



January 19-20, 2011, Athens, Greece
IAGG/WHO/SFGG Workshop n°3
“Promoting access to innovation and clinical
research for frail old persons”

How might deficit accumulation give rise to frailty?

Invited presentation to the IAGG/WHO/SFGG Workshop on Frailty
scheduled for Athens, Greece on January 20 & 21, 2012

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December 2011-12-02

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Abstract

Frailty is a multiply determined vulnerability state. People who are frail are at risk of many adverse health outcomes, including death. For any individual, this risk can only be expressed probabilistically. Even very fit people can suddenly die or become catastrophically disabled, but their risk of both is much lower than a very frail person, who might nevertheless suddenly succumb without worsening health.

Frailty occurs with ageing, a stochastic, dynamic process of deficit accumulation. Deficits occur ubiquitously at subcellular levels, ultimately affecting tissues, organs and integrated organ action, especially under stress. Some people are disposed to accumulate deficits at higher rates, but on average, deficit accumulation varies across the life course and likely is mutable. In this way, the clinical definition of frailty is distinct from the statistical definition, which sees frailty as a fixed factor for an individual.

Recent, early animal work links subcellular deficits to whole body frailty. In humans, clinically detectable health deficits combine to increase the risk of adverse health outcomes. The rate of deficit accumulation occurs with remarkable regularity around the world, as does a limit to frailty. Of note, when 20+ deficits are counted, these characteristics are indifferent to which deficits are considered.

The expression of risk in relation to deficit accumulation varies systematically. For example, at any given level of deficit accumulation, men are more susceptible to adverse health outcomes than are women. Likewise, in China, the lethality of deficit accumulation appears to be higher than in Western countries. In consequence, it may be necessary to better distinguish between frailty and physiological reserve; the latter may apply chiefly in relation to microscopic deficits. The expression of frailty risk in relation to deficit accumulation depends on the environment, including both the physical and social circumstances in which people find themselves.

Key words: frailty, deficit accumulation, frailty index, aged, frailty phenotype, physiological reserve, mathematical gerontology, stochastic dynamics.

As is well known, two general approaches are used to characterize frailty.^{1,2,3} One sees frailty as a phenotype, with five key clinical features,⁴ that sometimes are expanded to include impairments in cognition and mood,⁵ or at other times reduced to just impaired mobility⁶ or grip strength.⁷ Another sees frailty arising as a consequence of the accumulation of deficits.⁸ The two approaches have in common the idea that frailty is a multiply determined vulnerability state, putting people at risk for a range of adverse health outcomes, including death. They also view frailty as an individual characteristic, and one that can change over the life course. (This is in contrast to the statistical definition of frailty, which sees it as a fixed individual factor,⁹ similar to Beard's notion of a longevity factor.¹⁰) The two also share the idea that frailty underlies the variable vulnerability to adverse outcomes of people of the same chronological age. This last means that both approaches to measuring frailty have been validated in relation to mortality prediction; this is a reasonable, if rough standard, but there is more to frailty than mortality prediction, a point elaborated below. Acknowledging that this is only one view, the purpose of this paper is to consider how deficit accumulation might give rise to frailty. It will do this by first sketching clinical deficit accumulation and then considering how this might link to deficit accumulation at the subcellular and tissue level.

Frailty as clinical deficit accumulation – the Frailty Index

The strong case for frailty as deficit accumulation reads like this. As people age, they are more likely to die. But not everyone of the same age has the same risk of death. What accounts for the relationship between age and death? As people age, they are more likely to have things wrong with them. The more things they have wrong with them, the more likely they are to die. Not everyone of the same age has the same number of things wrong with them, and it is this variability in the number of things they have wrong with them which accounts for the variable likelihood of death of older adults of the same age.

