**Changes in health among the participants of the Framingham Heart Study from 1960s to 1990s: Application for an index of cumulative deficits**

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## ABSTRACT

We used an index of cumulative deficits (DI) to investigate whether improvements documented in the general population along major health dimensions were evident at the basic level of health assessment associated with small changes in the aging-related health deterioration. We considered the 9th (performed in 1964) and 14th (1974) Framingham Heart and 5th (1991-1995) Offspring Study exams and selected 37 small-effect deficits to construct the DIs. The 37-deficit DI shows trends for improvements in health for the 5-year age groups ranging 55-to-75 years between the 1960s and 1990s. We identified also deficits-specific DIs which age patterns tend to exhibit upward trends (5-deficits DI), no trends (18-deficits DI), and downward trends (12-deficits DI) between the 1960s and 1990s. The 12-deficits DI is stronger predictor of the long-term mortality risks than the other indices. The analyses show favorable tendencies when health either did not change or improved over time for the most serious small-effect traits.

**Key words**: Public health, Population characteristics, Age distribution.

## INTRODUCTION

Numerous studies have documented improvements in the health of the general population during the 20th century (reviewed in [1]). These improvements were documented along a number of dimensions of health reflecting the process of population health change (e.g., a simplified pathway is: risk factors → disease → loss of functioning → disability → death [1]). Most studies of health trends (apart from mortality changes) in recent years have emphasized positive changes in disability prevalence among older individuals (e.g., [2,3]). Improvements in physical, cognitive, and sensory limitations were recently summarized in [3]. Trends in diseases are not so positive; most studies suggest an increasing chronic disease burden, including consistent estimates of upward trends in heart disease prevalence during the 1970-to-1990 period from several major studies (e.g., National Health Interview Survey, Framingham Heart [FHS] and Offspring [FHSO] Studies, Minnesota Heart Survey) [1]. Studies of temporal changes in disease risk factors were largely focused on heart diseases and cancer and provided mixing evidences [1,4].

Another approach to the assessment of health status is based on global health characteristics. One such characteristic is self-rated health, which is viewed as a summary of overall health status due to its high predictive power of death. Measures of self-rated health show a consistent decline in the prevalence of individuals who rate their health as poor during the 1980s and 1990s, a trend that was more pronounced among the elderly than among the younger population [5-7].

Major health dimensions provide some indications of trends in severe health conditions (e.g., disease, disability, self-perceived health). Will these trends continue in the future? To answer this question, a mechanism driving changes in severe health conditions has to be understood. This is a motivation for studies of trends in risk factors. Understanding the importance of trends in less severe health conditions leads to yet another focus of recent research which is not simply on risk factors but on symptoms and signs [8]. Insights on changes in these factors might provide more precise clues on future changes in population health. The challenge facing such studies is the large number of various symptoms and signs and the small or inconsistent effect of each on health/mortality risks. The aggregate effect of several such small-effect factors, however, might be more informative. This is an underlying paradigm of recent developments of a new promising instrument which is called a *frailty index* [9-11] or an *index of cumulative deficits* [12,13]. The concept of a *cumulative health deficits index* (DI) also appears to be useful in studies of aging, health, and survival for which the DI is a promising alternative to chronological age for characterizing aging-associated processes in individuals and for improved predictions of chances of adverse events [11-20]. Consequently, the DI can be an indicator of changes in health on the level of small-effects traits (e.g., signs, symptoms), and, simultaneously, can serve as a characteristic of global health/well-being.

This study investigates trends in the health status in sample of adult and elderly individuals participating in the FHS/FHSO using a new instrument, the DI, which aggregates small-effect variables routinely collected during the 1960-to-1990 period. Unlike other studies, the focus of this work is on a broad spectrum of such traits.

