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"PREDICTING" PARENTAL LONGEVITY FROM OFFSPRING ENDOPHENOTYPES: DATA FROM THE LONG LIFE FAMILY STUDY (LLFS)

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Abstract

While there is evidence that longevity runs in families, the study of long-lived families is complicated by the fact that longevity-related information is available only for the oldest old, many of whom may be deceased and unavailable for testing, and information on other living family members, primarily descendents, is censored. This situation requires a creative approach for analyzing determinants of longevity in families. There are likely biomarkers that predict an individual's longevity, suggesting the possibility that those biomarkers which are heritable may constitute valuable endophenotypes for exceptional survival. These endophenotypes could be studied in families to identify human longevity genes and elucidate possible mechanisms of their influence on longevity. In this paper, we analyze data collected in the Long Life Family Study (LLFS) investigating whether indicators of physiological state, cognitive functioning and health/well-being among offspring predict longevity in parents. Good predictors can be used as endophenotypes for exceptional survival. Our analyses revealed significant associations between cumulative indices describing physiological state, as well as a number of offspring phenotypes, and parental lifespan, supporting both their familial basis and relevance to longevity. We conclude that the study of endophenotypes within families is a valid approach to the genetics of human longevity.

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Keywords

determinants of life span; probands; incomplete data; longevity in families; genetics of human longevity

Introduction

Longevity was documented to run in families as early as the beginning of the 20th century (Pearl, 1922) with heritable factors of both genetic and non-genetic origin theorized to contribute to this pattern (Franceschi et al., 2007). Family studies, in which heritable intermediate phenotypes associated with longevity (called endophenotypes, EPs) are measured among multiple family members, can generate useful insights and ideas about determinants of longevity by studying the effects of these phenotypes on life span (Martin et al., 2007; Perls and Terry, 2003). Identification of such EPs can offer additional avenues for exploring determinants of familial patterns of longevity (Martin et al., 2007; Melzer et al., 2007). The idea is that etiologic factors influencing such EPs (especially genes) are also those affecting longevity (Atzmon et al., 2006; Barzilai and Shuldiner, 2001).

Ideally, evaluating the predictive power of EPs for longevity can be assessed using data on life spans and EPs collected in a series of individuals. However, such ideal complete data are often unavailable. While life span is known for deceased individuals, measurement of endophenotypes is usually not possible and, conversely, life span is censored in living individuals where it is possible to measure endophenotypes. Thus, incompleteness is a fundamental property of family data on exceptional longevity. This situation requires nonstandard approaches for analyzing the effects of EPs on longevity from incomplete data. It is clear that estimates of the effects of selected EPs on life span obtained in the case of incomplete data will be less reliable than those calculated from complete data. In this situation one alternative is to assess effects of individual offspring EPs on parental longevity and to combine this information into cumulative indices and repeat the analysis. The effects of the cumulative indices can be significant even if the contribution of each individual EP is small or insignificant (Landgren et al., 2005; Perls and Terry, 2003).

In this paper, we used data from the Long Life Family Study (LLFS) to investigate associations between indicators of physiological state, cognitive functioning, and health/well-being status measured in individuals ages 70 and above and the life spans of their parents. The LLFS collects information about life spans and characteristics hypothesized to affect them in families identified for their exceptional longevity. We set out to establish the validity of these measures as endophenotypes of longevity by examining their association with life spans of parents (Martin et al., 2007). Verification of this relationship will allow us to investigate the familial underpinnings of longevity by studying the endophenotypes, which can be measured on living family members. To test these associations we investigated the relationships between individual EPs as well as cumulative indices measured in the offspring with life spans of their parents.

More specifically, we addressed the following question: which EPs in the offspring were strongest predictors of longevity in their parents? We began by evaluating separately, effects of each selected characteristic in the offspring on the longevity of their mothers and fathers. We then explored the effects of several cumulative indices created from this list and compared results obtained using these indices with those obtained using each characteristic individually.

