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Health-Related Phenotypes and Longevity in Danish Twins

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Aging studies can be facilitated by refocusing from longevity phenotypes to their proxies (intermediate phenotypes). Robust selection of the intermediate phenotypes requires data on such phenotypes and life span measured in the same individuals, which is not always the case in aging studies. A promising approach is to select intermediate phenotypes using information on longevity measured in related individuals. We evaluated feasibility of this approach focusing on 32 geriatric diseases as potential intermediate phenotypes of longevity assessed in the Longitudinal Study of Aging Danish Twins. Our analyses reveal that geriatric diseases measured in some family members can predict life span in the other family members both individually and cumulatively ensuring that this approach for selection of intermediate phenotypes is feasible. The cumulative-trait approach is more promising for such studies compared with the individual-trait approach. Heritable health dimensions contributing to a decrease of life span have sex-insensitive and sex-specific components.

Key Words: Twins—Heritability of longevity—Longevity phenotypes—Endophenotypes.

LONGEVITY tends to cluster in families (1). Family clustering of long-lived individuals can be attributed to both genetic predisposition and environmental factors (eg, health-related life styles, nutrition) that are shared by the family members (2). Despite the studies of various factors that can potentially contribute to longevity, determinants of longevity remain largely unknown (3,4). The major problem of such studies in humans is that they lack the respective data that could provide information on the whole life history health-related factors (genetic, nongenetic, and their interaction) contributing to exceptionally long life span in the same individuals. This situation calls for development of indirect methods of studying determinants of human longevity.

Given the advantage of longevity studies in which the same individuals are followed up over extended period of time, promising approach could be focusing on proxies (intermediate phenotypes) for an ultimate longevity phenotype (5,6), which, ideally, should be measured early in life (7,8). Provided that such intermediate phenotypes are predictive of longevity, they can substitute the longevity outcomes. The question, however, is how to ensure that such intermediate phenotypes *do* predict longevity. A direct method is to link life span with intermediate traits measured in the same individuals. This is, however, again the same rare situation in human data on aging and longevity. Meanwhile, such studies often assess not only extensive information on potential intermediate longevity-related phenotypes for the respondents but also information on life span of their relatives (eg, family members: parents, siblings). Assuming that long-lived families likely share common phenotypes, it is then plausible to associate information on intermediate phenotypes measured in some family members with life span measured in the other family members. Provided these phenotypes are heritable, they can be considered as candidate-heritable intermediate phenotypes of longevity (called endophenotypes, EPs) (2,9).

Is such an approach really feasible? The insights can be gained by considering longevity-related phenotypes in twins. In this study we considered whether the 32 geriatric diseases documented in twins who participated in the Longitudinal Study of Aging Danish Twins (LSADT) can serve as potential EPs of longevity individually or cumulatively.

Methods

Data

The LSADT (10,11) focuses on 4,731 individual twins who were enrolled into at least one of the five surveys performed in 1995 ($N = 2,579$; mean age [MA] = 81.1 years; standard deviation [SD] = 5.0 years), 1997 ($N = 2,172$; MA = 80.6 years; $SD = 5.4$ years), 1999 ($N = 2,709$; MA = 77.8 years; $SD = 6.0$ years), 2001 ($N = 2,448$; MA = 77.7 years; $SD = 6.1$ years), and 2003 ($N = 1,844$; MA = 79.1 years; $SD = 5.9$ years) at ages 70+ years at the time of intake assessment. Of those, 2,304 were a part of a surviving twin pair: 902 monozygotic (MZ) and 1,322 dizygotic (DZ) twins, as well as 38 same-sex twins of unknown zygosity and 42 opposite-sex DZ twins. The other 2,427 were single-twin survivors. The target population was

based on the Danish Twins Registry, which included nearly all twin pairs born in Denmark between 1870 and 1910 and all same-sex pairs born between 1911 and 1930 who survived past age 15 years. The questionnaire involves a 1-hr in-person interview with each participant performed by trained interviewers with substantial experience in interviewing the elderly. A proxy respondent is used in the case of a physical or mental handicap that prevents the participant's own responses. The interviews cover six major areas: (i) health status, medical conditions, subjective health, height, and weight; (ii) physical functioning, activities of daily living, instrumental activities of daily living, and the use of assistive devices; (iii) cognitive functioning and delayed word recall; (iv) depression symptomatology; (v) sociodemographic, education, marital status, and household composition factors; and (vi) social functioning and activity levels.