## METHODS

### The FHS and FHSO data

Beginning in 1948, 5,209 respondents (46% male) aged 28–62 years residing in Framingham, Massachusetts were enrolled in the famous Framingham Heart Study. The FHSO dataset consists of a sample of 3,514 biological descendants of the FHS Cohort, 1,576 of their spouses and 34 adopted offspring for a total sample of 5,124 subjects; 48% male. The FHSO subjects were enrolled in 1971-1975 using research protocols similar to those of the FHS so that comparisons of the results from the FHSO and the FHS could be made. Selection criteria and study design have been described [21,22]. These cohorts have been followed for the occurrence of certain diseases (e.g., heart disease, cancer, diabetes mellitus) and death. Examination also included an interview, physical examination, and laboratory tests.

### The cumulative deficits approach

In traditional analyses, traits with small, inconsistent, or non-significant contributions to risks of adverse health outcomes are usually ignored. When the number of such traits is large enough, however, their cumulative effect on chances of future adverse events may become significant and, thus, an integrative or cumulative measure (i.e., the DI) might be more informative compared to individual traits [12-15,20]. In addition, the proportion of such various health characteristics taken from a wide list of potential disorders accumulated up to a given age might be a good characterization of the level of aging-associated decline in health status at this age [12-15,20]. If the DI is constructed from a set of small-effect traits, it can capture small decrements in declining health with aging, hopefully, informing about health problems long before clinically manifested conditions.

The conceptual framework behind the DI can be summarized in a simplified scheme in which the individual's vulnerability state can be characterized by a proportion of failed units out of a large number, *N*, of such units (subsystems). The failure of each unit is associated with a "deficit". The proportion of deficits accumulated by age *x* characterizes individual's health/well-being status and affects chances of further health deterioration and death. The data often do not allow for observing failures of all the *N* units. Therefore, an empirical estimate of this proportion in a given individual, i.e., the *DI(x)*, can be calculated by selecting a set of *M* units out of a list with *N* units, summing the number of failed units from the selected set *M* up to age *x*, *m*(*x*), and dividing this sum by *M*, i.e., $DI(x)=m(x)/M$ [15,23-25]. Prior studies suggest that the properties of the DI are weakly sensitive to the choice of the subset *M* [18].

### Analyses

The evaluation of trends in the age patterns of DI is constrained by several factors. First, ideally, the DIs have to be constructed using a wide set of heath-related conditions (see above Section). Second, survey instruments have to be comparable over time. Third, the range of intersecting ages should be as large as possible. Fourth, the surveys/exams should be well separated in time. Finally, selected samples have to be of adequate size. To address all these constraints, the same sets of 37 deficits (Table 1) with comparable diagnostic procedures across all years was selected from two representative exams of the FHS ($9^{th}$ FHS exam performed in 1964; N=3833; age range is 44-78 years; mean age (MA) $\pm$ standard error=59.0 $\pm$ 0.13 years and $14^{th}$ FHS exam performed in 1974; N=2871; age range is 55-88 years; MA=67.5 $\pm$ 0.14) and one representative exam of the FHSO ($5^{th}$ FHSO exam performed in 1991-1995; N=3799; age range is 31-78 years; MA=55.0 $\pm$ 0.16). Seventeen deficits were either dichotomous (yes, or no) or dichotomized for the sake of consistency between exams. The remaining 20 deficits were rescaled to the unit interval to reflect the degree of abnormality, e.g., the urinary sugar level was recoded as negative (0 or no deficit), doubtful (0.5) and positive (1 or yes deficit).

**Table 1 about here**

The construction of the DI handles the problem of missing answers by counting only those questions which were explicitly answered. To ensure that missing answers do not bias the weight of deficits, however, all analyses were performed with individuals, for whom information on any of the selected 37 deficits was missing, excluded. The age range in all analyses was limited to that which is common for all exams, i.e., from 55 to 78 years. These yielded samples of N=2117 (MA=$63.9 \pm 0.13$) for the 9$^{th}$ FHS, N=2471 (MA=$65.6 \pm 0.12$) for the 14$^{th}$ FHS, and N=1274 (MA=$63.1 \pm 0.15$) for the 5$^{th}$ FHSO exams.

