Chinese adults: a seven-year prospective study. J. Nutr. Health Aging 21 (6), 648–654. https://doi.org/10.1007/s12603-016-0798-7.

Whitehead, J., Hildebrand, B., Sun, M., et al., 2014. A clinical frailty index in aging mice: comparisons with frailty index data in humans. J. Gerontol. A Biol. Sci. Med. Sci. 69 (6), 621–632. https://doi.org/10.1093/gerona/glt136.

Yanagawa, B., Graham, M.M., Afilalo, J., Hassan, A., Arora, R.C., 2018. Frailty as a risk predictor in cardiac surgery: Beyond the eyeball test. J. Thorac. Cardiovasc. Surg. 201 (18), 32301–32308. https://doi.org/10.1016/j.jtcvs.2018.08.054. S0022-5223 [Epub ahead of print].

Yang, M., Zhuo, Y., Hu, X., Xie, L., 2018. Predictive validity of two frailty tools for mortality in Chinese nursing home residents: frailty index based on common laboratory tests (FI-Lab) versus FRAIL-NH. Aging Clin. Exp. Res. 30 (12), 1445–1452. https://doi.org/10.1007/s40520-018-1041-7.