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Unconventional Views of Frailty

Review Article

Frailty in Relation to the Accumulation of Deficits

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This review article summarizes how frailty can be considered in relation to deficit accumulation. Recalling that frailty is an age-associated, nonspecific vulnerability, we consider symptoms, signs, diseases, and disabilities as deficits, which are combined in a frailty index. An individual's frailty index score reflects the proportion of potential deficits present in that person, and indicates the likelihood that frailty is present. Although based on a simple count, the frailty index shows several interesting properties, including a characteristic rate of accumulation, a submaximal limit, and characteristic changes with age in its distribution. The frailty index, as a state variable, is able to quantitatively summarize vulnerability. Future studies include the application of network analyses and stochastic analytical techniques to the evaluation of the frailty index and the description of other state variables in relation to frailty.

FRAILTY is a nonspecific state of increasing risk, which reflects multisystem physiological change. It is highly age-associated. The physiological changes that underlie frailty do not always achieve disease status, so that some people, usually very elderly, are frail without having life-threatening illness. These statements about frailty are relatively noncontroversial. More controversial is how to operationalize frailty in clinical practice and for research (1–6). We and others have done so by considering frailty in relation to the accumulation of deficits (7–12). Here, we review how studying deficit accumulation can help elucidate frailty, its relation to aging, and its mechanisms. We focus on mathematical and clinical aspects.

Background

The frailty index score is calculated as the proportion of potential deficits that are present in a given individual, as elaborated below. The frailty index recognizes that frailty is multifactorial and dynamic (13,14). We first tried to define frailty by combining integrated items—and traditional foci of gerontologists—such as cognition, mobility, continence, and function (14). Although this gave good construct (15) and predictive validity (14,16), it left much variance unexplained, and did not consider relative fitness. We aimed for a measure that could evaluate impairments in many systems, accommodate change, was graded, and was conceptually simple. By combining items in a single index, we can consider frailty in absolute and relative terms, according to this probabilistic consideration: The more things individuals have wrong with them, the higher the likelihood that they will be frail. We now consider each part of that statement.

What should be counted as ''things that individuals have wrong with them''? We consider symptoms, signs, disabilities, diseases, and laboratory measurements, which we term *deficits*. The frailty index uses a range of deficits that are readily available in survey or clinical data. (Examples are available at: http://myweb.dal.ca/amitnits/STable.htm.) A standard Comprehensive Geriatric Assessment (CGA) (17), for example, records about 40 items, some of which are self-reported (e.g., ''how would you rate your health''), others ascertained by tests [e.g., Mini-Mental State Examination (18)], and still others by clinical evaluation (e.g., congestive heart failure) or laboratory measurement (diabetes mellitus). These can be combined by simply adding them—for example, a 1 for each deficit that is present, a 0 when they are absent, and a fraction when they are present to a limited extent (e.g., health as good = 0, fair = 0.5, poor = 1) (19,20). Obviously, there are many ways to count, for example, 10 deficits from a total of 40, but as illustrated below, the resulting index score (10/40 = 0.25) has many characteristic features, even if the composition is not the same between individuals. Whereas it is understandable to be concerned about the specific nature of the variables that might be included in the frailty index, our experience suggests that, when some sufficiently large number (roughly, about 40) variables are considered, the variables can be selected *at random*, and still yield comparable results of the risks of adverse outcomes (21).

What we mean by ''the higher the likelihood that they will be frail'' is a greater risk of adverse outcomes (e.g., death, institutionalization, health services use, further deficit accumulation). Still, we note that frailty is neither necessary for death (even very fit people can die unexpectedly, as in an accident) nor is it sufficient (even at the highest level of the frailty index, the median survival time is > 1 year). Moreover, although death is individual, the mortality rate is a group statistic, so our inquiries are necessarily probabilistic. Furthermore, we are not concerned about mortality