For more reliable estimates, the patterns of the respective characteristics were plotted for 5-year age cohorts in each exam. First, they were computed for each deficit to elucidate whether there were consistent trends on an individual-deficit level. Next, the patterns for the DIs composed of different numbers of deficits were evaluated. The Cox proportional hazard regression model was used to evaluate the effects of the DIs—all as measured in the baseline exams—on the hazard of death considering deaths that occurred within the maximum follow-up period for the 14$^{th}$ exam, i.e., 24 years (the last known vital status assessment was at the 25$^{th}$ exam performed in 1998). The regression models were sex and age adjusted.

## RESULTS

These analyses show, first, that the traditional approach of considering trends over time in individual traits associated with selected medical or lab exams (Table 1) generally fails. Specifically, only two deficits out of 37 (i.e., increased antero-posterior diameter [IAPD] and venous insufficiency or varicose veins [VV]; Table 1, group 4) showed consistent and significant downward trends over time in the 5-year age patterns. No definitive conclusions (except trivial on inconsistent trends) can be made about trends in the age patterns for other deficits. An advantage of the approach based on the DI is that the cumulative effect of traits with such non-consistent behaviors may be more informative.

Figure 1 shows age patterns for (a) the full 37 deficits DI ($DI_{37}$) as well as for (b) the 35-deficits DI ($DI_{35}$) with IAPD and VV excluded. Downward trends indicating improvements in health are more pronounced for the $DI_{37}$ than for the $DI_{35}$ between the mid 1960s and the mid 1990s. This effect is, however, attributed to significant trends in the IAPD and VV.

**Figure 1 about here**

Analysis of trends in the age patterns for individual deficits allowed us to identify sub-groups of deficits with qualitatively different trends over time. Specifically, we identified 18 deficits (Table 1, group 1) each of which exhibits no trend. These deficits were gathered into the respective DI ($DI_{18}$) which characterizes health dimensions associated with no health changes. Five deficits (Table 1, group 2) showed inconsistent increasing trends over time. The respective DI is associated with worsening-over-time health dimension ($DI_5$). A third group of 12 deficits was characterized by non-consistent trends of decline over time. This group does not include the IAPD and VV and characterizes improving-over-time health dimension ($DI_{12}$). We also constructed alternative DI with these two deficits (i.e., IAPD and VV) included ($DI_{14}$).

As expected, Figure 2 shows no changes in health characterized by the $DI_{18}$ at younger ages (55-69 years). For older ages, the results are inconsistent: the $DI_{18}$ for ages 70-78 years tends to be lower at the 14$^{th}$ FHS exam compared to the 9$^{th}$ FHS and 5$^{th}$ FHSO exams. The $DI_5$

shows a pattern of increase over time (although due to small number of deficits included, this is not entirely convincing). The $DI_{14}$ and $DI_{12}$ exhibit significant downward trends from the mid 1960s to the mid 1990s for all age groups except 75-78 years. It is important to recognize that the $DI_{12}$ is constructed without the IAPD and VV deficits.

**Figure 2 about here**

Are the respective DIs relevant to health deterioration with aging? To address this question, we evaluated the relative risks of death attributable to the $DI_{18}$, $DI_5$, and $DI_{12}$ in multivariate Cox regression analyses of the pooled sample of participants of the 9$^{th}$ and 14$^{th}$ FHS and 5$^{th}$ FHSO exams with all three indices included. Figures 3a-c show that each of these indices can significantly predict death within certain periods of follow-up. The strongest determinant of the short-term risks of death is the $DI_{18}$. Its contribution into the hazard rate, however, declines when the follow-up time increases. In contrast, the contribution of the $DI_{12}$ increases when the follow-up time increases. The risks of death attributable to the $DI_{18}$ and $DI_{12}$ converge in the long-term perspective. The relative risk attributable to the $DI_5$ is insignificant for the short-term follow-ups. It first increases and than quickly saturates. The $DI_5$ provide the weaker and less significant estimates than the other two indices.