Data and Methods

The Long Life Family Study (LLFS) consists of families selected for exceptional familial longevity in the United States and Denmark. In the United States, the recruitment of families into the LLFS is carried out by field centers located in Boston, New York and Pittsburgh. In the United States, potentially eligible individuals and their families are identified through two main sources (1) mailings of study information to Medicare enrollees, aged 80 and older who reside within a two hour driving distance from one of the three field centers, and (2) individuals who contact the field centers in response to media events, including television appearances, newspaper stories, and advertisements. Individuals who contact a field center or who consent to be contacted in response to mailings, are interviewed over the telephone to assess eligibility and willingness to participate in the LLFS. Study eligibility criteria consist of the following: the family must have two living siblings aged 80 and above, two living offspring of one or more of the siblings, and a living spouse of one of the offspring (a control subject). In addition, the family must demonstrate exceptional longevity based on a Family Longevity Selection Score (FLoSS), which is a summary measure based on the survival experience of the oldest living generation of siblings relative to what would be expected based on birth cohort life tables (Sebastiani et al., 2009). Families with members of this generation who are still alive and larger sibships are given higher priorities. Finally, an eligible family will be enrolled in the study if at least 3 family members (the proband, at least one sibling of the proband, and one offspring of the proband or the sibling) indicate their willingness to participate.

In Denmark, the identification of potentially eligible probands and their families proceeds as follows. First, individuals who would be ages 90 and above during the study recruitment period are identified in the Danish National Register of Persons, which contains current information on names, including past names such as maiden names for women, addresses, place of birth, marriages, and vital status. Second, using information on the place of birth and the names, parish registers available in regional archives are searched to locate the parents of the elderly individuals in order to identify sibships. Based on the above information, potentially eligible families are identified and contact is made with potential probands to further assess the family's eligibility for and willingness to participate in the LLFS using criteria parallel to that used in the United States.

Once enrolled in the LLFS, field center staff collect information from the US and Danish participants using similar questionnaires and in-home physical examinations, covering such topics as socio-demographic characteristics, physical activity and functioning, health and medical history, cognitive functioning, mood and personality, anthropometry, blood pressure, and spirometry. In addition, blood is collected for laboratory testing. In this paper, we use data from approximately 700 individuals (about 600 US and 100 Danish subjects from about 300 different families) of the proband's generation (probands and their siblings) who had completed most the data collection and for whom a known age at death for at least one parent was recorded. In our analyses, we excluded data on life spans of parents who died as a result of accident, injury or war. To test whether gender difference in correlations between life spans of parents and their offspring takes place in other populations, we used the Framingham Heart Study data for the original and offspring cohorts.

The Framingham Heart Study Data

In the year 1948, the study recruited 5209 non-institutionalized white subjects (2336 males and 2873 females between the ages of 28 and 62 in the town of Framingham, Massachusetts) with the purpose to evaluate the relationship between potential risk factors determined in individuals, who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke, to the subsequent development of disease and death. For more than 50 years, the participants of the original cohort have been reexamined biennially for a physical examination,

laboratory tests, detailed medical history, and extensive cardiovascular history. The Offspring cohort (FHSO) was launched at Exam 1 in 1971 (8/1971 – 9/1975) using research protocols similar to those of the FHS and has on average been examined every 3 to 4 years since enrollment. The sample included 3,514 biological descendants of the Original Cohort, 1,576 of their spouses and 34 adopted offspring for a total sample of 5,124 subjects (52% females).

Methods

To examine the associations between selected EPs and parental longevity, we selected phenotypes measured in the probands and their siblings from five distinct health-related domains available in the LLFS. All together 18 EPs were selected for analysis: 1). *Physiological and anthropometric measures:* total cholesterol (CHOL; mg/dL), fasting blood glucose (BG; mg/dL), hematocrit (HCT; %), systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg), pulse pressure (PP; mm Hg), pulse rate (PR; beats/min), body mass index (BMI; kg/m^2), forced vital capacity (FVC; mL), and forced expiratory volume in 1 second (FEV1; mL). 2). *Physical functioning:* grip strength (GRIP, kg). 3). *Cognitive functioning:* total MMSE score (MMSE). 4). *Socio-demographic and lifestyle indicators:* low education ("1" if below high school, "0" otherwise) (EDUC), no moderate physical activity (walking/exercise at least 1 hr/week) (MODACT), no intensive physical activity (walking/exercise at least 3 hrs/week) (INTACT), low income ("1" if hard to pay for basics, "0" otherwise) (INCOME). 5). *Disease history:* has hypertension (HYPERT) and/or cancer (CANCER).

