New horizons in frailty: ageing and the deficit-scaling problem

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Abstract

All the current frailty measures count deficits. They differ chiefly in which items, and how many, they consider. These differences are related: if a measure considers only a few items, to define broad risks those items need to integrate across several systems (e.g. mobility or function). If many items are included, the cumulative effect of small deficits can be considered. Even so, it is not clear just how small deficits can be. To better understand how the scale of deficit accumulation might impact frailty measurement, we consider how age-related, subcellular deficits might become macroscopically visible and so give rise to frailty. Cellular deficits occur when subcellular damage has neither been repaired nor cleared. With greater cellular deficit accumulation, detection becomes more likely. Deficit detection can be done by either subclinical (e.g. laboratory, imaging, electrodiagnostic) or clinical methods. Not all clinically evident deficits need cross a disease threshold. The extent to which cellular deficit accumulation compromises organ function can reflect not just what is happening in that organ system, but deficit accumulation in other organ systems too. In general, frailty arises in relation to the number of organ systems in which deficits accumulate. This understanding of how subcellular deficits might scale has implications for understanding frailty as a vulnerability state. Considering the cumulative effects of many small deficits appears to allow important aspects of the behaviour of systems close to failure to be observed. It also suggests the potential to detect frailty with less reliance on clinical observation than current methods employ.

Keywords: frailty index, phenotype, deficit accumulation, aged, animal models, older people

Overview of frailty and its measurement

The term frailty emerged from two separate streams of inquiry. In 1979, Vaupel et al. [4] described as ‘frailty’ the tendency for some people to be long-lived. They view frailty as an attribute of the individual, largely fixed from some young age. Geriatricians, in contrast, largely see frailty as an individual’s increased risk of adverse outcomes; this risk often varies with age. Geriatricians’ early thinking was influenced by the then unresolved question of ‘targeting’. Initial trials of comprehensive geriatric assessment had made clear that specialized geriatric interventions were most effective when targeted to elderly people at high risk [5]. These people we now recognize as frail.

Not everyone of the same age has the same risk of adverse health outcomes. The greater vulnerability of some people compared with others of the same chronological age is understood as frailty. Frailty increases with age, is multiply determined, and compromises an individual’s ability to withstand physiological stressors. Frailty is often described as resulting in compromised physiological reserve [1–3].

This paper addresses how frailty seen in patients relates to what happens at the cellular and subcellular levels in ageing. It is motivated by the practical consideration of what constitutes a countable deficit. Here, we consider how frailty is viewed, summarize key aspects of deficit accumulation, review work that bridges subcellular to macroscopically visible deficits and consider consequences for clinical research.
Of course there is more to frailty than being the successful target of a geriatric intervention. Two recent reviews have outlined many ways to measure frailty clinically [6, 7]. There is no consensus on which measure to use, although all measures count deficits. Even so, they differ in the nature and number of items which they consider; two 2001 studies offer contrasting views. One proposed frailty as a syndrome [1]. Five items available in the data set of a large prospective cohort study were selected as defining frailty: weight loss, impaired grip strength, slow walking speed, self-reported exhaustion and reduction in high-order functional activities (e.g. heavy housework, lawn mowing). A person with three of the five was said to demonstrate the ‘frailty phenotype’. Contrarily, people with none of the five were ‘robust’ and people with one or two were ‘pre-frail’. Survival varied between the three groups, with the frail having the worst outcomes (Figure 1A). This finding has been extensively cross-validated, although the cut-point for what defines pre-frail and frailty has varied [8–10].