**Figure 3 about here**

Finally, we renormalized the respective relative risks to elucidate how deadly each deficit included into the respective DI is within the same range of change of the DIs. Such renormalization can be done as follows. For instance, the $DI_{18}$ ranges between 0 and 48%, whereas the $DI_{12}$ ranges between 0 and 43% (Figures 3a,c). We recalculated the risks over the same unit interval since the ranges of change for these indices are different. Then we recalculated the risks for one deficit in each index since the number of deficits is different. Then the relative risk attributable to one deficit (assuming a uniform distribution of risk over the deficits) from those included into the definition of a given DI normalized to the reference DI (e.g., the $DI_{18}$) is

$$RR_{DI_i}^{DI_{18}}(1) = \exp\left(\beta \frac{range_{DI_i}}{range_{DI_{18}}} \frac{1}{i}\right), \qquad (1)$$

where $i$ is the number of deficits in the respective DI. Figure 3d shows that the relative risks renormalized according to (1) for the $DI_{18}$ are larger than those for the $DI_{12}$ and $DI_5$ for smaller follow-up periods. For larger follow-ups (more than 14 years), the deficits included into the $DI_{12}$, which characterize health improvement over time, become stronger predictors of death than the deficits from the other two indices.

## DISCUSSION AND CONCLUSIONS

The results show a high potential of an approach of cumulative deficits for characterizing the aggregate effect of small-effect health-related traits (Table 1). Specifically, traditional analysis of trends in the age patterns of individual deficits identified only two (i.e., IAPD and VV) out of 37 deficits that showed consistent trends over time. The DI constructed on the basis of all 37 deficits shows trends for improvements in health status for the 5-year age groups ranging from 55 to 75 years between the mid 1960s and the mid 1990s (Figure 1). These trends, however, were attributed to the effect of these two deficits, because no convincing trends were seen for the $DI_{35}$ (i.e., with the IAPD and VV excluded).

The analyses reveal that the non-convincing results for the $DI_{35}$ are due to this index aggregating small-effect traits for which the changes over time are of an opposite nature. Decomposing the set of 35 deficits (i.e., excluding the effect of the IAPD and VV) according to potential trends for each deficit (i.e., no, upward, or downward), we constructed the respective DIs characterizing health dimensions associated with no health changes ($DI_{18}$), health worsening ($DI_5$), and health improving ($DI_{12}$) over time to elucidate whether such aggregations of small-effect traits can be more informative. Aggregation of the 12 deficits with inconsistent downward trends into the $DI_{12}$ shows that such an index is capable of a more informative characterization; the $DI_{12}$ exhibits significant downward trends indicating improvements in health for the 5-year age groups ranging from 55 to 75 years between the 1960s and 1990s (Figure 2). The results for the $DI_5$, which was intended to characterize worsening-over-time health dimension, are not as convincing as for the $DI_{12}$ because of small number of deficits used for construction of the $DI_5$.

Although the $DI_{18}$, $DI_5$, and $DI_{12}$ are significantly predictive of the mortality risks within different time horizons (Figure 3), their relationships to the risks are not identical. The mortality risks associated with the $DI_5$, i.e., health worsening over time, are the least significant. The mortality risks attributable to the $DI_{18}$, which characterizes no changes in health over time, dominate within shorter time horizons. The $DI_{12}$ is the strongest predictor of the long-term mortality.

Thus, the analyses show that a cumulative deficits approach might be an efficient tool for analyzing the effect of a large number of traits for which individual effects on survival are small, inconsistent, or non-significant. They show favorable trends such that health of the FHS/FHSO participants either did not change or improved over time for the most serious small-effect traits. This corroborates early findings [8] and provides a broader perspective on health trends because of the wide spectrum of the deficits that was considered.