Analyses

The longevity analyses often focus on the effect of selected phenotypic markers including physiologic indices (eg, blood pressure, cholesterol (3,12,13)) and aging-associated health conditions (eg, coronary heart disease (14)). Many diseases represent a major factor limiting human life span. Consequently, they are tightly coupled with the longevity phenotype (2) and, thus, can be potential candidates for the EPs of longevity. It is then logical to address the major goal of this article (ie, to assess feasibility of the approach on selection of EPs by using the relevant health information in some family members and information on life span measured in the other family members) focusing on geriatric diseases consistently measured in Danish twins.

It is obvious, however, that not one but various diseases limit longevity. Some diseases can be considered as major factors limiting longevity; the others can contribute moderately. Detection of the intermediate phenotypes providing modest contribution to the longevity phenotype requires a large sample size that is not the case for many studies. A possible way to resolve this problem is to consider a cumulative effect of such minor-effect health traits on longevity (called cumulative approach). Consequently, our idea for the analyses is to pay attention not only to a single particular disease but also to an aggregate effect of distinct diseases on longevity. Following this idea, we selected all (32) aging-related health traits consistently measured in each of the five LSADT waves (Table 1).

To increase the statistical power, we pooled records on twins participating in different LSADT waves ($N = 11,752$). Of those, there were 5,695 records corresponding to unpaired twins (ie, second twin from the pair did not participate in the survey). These twins were dropped from the analysis to minimize the bias associated with unknown health factors for nonparticipating twins. The remaining 6,057 records were associated with twin pairs in which each twin in the pair participated in the survey at least once. In the LSADT, twins in the pair were coded arbitrarily. Following the convention for twins (15), one twin in the pair is hereafter referred as a twin and the other (ie, his/her sibling) as a co-twin. Each twin can be also considered as a co-twin (especially because of their arbitrary coding). Therefore, we can keep the pooled sample of twins and co-twins in the following analyses.

To meet the goal of the article, we have to know information on total life span (known at the date of death) for at least one twin from the pair, that is, either for twin or co-twin. Of 6,057 records, such information was available for 4,131 twin assessments (1,581 male participants): 1,548 MZ (598 male participants), 2,400 same-sex DZ (889 male participants), 90 opposite-sex DZ (42 male participants), and 93 twins (52 male participants) of unknown zygosity or with missing information on zygosity. Of 4,131 twin records, there were 922 records for deceased twins whose co-twins were alive and 1,199 records for deceased co-twins whose twins were alive. The vital status was assessed as of January 1, 2008. The remaining 2,010 records were for the case when both twins and co-twins died before or on January 1, 2008. Therefore, for further analyses we have information on total life span for 2,932 twins (ie, 2,010 + 922) and for 3,209 co-twins (ie, 2,010 + 1,199).

The two-tailed t test was used to assess the difference in the mean life spans in "healthy" and "unhealthy" samples. The "unhealthy" sample was defined if twins reported on health traits in at least one of the five LSADT surveys. Consequently, those twins who did not report such traits were considered as "healthy" for the purpose of the analysis. To meet the goal of the article, we performed two types of the analyses. For the first type (primary procedure) health status was measured in twins, whereas longevity information was taken for their co-twins (ie, measured not in the same but in related individuals; $N = 3,209$). The analysis of the situation when the mean life span and health status were assessed in the same individuals (ie, in twins; $N = 2,932$) was considered as a control procedure. If both these analyses are concordant (ie, they show the same type of the association of potential intermediate phenotypes with longevity) and the results are significant, the analyzed health traits can be considered as EPs of longevity. Consequently, selection of EPs by using the relevant health information in some family members and information on life span measured in the other family members could be deemed feasible.