These EPs (selected in offspring) were used for empirical and regression analyses of their association with life spans in parents. They were also used to create age-adjusted dichotomous indices and aggregate cumulative indices to predict the means of the life span distribution of the parents. In the construction of these indices, we used the fact that mortality risk is a function of physiological state represented by a number of physiological variables (Yashin et al., 2006).

The creation of dichotomous indices—We first evaluated the average age trajectories of EPs in domains 1–3 in five-year age groups starting with the age group 70–74, the youngest ages of the siblings of the probands, up to age 100+ years. Then for each measured EP, except for FVC, FEV1, GRIP, and MMSE, we assigned values "0" or "1" to a new covariate if the value of the measured EP for a study participant was below ("0") or above ("1") its mean value for a given age group. For FVC, FEV1, GRIP and MMSE, we assigned "1" if the value was below the age-group specific mean and "0" otherwise. These assignments were done separately for men and women. In this coding procedure the value "0" corresponds to an expected beneficial effect of the deviation from the mean on parental survival. The coding of variables in domains 4 and 5 were not based on age-specific means but rather a value "1" was assigned if the answer to a respective indicator was "yes" and "0" otherwise.

Our second and third dichotomous indices were based on tertiles and quartiles of the respective age-specific distributions of the EPs. Again, for all covariates except FVC, FEV1, GRIP, and MMSE, the variable was coded "1" if the observed value belonged to the *upper* tertile (quartile) of distribution and "0" if it belonged to the *lower* tertile (quartile). For FVC, FEV1, GRIP, and MMSE, we assigned "0" if the observed value belonged to the *upper* tertile (quartile) of distribution and "1" if it belongs to the *lower* tertile (quartile). All individuals whose values fell outside of the upper or lower tertiles (quartiles) were excluded from the analyses using these two indices.

We also evaluated the possibility that the dependence between offspring EPs and the parental mortality risk was U-shaped. To do so, we compared mortality risks in parents for offspring having values of their EPs in tertiles and (quartiles) of respective distributions. The

dichotomization procedure was similar to that described above but we assigned “1” if the observed value of EP belonged to the *upper or lower* tertile (quartile) of respective distribution and “0” if it belonged to the *middle* tertile (quartiles). We found a U-shaped association for BMI, for dichotomizations based on tertiles and quartiles and only for mothers’ life spans (significant at the 0.01 level). Results reported in Tables 1, 3 assume dichotomizations based on a U-shaped association for BMI.

The creation of indices based on cumulative proportions—For each individual, we also calculated the proportion of all values coded “1” among the 18 EPs based on the three dichotomized indices (means, tertiles and quartiles) described above. We assigned the value “1” to the cumulative index if at least half of the EPs had a value of “1” and “0” otherwise (denoted by PROPHALF in Tables 1, 3). Similarly, we evaluated covariates PROPTERT and PROPQUAR by assigning “1” when at least 2/3 (3/4) of the 18 EPs were coded “1” and “0” when less than 1/3 (1/4) of the dichotomous variables were coded “1”. All individuals whose covariate values fell between the upper and lower tertiles (quartiles) were excluded from the analyses using PROPTERT and PROPQUAR. Individuals having less than four observed covariates were also excluded from calculations of the three cumulative indices.

The creation of indices of physiological state based on cumulative proportions—The 18 EPs used in the construction of the above indices tap into multiple aspects of health and wellbeing and thus their effects can be somewhat difficult to interpret. Therefore, we also examined the associations between parental longevity and selected offspring EPs commonly used to describe an individual’s physiological state. These 10 physiological EPs (BG, BMI, CHOL, DBP, FEV1, FVC, HCT, PP, PR, SBP) were used to construct additional indices of cumulative proportions PROPHALF, PROPTERT, and PROPQUAR dichotomized using means, tertiles and quartiles of respective distributions as described above. These indices provide simple summary measures that characterize an individual’s multidimensional physiological state.