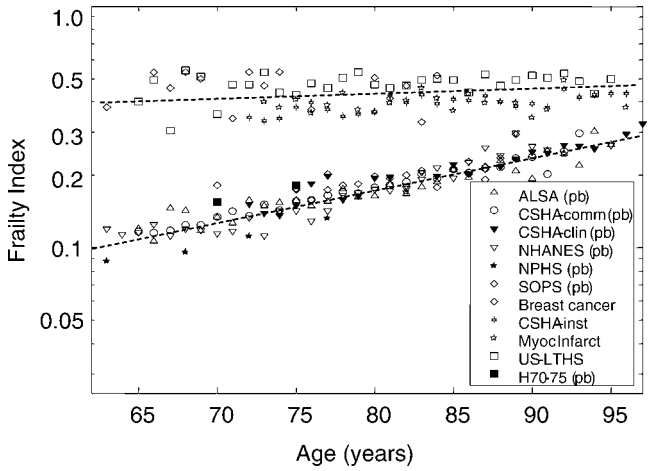

Figure 1. Relationship between the frailty index and chronological age for seven population-based (pb), community-dwelling samples ($n = 33{,}581$) (ALSA [Australian Longitudinal Study of Aging], CSHA-screen [Canadian Study of Health and Aging screening sample], CSHA-exam [clinical examination sample, H-70, Gothenburg study, Sweden], NPHS [National Population Health Survey, Canada], NHANES [National Health and Nutrition Examination Survey, United States], and SOPS [Sydney Old Persons Study, Australia] and 2573 people from two institutional (CSHA-inst CSHA wave 1 institutionalized sample; US-LTHS-inst National Long Term Care Survey, United States) and two clinical studies (Breast cancer [cohort of metastatic breast cancer survivors, Canada] and MyocInfarct [Improving Cardiovascular Outcomes of Nova Scotians; ICONS, Canada]). Lines show the regression of mean frailty index with age. For community-dwelling people, the line parameters are: slope = 0.029 (95% confidence interval = 0.0267, 0.0301) and intercept = –4.012 (–3.872, –4.142) [from Mitnitski et al. (24)].

prediction; instead, mortality prediction has served as a means of validating the concept. Were our focus mortality prediction, we would have given heavy weight to chronological age, or diseases of known lethality, such as late-life cancer (22). Rather, we view frailty such that chronological age can be understood as a contextual factor—for example, as providing an expected value for deficit accumulation. Our model suggests that the effect of chronological age on adverse outcomes can be negligible when deficits are taken into account (20,21,23,24).

Still, apparent intuitiveness would be no advantage if it gave unintelligible or trivial results, but the self-evident statement that people with more things wrong are more likely to suffer an adverse event is quantifiable with the frailty index, and manipulating the resulting data gives rise to insights (including hints of mechanisms) that are not self-evident. Before considering these mathematical aspects, we first summarize some essential features. On average, deficits accrue at a characteristic rate. In elderly people from four developed countries, the mean rate of deficit accumulation across ages was close to 0.03 (observed range 0.02–0.04) per year on a log scale (Figure 1) (24). Note that the samples differed not just by country, but were collected up to 20 years apart and used different variables (e.g., self-report, clinically assessed, laboratory measures). Moreover, the frailty indices used different numbers of variables (from <30 to 70). The only restrictions on variables we used were that they reflected deficits (cf. attributes—e.g., such as eye color) accumulated across ages, and had <5% missing values. Although a recent Chinese estimate put the rate of deficit lower (at about 1.4%) (8), this appears to reflect a survivor effect after age 87 years. By contrast, the frailty index has otherwise correlated very highly (typically > 0.96) with age (12,24,25). In addition, women accumulate more deficits than men do, even though, for any given level of deficits, men have the higher mortality rates (8–12,24). In contrast to community dwelling people, in the institutional and clinical cohorts, the frailty index was high at all ages, and thus showed no relationship to age, consistent with high levels of frailty in those settings (24).

Mathematical Explorations in Relation to Mechanisms

The frailty index approach has a certain similarity to other quantitative approaches. Vaupel and colleagues (26) proposed that a largely undefined ''frailty'' could account for heterogeneity in health status to explain mortality outcomes (26). The origin of this frailty was hypothesized to come from genetic differences, and this was addressed in a mathematical model incorporating the pleiotropy of several genes (27).