There is reasonable evidence for this view that variable deficit accumulation is associated with variability in the risk of adverse health outcomes.¹¹ To interpret the evidence a few methodological points need to be reviewed. First, the notion of “things people have wrong with them” has been operationalized as “health deficits”. A health deficit can be any symptom, sign, laboratory measurement, disease or disability. In contrast to the *highly* specified items that make up the frailty phenotype, what gets counted as a health deficit is *hardly* specified at all. In fact, the only criteria are that any candidate health deficit for inclusion in a frailty index should increase with age, have a prevalence of at least 1%, have <5% missing data, are related to an adverse outcome and cover several organ systems. In addition, enough deficits should be considered so that all relevant bodily systems can be covered, as well as their impact on function. The health deficits qualitatively should cover more than just co-morbidities; as they assay impact on function they should include items such as measures of mobility, strength, physical activity and health attitude. Quantitatively, as few as 20 items can be considered, but in general, more robust estimates are found when the frailty index includes 50 or more potential health deficits; after about 70 such deficits, there appears to be little gain in precision. When many deficits exist which meet these criteria, they can be sampled at random with little impact on overall risk classification,¹² although the more items that are selected, the narrower the confidence limits.¹³ By virtue

of the liberal criteria for inclusion as a deficit, many clinical and population datasets have enough information in them for deficit accumulation to be studied using existing data. Likewise, a typical Comprehensive Geriatric Assessment carries enough information for frailty to be operationalized – and graded – even without performance measures, or the precise items used in the frailty phenotype or like operational definitions that require.¹⁴ In either setting deficits can be counted in a frailty index.

A frailty index is the measure by which the risk of adverse health outcomes is calculated. A frailty index counts deficits and standardizes the deficit count for an individual in relation to the total number of deficits considered. In short, the frailty index score for any individual is the ratio of deficits present in that individual to the number of deficits counted. Consider, for example, that a health survey data set has 50 variables that each meet the criteria for being considered as a health deficit. Someone who had none of these would have a frailty index score of $0/50 = 0$. (This is also referred to as the “zero state” of frailty and has particular significance, discussed below.) Someone with 35 things wrong would have a frailty index score of $35/50 = 0.70$. As it turns out, this, and not 1.0, is the likely maximum frailty index score.

Around the world, across different data sets, and using different variables and different numbers of the same variables to calculate a frailty index, community-dwelling people accumulate deficits at about the same rate – about 3% per year, on a log scale.¹⁵ Deficit accumulation in theory starts before birth. Empirically, it can be demonstrated from about age 15 onwards. **[Figure One]**. Figure One, which reports a 40-item frailty index, shows its distribution over 7 successive waves of a cohort study. Several features are remarkable. First, the distribution is about the same each year, with the notable exception of slightly fewer people each year who have nothing wrong with them. Next, even though the cohort has aged 14 years, the upper limit of the frailty index for the 99% of the population does not exceed 0.67.¹⁶ That is because, on average, the risk of death is closely linked to the value of the frailty index. The fact that the maximum value is much less than 1.0 reflects the common sense clinical observation that an individual might be as sick as they can be without having every known disease.

Although health deficits should cover both impairments in a range of body systems and some evidence that these deficits are impactful, some commentators insist that no definition of frailty should include mention of disability.^{17,18} As with other groups,¹⁹⁻²⁸ this is not a convention to which we subscribe. Amongst other reasons, the great majority of frail older adults have some degree of disability, especially when the “physical activity” criterion of the frailty phenotype is operationalized as impairment in household chores, mowing the lawn or gardening.²⁹ Excluding disability from the evaluation of frailty also undermines the strategy of staging frailty, which is essential for clinical decision making. Given that people with a greater degree of frailty are more at risk of adverse outcomes than those with a lesser degree of frailty, and that the notion of frailty is meant in part to explain why some people of the same age have worse outcomes than others do, then being able to stage frailty is highly desirable, as well as being empirically demonstrable. Even so, some individual variability is inherent in the stochastic nature of deficit accumulation, as well as in the variable environments in which older adults might find themselves. What is more, even systems with no redundancy and no ability to repair – a radioactive decay curve illustrates an extreme example³⁰ – will show variable survival.

How do deficits come about?