To examine the effects of the above indices on the life spans of the parents of the probands and their siblings we compared the average life span of parents whose offspring had a value “1” for a given index to the average life span of parents whose offspring had a value “0”. These comparisons were performed separately for life spans of mothers and fathers and by combining all offspring and separately for daughters and sons. The significance of differences was estimated using a two-sample, two-tailed t-test with unequal variances with MATLAB’s Statistical Toolbox (MathWorks Inc.).

Cox regression analyses—We used the Cox regression analyses to examine effects of the original (non-dichotomized) 18 EPs (individually and jointly) on the life spans of mothers and fathers (in joint analyses, PP was excluded from the list of EPs because of a linear dependence between variables DBP, SBP and PP). To estimate the influence of deviations of the values of EPs from their age-specific means on parental life spans, we also estimated modified models with age-specific means (calculated in five-year age groups) subtracted from the values of EPs. These analyses complemented the analyses of dichotomous indices described above.

Sensitivity analyses—Note that all these analyses treat siblings as independent observations. In reality, we have data on multiple sibs predicting the same parental longevity, so the observations are generally not independent. There are two potential issues related to this. First, treating siblings as independent observations may affect tests of significance. Second, it may result in a reduction of the effect of observed index on parental life spans when siblings have opposite values of a given index. We used two approaches to check the sensitivity of our empirical results to such familial clustering. First, we repeated analyses generating 100 “independent” samples randomly selecting one individual from each family and evaluated

average estimates for such "independent" samples. Second, we investigated the sensitivity of our results to the presence of families in which siblings have opposite values of a given index excluding such families from analyses. In the Cox regression analyses, to check the sensitivity of results to such familial clustering and to account for the intracluster (familial) dependence, we applied a robust sandwich covariance matrix estimate by Lee et al. (1992) in evaluation of respective p-values for individual parameters in the Cox regression model (in joint analyses of all original EPs) using SAS/STAT software[1]. Results of these sensitivity analyses can be found in online Supplementary data.

Results

Effects of dichotomous EPs

We began by constructing the dichotomous covariates based on the means, tertiles, and quartiles for the 18 EPs separately for the Danish and the U.S. samples, and investigated the associations between each covariate and the mean life spans of mothers and fathers. We found the effects of many covariates based on deviations from the mean to be similar in the Danish and U.S. samples. However, these associations were weaker in the Danish sample, most likely due to its smaller size. Although the index based on the means takes advantage of information on all individuals, its disadvantage is that the effects of some EPs on parents' life spans may be small because EP values which are proximate but nevertheless located on the opposite sides of the mean may have similar effects on parental life spans. Our indices based on tertiles and quartiles permit a greater contrast and provide additional insights into the relationship between parental life spans and offspring characteristics. Again the results were similar in the US and Danish samples, with the associations being weaker in the Danish data.

To increase the accuracy of the estimates we pooled the Danish and the U.S. data, and repeated the above analyses on the combined sample. Although relatively few EPs exhibited statistically significant associations with parental life spans, the results for most EPs related to physiological state as well as income and education were in the expected direction with more favorable values in the offspring associated with greater parental longevity. At the same time, these associations were more likely to be statistically significant for the life spans of mothers than fathers. Table 1 presents results based on the dichotomized indices, except for BMI. The association between offspring BMI and parental longevity is calculated assuming a U-shaped dependence (see section Data and Methods).

Results of Cox regression analyses

In addition to these empirical analyses, we used the Cox regression analyses to examine effects of the original (non-dichotomized) 18 EPs (individually and jointly) on the life spans of mothers and fathers. In joint analyses of original EPs (without subtracted age-specific means), only BG measured in daughters showed a significant effect on fathers' life span ($\beta = -0.009$, $p = 0.028$). In analyses of modified EPs (subtracted age-specific means), the effect of daughters' BG on fathers' life span remained significant ($\beta = -0.009$, $p = 0.024$). In addition, CHOL in all offspring showed a significant effect on fathers' life span ($\beta = -0.003$, $p = 0.03$). Results of separate analyses of original EPs are shown in Table 2. The table reveals that a number of EPs showed a significant relationship with parental longevity, including those that were significant in dichotomized analyses presented in Table 1 (BG, BMI, SBP, FVC, and EDUC). In separate analyses of modified EPs (subtracted age-specific means), the list of EPs with significant effects for fathers-daughters, fathers-sons, and mothers-sons remained the same. For fathers-all offspring, BMI is added to the list ($\beta = 0.018$, $p = 0.047$). For mothers-daughters, FEV1,

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FVC and GRIP dropped out from the list. For mothers-all offspring, PP ($\beta = 0.004$, $p = 0.047$) is added to the list.