Our approach of quantifying deficit accumulation yields some understanding of the vulnerability of both individuals and groups. For example, the distribution of the index shows both characteristic changes with age (28) and a limit that does not depend on age (29). Here, however, we focus on two findings that hint at biological mechanisms: changes in the heterogeneity of health with age and transitions between health states. The average rate of deficit accumulation increases monotonically with age, as does the standard deviation, underlying the generally accepted contention that, with age, health status becomes more variable. Importantly, however, only *absolute* heterogeneity in health status (e.g., as measured by the variance) increases with age. Relative heterogeneity decreases with age, as illustrated by the coefficient of variation, which is the ratio of the standard deviation to the mean. We have found that the coefficient of variation of the frailty index consistently decreases with age (Figure 2) (28,30).

The decrease with age in the coefficient of variation has theoretical implications. Ashby's theory of ''requisite variety'' (31,32) suggests that, if the number of insults faced by an organism overwhelms the number of responses that it can mount, the system will fail. Therefore it is reasonable to expect that, as systems age, they lose variety in their response repertoires, here captured, at the group level, by the coefficient of variation. Furthermore, a simple stochastic process of deficit accumulation yields a power-law relationship between the mean frailty index m and its coefficient of variation, $v \sim m^{-1/2}$ (30). The same exponent ½ has also been found in the relationship between the average flux in complex networks, and its fluctuations as measured by its standard deviation (33). Consistent with the exponent representing influences external to the network, we interpret this to mean that large environmental effects—for example, cohort effects—become less important closer to the end of life, where more proximate effects dominate. In consequence, at extreme old age, people become more susceptible to smaller

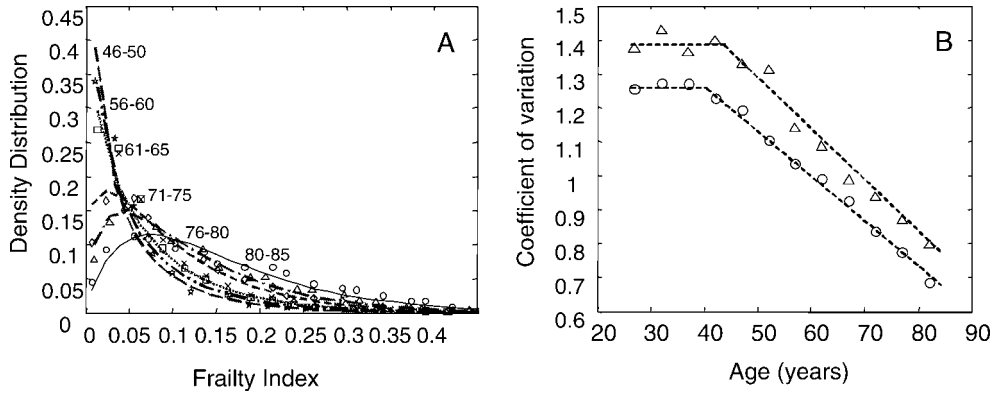

Figure 2. Changes with age in the frailty index. **A,** Change in the shape of the distribution, both sexes. **B,** Change in the coefficient of variation separately in men (*triangles*) and women (*circles*) [from Rockwood et al. (28)].

perturbations. That the coefficient of variation itself can be summarized in network analyses is of considerable interest, and is motivating further inquiries by our group.

Aging involves many interacting processes, in which stochastic components play a key role—even in genetically identical twins raised in a constant environment (34). With aging, damage accumulates in cells and tissues, whether by random (35) or genetic (36) mechanisms, involving subcellular and organ-specific pathways (37). Each results in declines in functional capacity (38,39) and redundancy exhaustion (40). Our modeling (23) reveals stochastic mechanisms and opens the prospect of using powerful analytical techniques derived from the theory of stochastic processes (41). A modified Poisson model with two nontrivial parameters gives a unified description of transitions to worse health states, health improvements, and mortality. The probability of transitions between n (at baseline) and k deficits can be expressed as the following:

$$P_{nk} = \frac{\rho_n{}^k}{k!} \exp(-\rho_n)(1 - P_{nd}),$$

where P_{nd} is the probability to die during the time between two consecutive assessments, $\rho_n = \rho_0 + b_1 n$, and $P_{nd} = P_{0d}$