The analyses were performed separately for male participants and female participants because of the difference in their life spans. First, we tested the difference in the mean life spans for healthy and unhealthy individuals as defined by a single particular health trait listed in Table 1. A positive (negative) difference means that life spans of healthy individuals are larger (smaller) than that of unhealthy ones. Columns (or rows in Table 2) denoted

Table 1. Estimates of the Difference Between Mean Life Spans (Measured in Years) for Twins Without and With a Given Health Trait

		Male Participants		Female Participants	
N	Health Traits	Twin†	Co-Twin‡	Twin†	Co-Twin‡
1	Diabetes	**1.8*****	**1.4****	1.9***	−0.8
2	Osteoarthritis	−0.8	−0.6	−0.2	0.9***
3	Rheumatoid arthritis	1.3	−0.8	−0.6	0.0
4	Gout (podagra)	0.0	−1.6*	***0.6***	***1.3****
5	Osteoporosis	**3.5****	**2.2**	0.9*	−0.2
6	Chronic bronchitis	1.0*	0.1	***2.5******	***1.7******
7	Tuberculosis	**0.4**	**1.2**	1.1	0.2
8	Asthma	**1.4****	**0.6**	***3.1******	***1.9******
9	Cataract	−0.8	−0.1	−1.2***	−1.1***
10	Glaucoma	1.1	0.2	0.1	−2.2**
11	Sclerosis in eye	−1.5*	−2.2***	−2.1***	−1.6***
12	Thrombosis in eye	**1.7**	**1.4**	0.1	0.3
13	Meningitis	**1.4**	**2.5**	0.2	2.8*
14	Parkinson's disease	**1.6**	**1.0**	1.8	−2.2
15	Epilepsy	**1.9**	**1.5**	***1.3***	***0.4***
16	Migraine	**1.6***	**0.9**	−0.6	0.0
17	Cancer	**1.7*****	**1.6*****	1.8***	0.0
18	Stroke	1.9***	−1.2*	1.6***	0.0
19	Angina pectoris	**1.3**	**1.1**	***0.9****	***0.4***
20	Irregular heart rhythm	**1.0**	**0.9**	0.7	0.1
21	Treatment for hypertension	**1.4*****	**1.0***	***1.5******	***1.4******
22	Other heart problems	1.5*	−0.6	0.3	−1.2*
23	Bad blood circulation in legs	0.5	−0.3	0.7	−0.5
24	Gallstone	0.0	2.2***	−1.4***	−1.4***
25	Jaundice	**2.1***	**1.2**	0.6	0.0
26	Treatment for gastric ulcer	**1.0**	**0.4**	0.1	−0.7
27	Kidney disease	1.1	−0.2	1.1	−0.3
28	Kidney stones	**1.4***	**1.3****	−0.6	−1.3
29	Increased metabolism	0.3	1.7	***0.7***	***0.6***
30	Decreased metabolism	**1.9**	**1.2**	***2.9*****	***2.8******
31	Slipped disc	0.0	−0.8	***1.5*****	***2.6******
32	Paralysis of arms or legs	2.4***	−0.3	***2.1******	***1.0****

Notes: Bold = male-characteristic traits; bold and italic = female-characteristic traits. The minus sign in the table means that individuals having a given health trait live longer compared with individuals who do not have such a trait.

*$0.01 < p \leq .05$; **$0.001 < p \leq .01$; ***$p \leq .001$; other results are insignificant.

†Twin = life span and health are measured in the same persons (control procedure).