This view of frailty as a syndrome, defined by a few highly specified items, contrasts with viewing frailty as a state, operationalized using the frailty index approach; the latter has been contrasted as consisting of many hardly specified items. Deficits in the frailty index are ‘hardly specified’ in being any symptom, sign, disease, disability or laboratory abnormality that meet a few criteria. [11] A deficit should have a prevalence of at least 1%, be associated with an adverse outcome and accumulate with age, but should not saturate (i.e. not be present in >80% of people by any age <90 years). [12] In any data set, no candidate deficit should be included if it has >5% missing data. As a group, deficits need to cover several organ systems and number at least 30 items. The frailty index equals the number of deficits present in an individual, divided by the number of deficits counted. Counting deficits allows frailty to be stratified; people with more deficits are at higher risk of adverse health outcomes, including death (Figure 1B). The effects counted by the frailty index need not individually be large. In fact, even deficits that might not singly be significantly related to adverse outcomes can accumulate to compromise an organism’s viability [13]. But how small is not yet clear. Including laboratory abnormalities might offer insights, as discussed below.

A third 2001 frailty measurement study counted more deficits [17] than the five specified in the phenotype, but still required their precise measurement in a way that the frailty index did not [14]. In this way, the Groningen Frailty Indicator illustrates how many other contemporary frailty measures operate.

Frailty at the organ level: variable organ dysfunction

On average, organ system function declines with age. Unsurprisingly, such decline varies, both within and between individuals, even in people who are otherwise well. Estimates of peak oxygen consumption (VO₂) during a 400 m walk test varied markedly in healthy participants (60–91 years) in the Baltimore Longitudinal Study of Aging [15]. While 17% had peak VO₂ values that met disability criteria (<18 ml O₂/kg/min), a similar proportion had values >28 ml O₂/kg/min [15]. Considerable heterogeneity also exists in cardiovascular responses to upright bicycle exercise in healthy older participants [16]. Although age-related impairment in maximum heart rate, end-systolic volume, end-diastolic volume, ejection fraction and cardiac index can be seen in some, others perform at levels of younger adults [16]. Marked variability in the deleterious effects of age on skeletal muscle quality and mass also was reported in the Baltimore cohort [17, 18].

Such differential organ system vulnerability to adverse outcomes illustrates that frailty exists at the organ level. In
this way, a level in the scale of deficit accumulation is crossed, from the organ to the organism, in the sense of integrated organ function (e.g. deficits in mobility). Note too that before such organ damage becomes macroscopically visible, it often can be detected by laboratory, imaging or electrodagnostic tests, crossing a scale level from cells to tissues (e.g. asymptomatic to echocardiographically detectable cardiac dysfunction). As organ level deficits accumulate, they can give rise to symptoms or signs, thereby scaling up to clinically evident disease. Necessarily, what happens at the organ system is not independent of what happens in cells.

**Cellular deficit accumulation**

Cellular ageing arises when *damage* goes unrepaired, or is not removed, giving rise to *deficits*. Damage can arise endogenously (e.g. reactive oxygen species as by-products of metabolism) or exogenously (e.g. radiation, hypothermia, hypoxaemia). A host of repair processes and clearance mechanisms respond to inevitable damage [19]. Several protein kinases, glutathione, nucleoside and other enzymes contribute to the DNA repair response [20]. Telomerase represents a mechanism for the repair of chromosomal damage. Autophagy illustrates a clearance mechanism in both mitotic and post-mitotic cells [21, 22]. Repair processes are under genetic influence, which can vary across the life course [22]. How damage accumulates to give rise to deficits is stochastic [19]. When damage accumulates irreversibly, cell death can occur through apoptosis and perhaps also autophagy [20, 21].

**Mitotic cells**

In culture, mitotic cells show replicative senescence, in which growth is arrested after a limited number of divisions [23]. Prior to replicative senescence, changes in cell function can be detected. For example, skin fibroblasts from mice show impaired organisation of the extracellular matrix, a reduction in the plasticity of chromatin and changes in the structure of cytoplasmic filaments [24]. If this extends to human cells, then impaired functioning of connective tissue, bone and other cells that undergo high turnover (e.g. T cells, intestinal epithelium, liver) will result in organ dysfunction. From a deficit-scaling standpoint, individual skin cells can show increased production of collagenase; subsequent damage to the extracellular matrix contributes to macroscopically detectable wrinkles. Tracking the course of deficit accumulation in individual mitotic cells, for example, in cell culture models of senescence [25], would be of great interest.