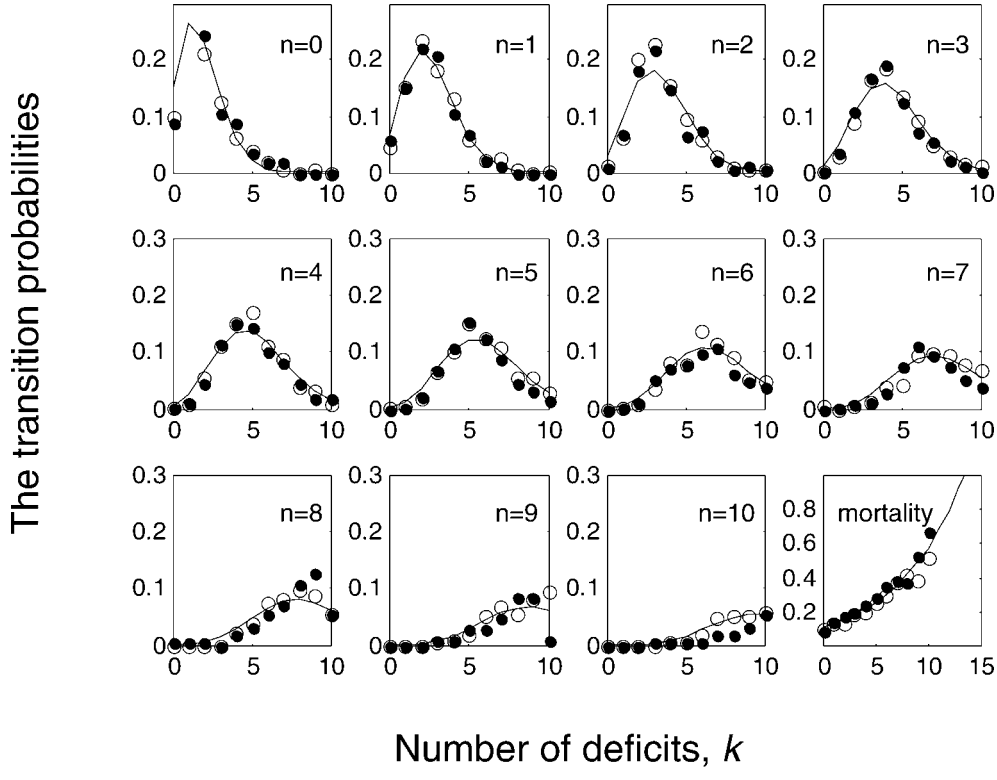

Figure 3. The probability of transition from n to k deficits, and to death (*bottom right*) in relation to the starting n deficits. Observational data of transitions from Canadian Study of Health and Aging (CSHA)-1 to CSHA-2 (*filled circles*) and from CSHA-2 to CSHA-3 (*open circles*). Estimates are presented for the model that combines transitions from CSHA-1 to CSHA-2 and from CSHA-2 to CSHA-3 [from Mitnitski et al. (23)].