‡Co-Twin = health status is measured in twins, whereas life span is measured in co-twins (primary procedure). Co-twin denotes a second twin in the pair.

as "Twin" summarize the results for the control procedure whereas those denoted as "Co-Twin" denote the primary procedure. Then, using these results, we selected those individual traits that could be considered as life limiting (irrespective of the significance of the estimates of the difference in life spans) and showed concordant patterns of the difference in life spans across procedures and grouped them into the respective cumulative comorbidity indices (CMIs). This aggregation helps to derive reliable conclusions when estimates for individual traits are insignificant or unreliable. Next, we tested the difference in the mean life spans for groups of twins characterized by these newly constructed indices. The analyses of the cumulative indices were performed for the mixed sample of MZ and DZ twins as well as for MZ and DZ twins separately to provide some arguments that the results can be applicable to other family members (eg, parents and offspring, siblings).

Results

Table 1 shows the difference between mean life spans measured in years for healthy twins (ie, twins having no given health trait listed in the second column) and for unhealthy twins (ie, those having such a trait). Column "Twin" indicates the difference when the life span and health information are measured in the same individuals (control procedure). Column "Co-Twin" summarizes the results when the information on life span is measured in the related individuals, that is, co-twins (primary procedure).

Analysis of individual traits shows that only a few of them exhibit a consistent effect for both procedures (primary and control) at a level of significance ($p \leq .001$), which is sufficient even given the correction for multiple comparisons. Particularly, for a positive difference this is the case for one trait (cancer) for male participants and for three traits (chronic bronchitis, asthma, and treatment for hypertension) for female participants. For female participants, we

Table 2. Estimates of the Effect of Dichotomous Cumulative Morbidity/Comorbidity Indices Measured in Twins on Longevity (Measured in Years) of the Same Twins as Well as on Longevity of Co-Twins

		Male Participants					Female Participants				
Index	Procedure	N0	Y0	N1	Y1	Y0-Y1	N0	Y0	N1	Y1	Y0-Y1
CMI_{M17}	Twin	355	85.7	786	83.4	2.3***	432	88.1	1,301	85.8	2.3***
	Co-Twin	402	84.4	828	82.4	2.0***	543	85.8	1,379	84.7	1.1***
CMI_{F10}	Twin	485	85.0	657	83.6	1.4***	736	87.7	1,000	85.3	2.4***
	Co-Twin	536	83.4	695	82.8	0.6	870	86.0	1,054	84.2	1.8***
CMI_{CMF5}	Twin	677	84.9	464	83.1	1.8***	940	87.4	793	85.1	2.3***
	Co-Twin	739	83.6	491	82.2	1.4***	1,067	85.7	855	84.1	1.6***
CMI_{MS12}	Twin	536	85.2	605	83.2	2.0***	682	87.0	1,050	85.9	1.1***
	Co-Twin	599	83.9	631	82.2	1.7***	846	84.8	1,075	85.1	–0.3
CMI_{FS5}	Twin	709	84.5	433	83.6	0.9*	1,231	86.9	505	84.9	2.0***
	Co-Twin	798	82.9	433	83.3	–0.4	1,425	85.4	499	83.8	1.6***
CMI_{M19}	Twin	340	85.8	801	83.5	2.3***	362	87.8	1,371	85.9	1.9***
	Co-Twin	387	84.5	843	82.4	2.1***	475	85.5	1,447	84.8	0.7*
CMI_{M13}	Twin	588	85.0	553	83.2	1.8***	745	87.0	987	85.8	1.2***
	Co-Twin	668	83.6	562	82.3	1.3***	880	85.2	1,041	84.8	0.5
CMI_{F12}	Twin	395	84.8	747	83.8	1.0**	509	87.8	1,227	85.7	2.1***
	Co-Twin	439	83.3	792	82.9	0.4	588	86.5	1,336	84.3	2.2***