Frailty occurs with ageing, a stochastic dynamic process of deficit accumulation. A standard view of ageing is that deficits arise first³¹ at subcellular levels, and ultimately affect tissues, organs and integrated organ action – i.e. function – especially under conditions of stress. A variety of examples exist, including many which overlap between key age-related diseases, such as Alzheimer's disease and diabetes mellitus, which affect glucose metabolism and are related to longevity in lower order animals³². Against this background, it might be tempting to see deficit accumulation simply as a matter of scale. Indeed, recent animal work has shown that the accumulation of deficits in other systems (such as changes in sodium handling or plasma glucose levels) is associated with both structural and functional changes in myocytes, and with impaired mobility.³³ It should be noted however that the scale varies amongst the items considered as health deficits in a frailty index. Some may well reflect relatively specific processes having become disordered (e.g. low bone density) whereas others are much less specific (e.g. "heart disease"). Still others integrate across a large number of organ systems, such as impaired mobility. These last have been named "clinical state variables".³⁴ The term was chosen to be exactly analogous to a state variable in a physical system, such as temperature, which reflects the average of the kinetic energies of the atoms which make up that system. The link between subcellular deficits and state variables needs to be better understood, so that a more quantitative and less metaphorical language can be employed.

Another consequence of the difference in scale between subcellular deficits and how function might be impacted is that is important to distinguish between levels of deficits. At any level, the presence of a deficit reflects that the capacity to resist or repair the insult which gave rise to the deficit has been overwhelmed. As we have seen, in humans, macroscopic deficit accumulation is tightly associated with mortality at the group level, where the relationship between the mean frailty index and the risk of death increases exponentially with typically very high fit, manifest, for example, by $r^2 > 0.95$. Even so, at the individual level, the outcomes of a given level of frailty range from improvement to stability to worsening to death. These probabilities occur with great regularity, described as a change in the Frailty Index which corresponds to a Poisson distribution.³⁵ Although mortality risk, for example, increases with age, even very fit people can suddenly die or become catastrophically disabled, but their risk of both is much lower than a very frail person, who might nevertheless suddenly succumb without worsening health. These probabilities are in turn influenced systematically by other factors, including social ones (such as social vulnerability)³⁶⁻³⁸ or the country in which a person lives. For example, in Canada, the frailty index mortality curve is convex to the baseline (**Figure 2**)³⁹ whereas in China, it is concave to the baseline.⁴⁰ (**Figure 3**). Systematic variability in the risk of an adverse outcome in relation to the number of deficits also varies in relation to factors more intrinsic to the individual, such as the level of exercise or education.^{41,42} What this variable tolerability appears to reflect is how deficits impact intrinsic repair capacity, which typically is termed "physiological reserve" or "physiological redundancy" and which perhaps can be measured separately.⁴³ Given variable life circumstances, it can be expected that some people are disposed to accumulate deficits at higher rates than others do, but on average, the tendency to deficit accumulation is variable, and likely mutable, and varies across the life course.⁴⁴

Conclusions

Frailty is a multiply determined vulnerability state which is related to ageing. Conceptually, it can be related to ageing in body systems and their integrated action, and that too can be related to subcellular deficit accumulation, although this needs to be tested empirically, as has begun with animal work. Considering frailty in relation to deficit accumulation allows the interval nature of the frailty index to be exploited to make frailty modeling more precise. It also poses an important challenge in clinical research, which is translate from the elegant reproducibility of the mathematics to the more divergent manifestations that frailty can take in humans.

Figure legends

Figure One. Mean value of Frailty Index at each study cycle as a function of age (n=14.127, population weighted) (Reproduced from CMAJ, Rockwood et al., 2011)