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Table 1. List of 37 deficits used in the analyses

| Group | N | Deficit | Group | N | Deficit |
|---|---|---|---|---|---|
| 1 | 1 | urinary sugar | 2 | 19 | ankle edema |
| | 2 | chronic cough | | 20 | discomfort in lower limbs while walking |
| | 3 | trouble with wheezing | | 21 | abnormal breast |
| | 4 | increase in dyspnea | | 22 | left ankle edema |
| | 5 | orthopnea | | 23 | right ankle edema |
| | 6 | paroxysmal nocturnal dyspnea | 3 | 24 | dyspnea or exertion |
| | 7 | chest discomfort | | 25 | thyroid exam: scar |
| | 8 | frequent coldness in one hand/foot | | 26 | thyroid exam: single nodule |
| | 9 | arcus senilis | | 27 | thyroid exam: multiple nodules |
| | 10 | xanthelasma | | 28 | thyroid exam: diffuse enlargement |
| | 11 | xanthomata | | 29 | other manifestation of thyroid disease |
| | 12 | distended neck veins | | 30 | abnormal breath sounds |
| | 13 | localized breast mass | | 31 | rales |
| | 14 | axillary breast nodes | | 32 | abnormal heart sounds |
| | 15 | peripheral pulses: dorsal pedis | | 33 | liver enlarged |
| | 16 | peripheral pulses: posterior tibial | | 34 | premature beats on ECG |
| | 17 | peripheral pulses: femoral | | 35 | pulmonary disease |
| | 18 | peripheral pulses: radial | 4 | 36 | increased antero-posterior diameter |
| | | | | 37 | venous insufficiency or varicose veins |

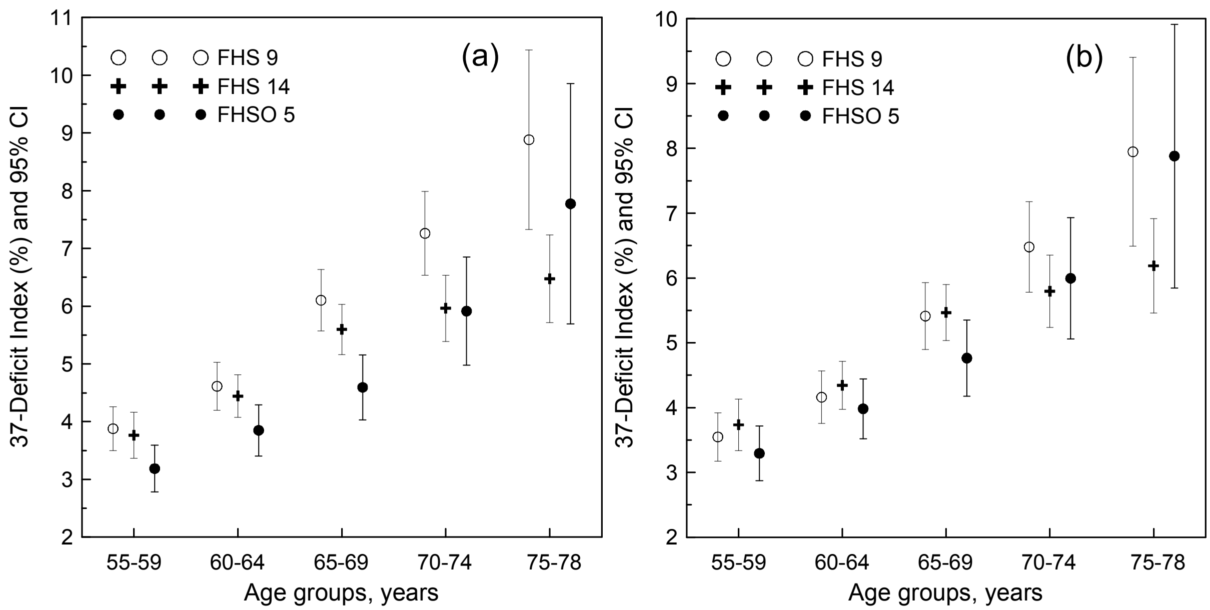


Figure 1. Age patterns of the DIs constructed using (a) all 37 deficits selected for the analyses and (b) reduced set of 35 deficits with group 4 (see Table 1) excluded for participants of the 9th and 14th exams of the FHS and 5th exam of the FHSO as denoted in the inset.