Notes: Twin = life span and health are measured in the same persons (control procedure); Co-Twin = health status is measured in twins, whereas life span is measured in Co-Twins (primary procedure). Co-Twin denotes a second twin in the pair. N0 = number of healthy twins (ie, twins having none of the selected traits); Y0 = mean life span of healthy twins (row "Twin") or their Co-Twins (row "Co-Twin"). N1 = number of unhealthy twins (ie, twins having one or more of the selected traits); Y1 = mean life span of unhealthy twins (row "Twin") or their Co-Twins (row "Co-Twin"). Note that the minus sign in the table means that unhealthy individuals live longer than healthy individuals. Sample sizes for healthy (N0) and unhealthy (N1) male and female twins or Co-Twins do not sum into the respective numbers for the combined samples of twins (eg, for CMI_{M17} $N = 355 + 786 + 432 + 1,301 = 2,874 < N = 2,932$) or Co-Twins (eg, for CMI_{M17} $N = 402 + 828 + 543 + 1,379 = 3,152 < N = 3,209$) because of missing data on health status. CMI = comorbidity index.

*$0.01 < p \le .05$; **$0.001 < p \le .01$; ***$p \le .001$; other results are insignificant.

also observe sufficiently significant effects for negative difference for three another conditions: cataract, sclerosis in eye, and gallstone. The negative difference means that twins themselves or co-twins of twins having such a trait tend to live longer compared with the case of no such traits. Concordance of the results across the primary and control procedures means that those health traits are likely heritable.

Despite these insights, for the majority of traits no definitive conclusions can be drawn. For this reason, we will refocus further analyses from individual traits to CMIs that might help to gain better insights. This strategy is also appropriate to reflect the complexity of the longevity phenotype, which can be affected by distinct intermediate phenotypes. Following the goal of the article, we will focus below on the case of life-limiting traits (ie, positive differences in Table 1). Then, we collect health traits that consistently (but not necessarily significantly) contribute to shortening the life span (a positive difference) in both procedures (indicating heritability) for each sex into separate CMIs.

Because the health traits were selected irrespective of significance, we adopted a representative cut point of 0.4 years and more for the difference in the life spans. This cut point was chosen as a balance between maximization of the number of traits to include in CMIs and reduction of the effect of stochasticity. Although this choice was largely arbitrary, we tested other cut points (0.3 and 0.6 years) to ensure that this uncertainty did not alter the main conclusions of the article. With a given cut point, there are 17 traits for male participants (1,5,7,8,12–17,19–21,25,26,28, and 30; Table 1, bold) and 10 traits for female participants (4,6,8, 15,19,21, and 29–32; Table 1, bold and italic) that meet our criteria. Only five health traits are common for male participants and female participants. Only two additional traits for male participants (24 and 29) and for female participants (2 and 13) could be selected if health and life span information would be not known for the same individuals.

Using these results, we constructed five basic CMIs by counting those traits an individual can acquire from the list of the: (i) 17 males' traits (CMI_{M17}); (ii) 10 females' traits (CMI_{F10}); (iii) 5 common traits for male participants and female participants (CMI_{CMF5}); (iv) 12 (=17–5) male-specific traits (CMI_{MS12}); and (v) 5 (=10–5) female-specific traits (CMI_{FS5}). For instance, if an individual has two traits from the list of the 17 males' traits, the respective $CMI_{M17} = 2$. We also constructed three auxiliary indices for the sake of comparison. Two of them are constructed using the 19 males' (CMI_{M19}) and 12 females' (CMI_{F12}) traits, which would be selected if health and life span information is not known for the same individuals. The third was constructed using the 13 males' (CMI_{M13}) traits for which the estimates of the difference in life spans were insignificant (ie, 5,7,8, 12–16,19,20,25,26, and 30 in Table 1). These indices were dichotomized using two strategies to explicitly reflect the effect of comorbidity. For the first dichotomization, we selected healthy state (characterized by no selected traits or, equivalently, by zero value of the respective index; we assigned "0" to this state) versus unhealthy state (ie, when an

Table 3. Estimates of the Effect of Dichotomous Cumulative Comorbidity Indices Measured in Twins of Different Zygosity on Longevity (Measured in Years) of the Same Twins as Well as on Longevity of Co-Twins