**Post-mitotic cells**

The human brain represents a well-studied example of ageing in post-mitotic cells, offering insights into how deficits might scale up. Initial clinico-pathological studies indicated that dementia arose in relation to the burden of intracellular plaques and extra-neuronal tangles. For some time, however, this has been recognized as incomplete [26]. Large-scale, prospective, community-based autopsy studies, which included people with normal cognitive function, reported that no cut-point of either neuropathological or ischaemic lesions that discriminates people with dementia from those without it. [27] In general, although synaptic density is key (less density, greater impairment), scaling from microscopic insults to cognitive dysfunction appears to reflect more the total burden of insults than that of any single lesion [28]. Likewise, variability in response (some people express clinical dementia at lower levels of plaque and tangle density than do others) suggests that concepts of reserve and repair capability are also needed. In other words, function does not follow morphology. Similarly, structural damage is not the same as a functional deficit. Deficits are more likely with more damage (and frailty is more likely with higher levels of deficit accumulation) but the full picture must include how the cells are able to repair, remove or tolerate damage. At least at the cellular level, it appears that not all subcellular damage gives rise to cellular deficits. More damage makes deficits more likely, but not inevitable [27, 28].

Experimental studies hold promise in making the distinction between structural and functional deficits. In animal studies, cardiomyocyte function declines with age, with key disruptions in intracellular calcium homeostasis [29–31]. With time, the inability of cardiomyocyte repair mechanisms, such as autophagy, to remove waste materials leads to the accumulation of aberrant proteins and the build-up of lipofuscin and defective mitochondria [30]. This can lead to the activation of cell death mechanisms [32]. Indeed, post-mortem morphometric investigations of hearts have shown progressive age-related myocyte loss, accompanied by hypertrophy of surviving myocytes, especially in males [33, 34]; even so, the link with clinical disease is not yet clear. Similar age-related findings have been reported in ageing rodent [29, 31] and non-human primate models [35], although age-dependent changes in cardiomyocytes do not always result in overt cardiac dysfunction [33].

To investigate how frailty might relate to cardiomyocyte dysfunction, we developed a frailty index in ageing mice [36]. We chose 12- (middle-aged) and 30-month-old (aged) animals, based on survival data from our colony of C57BL/6J mice (Figure 2A). Aged mice had higher frailty index scores than younger animals (frailty index = 0.43 ± 0.03 versus 0.08 ± 0.02; *P* < 0.001; Figure 2B) [36]. Further, high frailty index scores were associated with cardiomyocyte contractile dysfunction (Figure 2C and D) and cardiomyocyte hypertrophy (Figure 2E and F). This cardiomyocyte contractile dysfunction and hypertrophy would be predicted to result in tissue and organ hypertrophy and contractile dysfunction *in vivo*, although how these cellular deficits might scale to produce overt cardiac dysfunction in frail mice is the subject of ongoing inquiry.