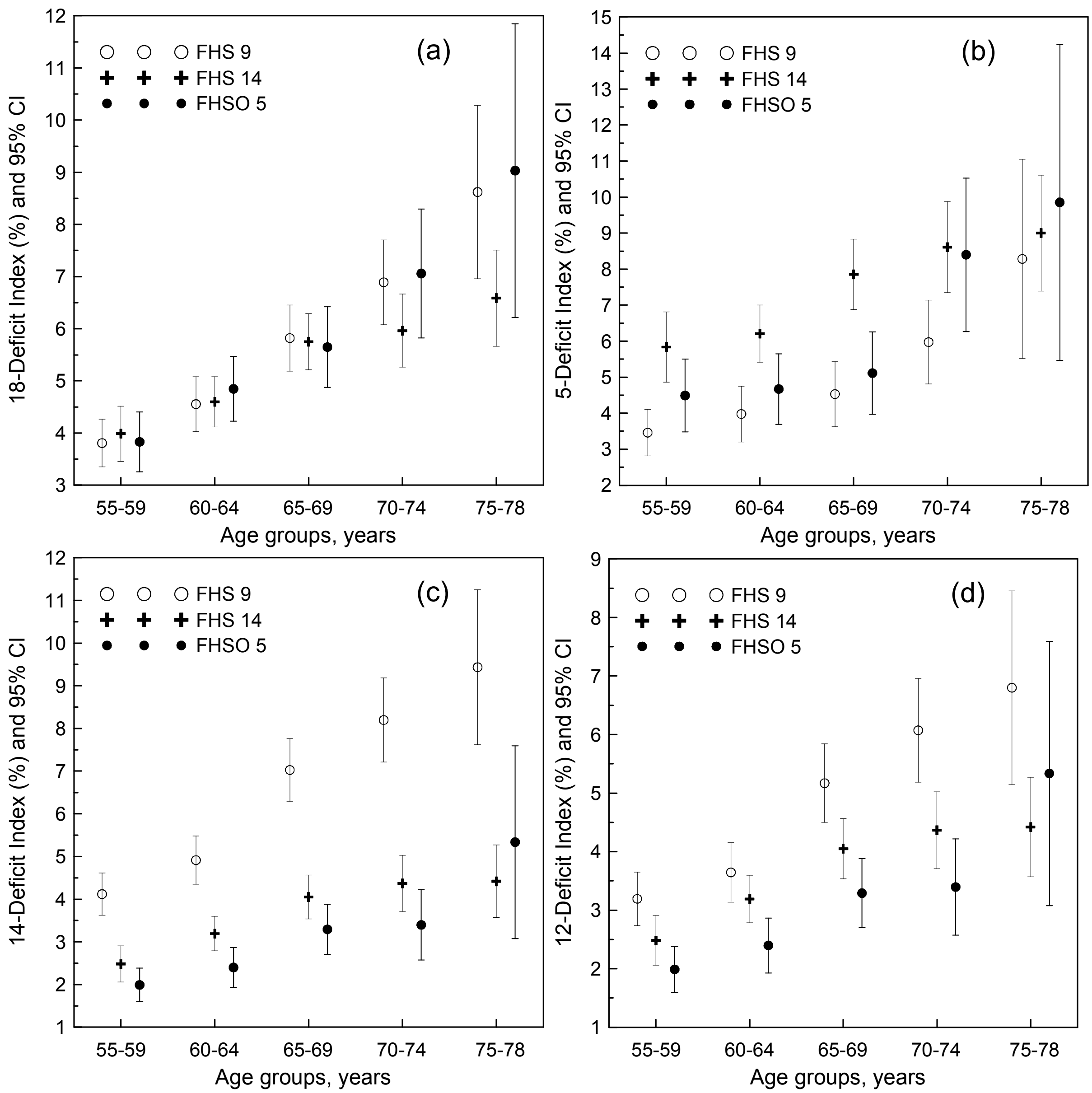


Figure 2. Age patterns of the DIs characterizing health dimensions associated with (c) no health changes ($DI_{18}$), (d) health worsening ($DI_5$), and (e and f) health improving ($DI_{14}$ and $DI_{12}$) over time.