	Male Participants				Female Participants			
	MZ		DZ		MZ		DZ	
Index	Twin	Co-Twin	Twin	Co-Twin	Twin	Co-Twin	Twin	Co-Twin
CMI_{M17}	2.7***	3.0***	1.9***	1.6***	2.3***	2.2***	2.5***	0.5
CMI_{F10}	1.9***	1.5**	1.3**	0.3	2.3***	2.4***	2.5***	1.4***
CMI_{CMF5}	2.1***	2.2***	1.8***	1.2**	2.0***	1.9***	2.5***	1.6***
CMI_{MS12}	1.9***	2.7***	1.7***	1.1**	0.6	0.3	1.3***	−0.8*
CMI_{FS5}	1.2*	0.3	1.0*	−0.4	2.5***	2.9***	1.7***	0.9*

Notes: Twin = life span and health are measured in the same persons (control procedure); Co-Twin = health status is measured in twins, whereas life span is measured in Co-Twins (primary procedure). Co-Twin denotes a second twin in the pair. Note that the minus sign in the table means that unhealthy individuals live longer than healthy individuals. MZ = monozygotic; DZ = dizygotic; CMI = comorbidity index.

*$0.01 < p \leq .05$; **$0.001 < p \leq .01$; ***$p \leq .001$; other results are insignificant.

individual can suffer from one or more of the diseases; we assigned "1" to this state). For the second dichotomization, we used the same healthy state (0) as above and we also selected comorbid state (ie, when an individual can suffer from two or more of the diseases; we assigned "1" to this state).

Table 2 represents the estimates of the effect of eight constructed CMIs dichotomized using the first strategy and measured in twins on mean life spans in the same twins (row "Twin") and co-twins (row "Co-Twin") measured in years. The analysis of basic five CMIs (first five CMIs in Table 2) reveals that healthy male twins (ie, for whom the value of the respective CMI is zero) live significantly longer than the unhealthy twins (ie, for whom the value of the respective CMI is one). This significance is high ($p \leq .001$) for all CMIs except female-specific CMI_{FS5}. The largest difference is seen for CMI_{M17} (2.3 years).

Similar associations are seen for CMIs that are characteristic of the male co-twins (CMI_{M17}, CMI_{CMF5}, and CMI_{MS12}), that is, the male co-twins of the healthy male twins live significantly longer ($p \leq .001$) than the male co-twins of the unhealthy male twins. The female-characteristic traits for male twins (collected into CMI_{F10} and CMI_{FS5}) have no effect on life span of the male co-twins. Again, the largest difference is seen for CMI_{M17} (2.0 years). The estimates of the differences of life spans for twins and co-twins are similar in both cases (eg, they are 2.3 years for twins and 2.0 years for co-twins for CMI_{M17}).

The healthy female twins characterized by basic five CMIs have significantly larger ($p \leq .001$) life span than the unhealthy female twins. The female co-twins of the healthy female twins characterized by female-characteristic CMIs (ie, CMI_{F10}, CMI_{CMF5}, and CMI_{FS5}) also live significantly longer ($p \leq .001$) than the female co-twins of the unhealthy female twins. Unlike the case of the male twins, however, male-characteristic CMI_{17} has a significant effect on the female twins' life span. This effect is attributed to the strong effect of the female twin–specific five traits (ie, CMI_{CMF5}) because the remaining 12 male twin–specific traits (ie, CMI_{FS12}) have no effect on the female twins' life span. The largest difference is seen for CMI_{F10} for both twins (2.4 years) and co-twins (1.8 years).

The effects of CMI_{M19} and CMI_{F12} (ie, the indices constructed using traits which would be selected if health and life span information was not measured in the same individuals) on longevity are similar to those of the basic indices (compare with CMI_{M17} and CMI_{F10}). This suggests that the association of individual intermediate phenotypes (eg, gallstone for male participants and osteoarthritis for female participants in this study) measured in one family members with life span measured in the other family members may not always indicate that the effect of that trait is heritable. The association for cumulative indices, however, is more robust and indicates that the results would be unlikely altered if information on health status and life span is collected in different family members.