**Evidence for scaling in humans**

As yet, despite some hints [37–39], we have little direct evidence for scaling effects of microscopic deficits in humans.
Figure 2. Characteristics of a mouse model of frailty. (A) Kaplan–Meier survival curves for mortality in C57BL/6J mice showed that survival was similar in both sexes (log-rank test; \( P > 0.05 \), \( n = 230 \) male and 191 female mice). Arrows denote the ages of the middle-aged adult and aged animals. (B) Mean frailty index scores increased significantly with age (\( n = 12 \) mice; * indicates significantly different from comparison group, \( P < 0.001 \)). (C) Length of cardiomyocytes from aged male mice plotted as a function of the frailty index. Cardiomyocyte length increased linearly with increasing frailty index scores (\( r^2 = 0.76; P = 0.001; n = 10 \) myocytes). (D) Cardiomyocyte length also increased as the frailty index increased in cells from females (\( r^2 = 0.58; P = 0.017; n = 9 \) myocytes). (E and F) The mean (± SEM) peak cardiomyocyte contractions declined significantly as the frailty index increased in cells from male and female mice. Myocytes were stimulated at 6 Hz and contractions were expressed as fractional shortening (\( n = 10 \) myocytes from aged males and nine myocytes from aged females. In (C) and (D), data were fitted with a simple linear regression; \( P \)-values and \( r^2 \) values (coefficient of determination) were calculated for each line. In (E) and (F), data were analysed with one-way ANOVA. * denotes significantly different from cells from mice with the lowest frailty index; † indicates significantly different from cells from mice with the highest frailty index [36].
Indeed, in at least two studies frailty index scores were not associated with telomere length [40, 41]. Likewise, one study found only modest links between a frailty index and immune senescence markers, at least when the markers were considered individually [40]. On the other hand, in another study, even though pre-vaccination IgG levels did not vary between frailty index groups; the immune response to pneumococcal vaccination was lowest in people with higher scores [42]. In short, investigation of scaling might require that more than one laboratory deficit is considered; likewise, the impact of frailty might be demonstrated less by single values and more by the response to a challenge. At present, little is known about how (sub)cellular deficits might scale, but in principle it seems reasonable that macroscopic deficits must reflect microscopic ones.

Again, Alzheimer’s disease (AD) offers one such example. In one community-based autopsy series, the summed influence of different types of neuropathological lesions, better than any single lesion, was associated with the clinical diagnosis of dementia [28]. An analogous case appears to hold in relation to risk factors. A re-analysis of dementia risk in the Canadian Study of Health and Aging showed that the probability of a clinical diagnosis of AD expression reflected the sum of many deficits that were not known as dementia risk factors [43]. Specifically, 19 health deficits were combined in a so-called ‘non-traditional risk factor index’. Not only were none otherwise known as dementia risk factors dementia (e.g. diarrhoea, foot problems), but most, individually, were not significantly associated with dementia. Even so, when combined, they showed a positive relationship with dementia. In a pattern similar to what is typically seen with a frailty index (Figure 3A) [44], the index of 19 non-traditional risk factors was also related to mortality [45] (Figure 3B). This relationship held in an age-adjusted multivariate model, and even trumped any traditional dementia risk factor.

A second line of evidence suggests that what happens at the cellular level influences what happens macroscopically. Again, the evidence is indirect. The distribution of the frailty index changes characteristically over successive 5-year increments [45] (Figure 4). Reading the panels from left to right, they illustrate what happens as the number of deficits that a person has at baseline increases from none \( (n = 0) \) to 10 \( (n = 10) \). Two changes are evident in the distribution of the number of deficits at follow-up frailty. First, areas under the curves diminish as baseline deficits increase; this chiefly reflects loss due to mortality. Secondly, the modes increase by one additional deficit: e.g. most commonly, people with one deficit at baseline have two deficits at follow-up; those with three at baseline have four at follow-up, and so on. Both changes suggest a general picture of slightly worse health: survival diminishes, and on average, survivors have more deficits. Even so, improvement in the health status can occur: at each non-zero baseline state, some people have fewer deficits, although even with as few as three deficits, no one improves to having no deficits 5 years later. We are concerned here only with the deficit count: not everyone with the same number of deficits has the same type of deficits.

Remarkably, despite this inter-individual variability, the overall pattern of change is stable: over successive 5-year intervals (indicated by the closed and open circles, the same pattern holds). In this way, deficits change more in accord with their number than with their nature. This suggests shared processes in regulating how damage is repaired or removed.