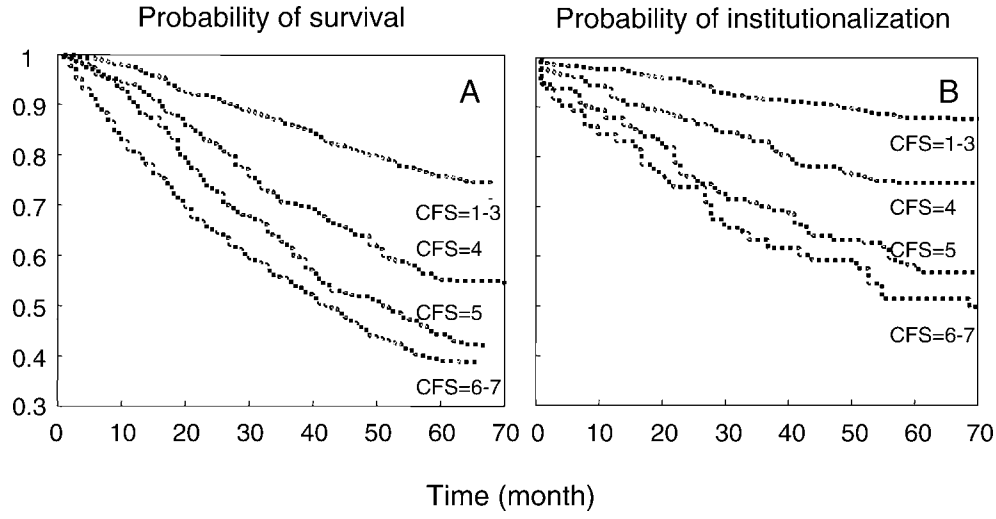

Figure 4. **A,** Kaplan–Meier medium-term survival curves (adjusted for age and sex) for individuals with different values of the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS). The number of people at the start of each group: $n = 952$ for CFS = 1–3; $n = 349$ for CFS = 4; $n = 305$ for CFS = 5; $n = 691$ for CFS = 6–7. **B,** Kaplan–Meier medium-term institutionalization curves (adjusted for age and sex) for individuals with different values of the Clinical Global Frailty Scale. The number of people at the start of each group: $n = 828$ for CFS = 1–3; $n = 256$ for CFS = 4; $n = 136$ for CFS = 5; $n = 66$ for CFS = 6–7 [from Rockwood et al. (16)].

$exp(b_2 n)$; ρ_0 and P_{0d} are the baseline characteristics. The two parameters b_1 and b_2 describe, respectively (given the current number of deficits), the increments of their expected change, and the risk of death (23). The very high model fit ($R = 0.99$) (Figure 3) with so few parameters has encouraged additional inquiries. The simple stochastic multistage model shows not only deficit accumulation but also its flip side. It shows that improvement is also possible and not so rare (roughly one third of the sample showed some degree of improvement in 5 years). Still, the likelihood of death increases exponentially with the number of deficits; therefore, in the long run, the negatives outweigh the positives.

Clinical Utility of Frailty Index Measures

Few clinicians would doubt that the more things that people have wrong with them, the frailer they will be, but few too would embrace a 70-item scale. For now, we have itemized the elements of a standard CGA to produce an FI-CGA (20,21). The FI-CGA has the usual properties of other versions—that is, it is highly correlated with age, shows a γ distribution, is higher in women, and correlates with several adverse outcomes, including institutionalization and health care use (Figure 4). If further cross-validated, an FI-CGA could aid clinical decision-making by indicating the degree of frailty, and thus the likelihood of an adverse outcome.

The FI-CGA, like other versions of the frailty index [including the widely used 5-item phenotype definition (42)] largely weights items equally. It might seem obvious to apply differential weights to the variables, so that cancer, for example, would be weighted more heavily than skin disease. Although in individual samples the performance of the index (e.g., in predicting death) can be improved by weighting (43), in general, weighting limits generalizability. For now, generalizability appears to have the greatest value; therefore we have pursued studies without weighting. Still, studies that might aid clinical decision-making (for example, by demonstrating how closely an individual has approached the theoretical limit of frailty) will require scrupulous attention to whether the price paid in precision is too high for the rewards in generalizability. Alternately, other groups might cross-validate an unweighted frailty index but use weighting for local use. Whether there are demonstrable levels or severity classes also needs careful investigation (16,44).

Future Directions

In addition to studies that further explore the frailty index's mathematical properties, evaluate the limit to frailty, locally cross-validate weighted and unweighted clinical versions, and investigate grades, we see other uses of the frailty index approach. We are keen that insights on frailty can translate into pragmatic techniques for geriatricians (45). Clearly, the frailty index does not define a syndrome, which is a collection of specific symptoms and signs. Instead, the frailty index can be considered as a state variable, in that it characterizes the whole health of individuals and validly classifies risk across a wide range of people (7,46). This does not contradict the idea of a syndrome; indeed, it should be the case that people classified as frail syndromically will have higher frailty index values than those who do not.

If the frailty index can be considered as a state variable, perhaps there are others. In our view, attention and concentration, function, and mobility and balance all seem to be logical candidates, as they are evolutionarily high order and integrate many pathways. Mobility and balance especially seem to have merit in the acute care setting, where they fluctuate with changes in an individual's overall state of health, can readily be tracked, have plain language descriptors, and are susceptible to quantification (47). Perhaps

the most ambitious application of the frailty index is as a means of summarizing the commonly invoked (but less commonly quantified) concept of biological age (7,8,12,48–50). Such studies might best be situated within the idea of biomarkers, and could thereby benefit from the considerable experience of those inquiries (51–53). For now, the evaluation of deficit accumulation index points out how we can embrace the complexity of frailty.

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