When we omit the traits that individually can significantly predict longevity (ie, using CMI_{M13}), the results remain qualitatively similar, ensuring the feasibility of the approach of cumulative minor-effect traits for such analyses.

Comorbidity makes the estimates even more pronounced especially when the number of traits included into the index definition is sufficiently large. For instance, the difference in the mean life spans for the healthy male *twins* and those who are in the comorbid state (2+ diseases) as characterized by CMI_{M17} becomes 3.1 years ($p < .001$) compared with 2.3 years as in Table 2. This difference in the mean life spans of the male *co-twins* of the healthy male twins and those who are in the comorbid state (characterized by CMI_{M17}) becomes 2.8 years ($p < .001$) compared with 2.0 years. The life span difference for healthy female twins and those who are in the comorbid state and characterized by CMI_{F10} becomes 3.5 (compared with 2.4) years ($p < .001$). The respective estimate for the life span difference of female co-twins is 2.9 (compared with 1.8) years ($p < .001$).

Finally, we evaluated the effect of zygosity on the mean life span differences (Table 3). Because we perform sex-specific analyses, we excluded opposite-sex DZ twins ($N = 85$) from these zygosity-specific analyses. Considering

male-characteristic CMIs (ie, CMI_{M17}, CMI_{CMF5}, and CMI_{MS12}) for male twins (columns "Twin"), we observe a consistent pattern of larger mean life span differences in MZ than in DZ twins with the largest difference 2.7–1.9 = 0.8 years for CMI_{M17}. No such consistent patterns are observed for female twins considering female-specific CMIs (ie, for CMI_{F10}, CMI_{CMF5}, and CMI_{FS5}). When life span is measured in co-twins (columns "Co-Twin"), the patterns are consistent for both such cases indicating that the effect is more pronounced in MZ twins than in DZ twins of both sexes. The mean life span differences are concordant between the primary and control procedures for these CMIs. Female-specific CMIs (CMI_{F10} and CMI_{FS5}) exhibit less convincing effects in male participants and vise versa, as expected.

Discussion and conclusions

The studies of aging and longevity can be facilitated by refocusing from the ultimate longevity phenotypes to their proxies, that is, intermediate phenotypes of longevity. Given that such intermediate phenotypes are heritable, they can be considered as EPs of longevity. Rigorous selection of the intermediate phenotypes requires the relevant health-related and life span information measured in the same individuals. Because this is not the case for many studies of aging and longevity, a promising approach to select intermediate phenotypes of longevity for individuals with known health information but unknown life span could be to use information on life span for the related individuals (eg, family members of the sample person). In this study we focused on twins who participated in the LSADT to investigate if such an approach for selection of the EPs of longevity could be really feasible. We focused on 32 geriatric diseases consistently assessed in participants of five waves of the LSADT. Because these diseases can contribute to longevity moderately, we considered effects of individual traits as well as their aggregate (cumulative) effect on longevity. This article provides several insights on longevity.

First, the analyses suggest that it is likely that EPs of longevity can be selected by considering the relevant health-related information in the sample persons and life span information in their relatives. Specifically, by evaluating the effect of each of the 32 health traits measured in male twins on life span in the same twins (control procedure) and in their co-twins (primary procedure), 17 traits were shown to be consistently associated with decreased life span of male twins themselves as well as of their co-twins. In the case when information on life span is not known for the sample person (ie, the situation when health is measured in twins whereas life span is known for co-twins only), only two diseases additional to those 17 could be selected on the basis of the association with life span of co-twins (Table 1). Similar situation is seen for females, ie, if information on life span is known for the sample person and her co-twin, we can select 10 diseases. In the case when the life span of co-twin is not known, only two additional diseases can be selected (Table 1).

Second, despite these promising results on selection of the individual traits as potential EPs, there is still uncertainty (eg, 19 vs 17 traits for male twins) in their selection if information on life span is not available for the sample person. Table 2 shows, however, that this problem can be readily resolved by refocusing from the individual-trait approach to the cumulative-trait approach. Indeed, in the latter case the estimates of the life span differences are more robust (compare CMI_{M17} and CMI_{M19} for male participants and CMI_{F10} and CMI_{F12} for female participants in Table 2).