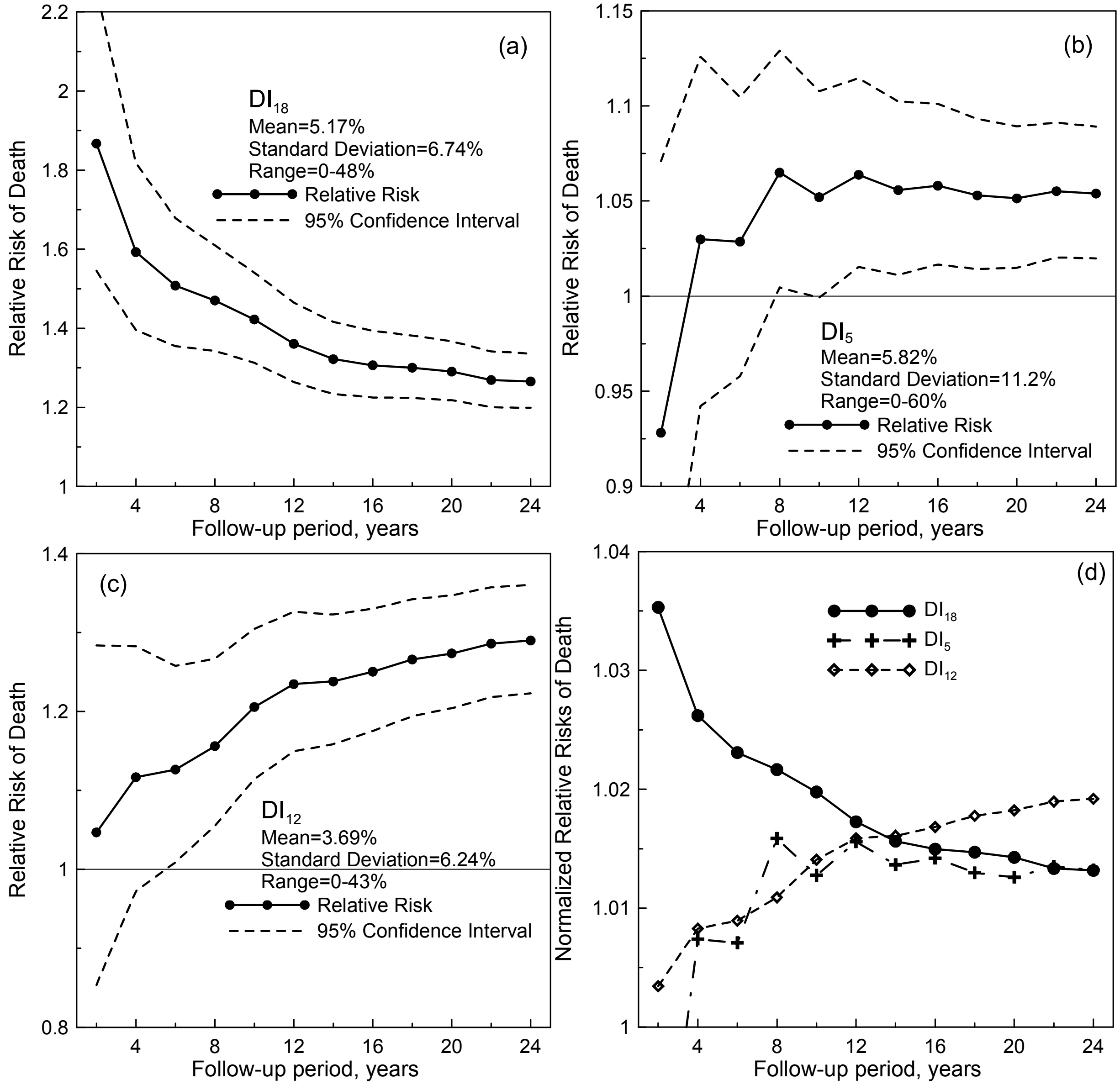


Figure 3. Relative risks of death evaluated for a 10% increase in the 18-deficits (a), 5-deficits (b), and 12-deficits (c) DIs. Insets show means, standard deviations, and range for the respective DIs. (d) The relative risks of death as renormalized for one deficit and recalculated for the same range of change of the respective DI.