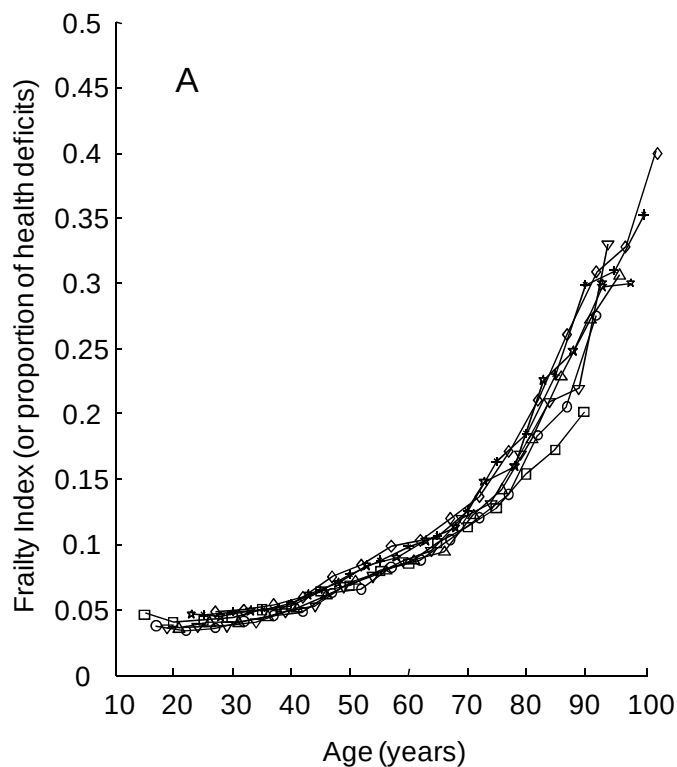


Figure Two. The probability of death as a function of the number of the Frailty Index during 4, 8 and 12 years amongst Canadians aged 55 years and older at baseline.(The data came for the NPHS and adapted from Mitnitski et al., 2007, Exp Geront]

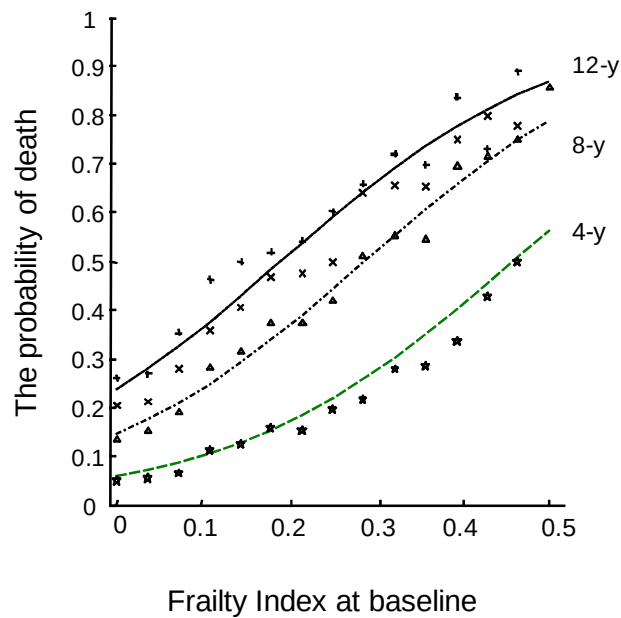
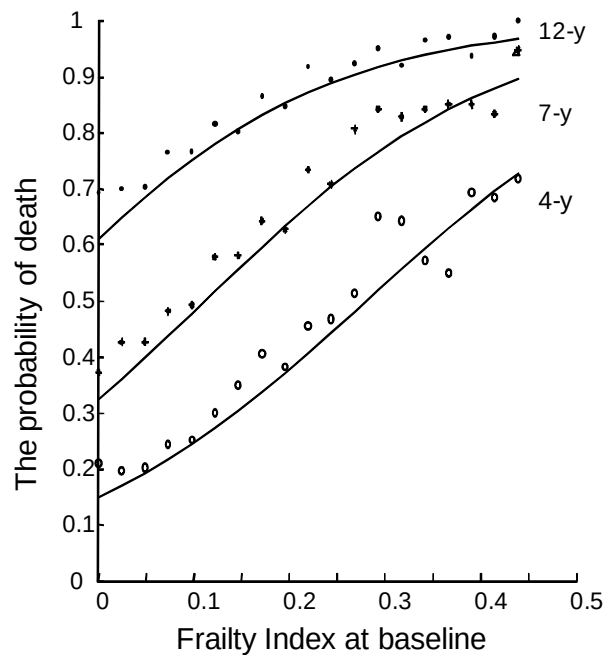


Figure Three. The probability of death as a function of the Frailty Index during 4, 7 and 12 years Chinese people aged 55 and over. [Reproduced from BMC Geriatric, Shi et al., 2011]



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