Third, the individual-trait approach appears to be of limited efficiency because the effect of individual traits on life span is of small significance or nonsignificant for the majority of traits (Table 1). Specifically, for male twins only cancer is consistently associated with decreased life span in both twins and co-twins at a level of significance ($p \leq .001$), which is sufficient even given the correction for multiple comparisons. Surprisingly, for female twins it is unlikely that cancer has a heritable component because life span of female co-twins does not depend on cancer conditions in female twins. For female twins there are three such conditions, that is, chronic bronchitis, asthma, and treatment for hypertension. Unlike the individual-trait approach, the cumulative-trait approach appears to be more efficient. This is because the estimates of the life span differences for cumulative indices become significant even if these indices are constructed using only those traits for which the estimates of the life span differences are not significant when they are analyzed individually (see the results for CMI_{M13} for male participants in Table 2).

Fourth, the data suggest that heritable health dimensions contributing to a decrease of life span can have components common for both sexes as well as sex-specific components. A common component for both sexes in this study includes five traits, that is, asthma, epilepsy, angina pectoris, hypertension, and decreased metabolism (see Table 1 and CMI_{CMF5} in Table 2). The female-specific component consists of five traits as well (Table 2: CMI_{CMF5}; gout, chronic bronchitis, increased metabolism, slipped disc, and paralysis). The male-specific health domain is the largest (12 traits; see nonintersecting bolded and bolded and italicized traits in Table 1 which are gathered into CMI_{MS12}).

Fifth, the results are largely stable against differences in the genetic overlap between the related individuals. Specifically, analyses of the mixed sample of MZ and DZ twins as well as of the sample stratified by zygosity reveal that estimates of the life span differences in twins whose health is characterized by cumulative indices remain similar. The estimates of the life span differences are the most pronounced in MZ twins and the least pronounced in DZ twins according to differences in genetic overlap. These results provide arguments that the procedures for selection of the EPs on

the basis of information on health in sample persons and on life span in their relatives are likely feasible not only for twins but also for other family members (eg, parents and offspring, siblings).

Sixth, despite all these promising findings, our results also clearly show that the effect of geriatric diseases measured in old ages on longevity is of moderate importance, explaining, generally, about 2 years in the life span difference. This fact is in line with conclusions from other studies suggesting that better focus on the early life health-related conditions (eg, risk factors, signs, symptoms, abnormal laboratory tests, minor health problems) could be more promising (2,16).

Of notice is that elaboration of cumulative comorbidity indices is a central issue of broad category of clinical models on the association of morbidity with mortality (see, eg, (17–19)). This fact provides additional evidence on importance of the cumulative-trait approaches in studies of health and aging as well. In fact, an importance of the cumulative approaches becomes evident, accepting the concept of systemic nature of changes in an aging organism. The theoretical basis for this concept is the evolutionary theory according to which the aging process is manifested by a gradual increase in the frequency of adverse events, disorders, or failures in various organs and systems of an organism at different levels of organization (20,21). Then, cumulative measures may capture an increase in vulnerability to death, which is a recognized characteristic of aging, and the frequency of disorders of diverse nature may have a more prominent role than their specific features in the association between cumulative measures and the mortality risk or longevity. This view is also supported by advances in elaborating comprehensive indicators of biologic aging (eg, (22, 23)), as well as by development of prognostic cumulative indices, for example, the Framingham risk score (24), the survival risk score (25), the frailty index, and the index of cumulative deficits (26–30).

In sum, the analyses suggest that EPs of longevity can be likely selected when the relevant information on the respective health-related traits is known for the sample persons, whereas information on life span is known for their relatives. The cumulative-traits approach appears to be more promising for such analyses compared with the individual-traits approach. Heritable health dimensions contributing to a decrease of life span have sex-insensitive and sex-specific components.

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