**Mechanisms by which frailty might emerge from subcellular deficits**

Subcellular deficits in one organ system correlate with a frailty index calculated from macroscopic deficits in other organ systems [36]. The mechanism by which frailty elsewhere is associated with frailty in a given cell type is not clear. Broadly, three possibilities suggest themselves: subcellular deficits in one organ system are not associated in any
mechanistic way. Put slightly differently, their relationship is simply that they share time as an exposure. Injury in one system neither protects against nor predisposes to injury in another system, but the more time that elapses, the greater the chance for any system to fail. Secondly, a shared mechanism of injury, or of an incomplete compensatory response, might affects more than one cell type [46, 47]. Despite some evidence for this, other work notably has shown no strong relationship, at least when considered individually in cross-sectional data \[40, 41\]. This would be expected if, as seems likely, there are many paths to frailty: cumulative effects need not have a shared basis across groups. Indeed, recent genome-wide association studies in humans show that low significance longevity alleles can accumulate to importantly affect survival \[48\]. Finally, it might be that failure in one system predisposes to failure in another at the system level. This is almost certainly so, and would serve as a complementary, more than an alternative explanation to other mechanisms. As a trivial clinical example, in a patient with anaemia of any cause, the impact of coronary artery disease is likely to be felt sooner than in a patient with a normal red cell count.

**Implications for measuring frailty**

The presence of laboratory abnormalities may offer some insight into how scaling works. While sometimes clinically detectable, laboratory abnormalities, and other investigations such as the measure of blood pressure, or electrocardiography, offer a means of detecting organ deficits prior to clinical disease expression. Whether a deficit index based only on routine blood work and like investigations would conform to the properties of a typical frailty index is unclear, but an intriguing possibility. Recent work on the measurement of deficits in aged mice lends support to this proposition, but awaits demonstration in humans.

**Conclusion**

People who are frail have problems in many organ systems, and the problems can be quantified in a frailty index that counts deficits. Even so, the deficit count suggests a relatively increased risk, not an absolute one, as risk can be enhanced by some factors (e.g. social vulnerability) \[49\] or mitigated by others (e.g. exercise) \[50\].
Deficits that are macroscopically detectable, even by laboratory or specialized testing, reflect deficits in organ systems. Even so, the line from subcellular deficits to clinically detectable ones will not be straightforward. Each deficit reflects an unrepaired insult and these insults need not have only one cause. What is more, the cellular deficits that scale to produce clinical frailty need to exist in several organ systems [12].

Thinking about the biology of frailty in this way offers insights and challenges. Animal research is highly reductionist, but a frailty index based on deficit accumulation in organs other than the one being studied can bridge between subcellular and whole-body events and whole-body events in the whole organism. In humans, a frailty index consisting of deficits in laboratory, imaging and electrodiagnostic tests might bridge between cellular, tissue and organ damage, illuminating how macroscopic deficits arise. The clinical challenges of how deficits scale include considering how interventions against frailty might offer insights into mechanisms. Interventions with widespread effects need to be evaluated; the impact across a variety of insults and intrinsic repair mechanisms needs to be evaluated. Exercise is a compelling example [51, 52, 53].

Progress in understanding frailty mechanisms will require substantial effort and better quantitative models. An approach that builds on everyday clinical experience, or intense study of animals as they age, coupled with feasible quantitative measures and analyses drawing on the mathematics of complexity seems a reasonable approach and is motivating further inquiries by our group.

Key points

- Ageing occurs when subcellular damage is either unrepaired or unremoved and accumulates to affect tissues and organ function.
- Frailty can be considered as a state of vulnerability to adverse outcomes resulting from the accumulation of deficits associated with clinical effects.
- Emerging experimental data relate whole organism frailty to subcellular deficit accumulation.

Conflicts of interest

With colleagues, K.R. has applied to various Canadian government schemes to commercialize a version of the frailty index, based on a comprehensive assessment, and an expanded version of the clinical frailty scale. To this end, they have asserted copyright on the new instruments and formed a company called Videx Canada. None of the work aimed for commercialization is referred to in this paper.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References

The very long list of references supporting this commentary has meant that only the most important are listed here and are represented in bold type throughout the text. The full list of references is given in Supplementary data available in Age and Ageing online.


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