Effects of cumulative proportions

The use of Bonferroni correction for multiple testing substantially reduces significance and alter the interpretation of the results for individual EPs presented in Table 1. An extremely conservative nature of the Bonferroni adjustments motivated constructing cumulative indices and performing analyses which do not require such correction. We also showed that cumulative indices better predict outcomes than individual traits (Kulminski et al., 2009;2008b) that further motivate the use of cumulative indices. We constructed indices of cumulative proportions for offspring using values of 18 EPs (see above for definitions) and evaluated their connection to parental life spans. The last three rows in Table 1 show the results for cumulative indices. They provide further evidence for an association between offspring characteristics and parents' life spans, although again the results reached statistical significance only for mothers' life spans. The largest significant (at the 0.01 level) difference was observed for PROPTERT for mother's life spans when dichotomization is based on quartiles. Mothers of the offspring with the more favorable characteristics lived on average 5.32 years longer than mothers of the offspring with less favorable EPs.

Effects of cumulative proportions based on EPs characterizing physiological state

As noted above, most associations between dichotomized indices based on EPs related to the offspring's physiological state were in the expected direction and several were statistically significant. Table 3 shows the results of the analysis using the cumulative indices based on 10 EPs characterizing physiological state and removing parents died before ages 60 (see section "Sensitivity analyses: Removing effects of premature death in parents" and Figure S1 in online Supplementary data). The table includes separate analyses for sons and daughters and mothers and fathers. The results lend further support for our earlier finding which showed the associations between offspring characteristics and the life spans of parents to be more highly significant for mothers than for fathers. At the same time, the differences between maternal life spans and daughters' and sons' characteristics are not substantial. As seen in Table 3, the association between the cumulative indices based on physiological state of the offspring was significant only for the life span of mothers (in addition, only PROPTERT based on quartiles for the fathers-sons pair was marginally significant). Similar analyses performed for cumulative physiological index based only on the U.S. data confirm the results shown in Table 3. The analyses based only on the Danish data produce non-significant results because of the small sample size. However, most associations for mothers and offspring have signs similar to those observed in the U.S. data (data not shown).

We performed several additional studies that further support the observed effects. Analyses that exclude families with "mixed" EPs in offspring (i.e., those having at least two offspring of respective sex with opposite values of the dichotomous index) strengthened the results reported in Table 3 (see section "Sensitivity analyses: Excluding families with "mixed" EPs in offspring" and Table S1 in online Supplementary data). Restricting the analysis to four physiological risk factors known to be associated with longevity in prior studies, such as BG, BMI, PP, and SBP (see Allison et al., 1999;Aviv, 2001;Levitan et al., 2004), and combinations thereof also increased the differences in parental life spans (see section "Simultaneous effects of select physiological EPs" and Table S2 in online Supplementary data). The reverse association, i.e., that parental longevity predicts values of EPs in the offspring, also takes place as Figure S2 in Supplementary data illustrates. These results provide us with additional insights about the relationship between parental longevity and offspring characteristics.

We also evaluated associations of parental life span with environmental factors such as smoking and heavy alcohol drinking (>=5 drinks/day) in their offspring. No significant differences between parental life spans of smoking and non-smoking offspring, as well as heavy drinking and other offspring were found. Note that proportions of smoking offspring of long-lived (life span from the upper quartile of the sex-specific life span distribution of the parental generation) and short-lived (life span from the lower half of the sex-specific life span distribution of the parental generation) parents did not differ significantly. Similar observation was true for proportions of heavy drinking offspring of long- and short-lived parents. Thus, environmental factors measured in offspring were not related with parental longevity in this sample.

The observed differences in parental longevity can be partially attributed to familial traits of non-genetic origin such as higher SES. Table 1 shows such effects of education and income. The sample size used in this study is too small to make reliable conclusions if the difference between trajectories of physiological indices in individuals with higher and lower SES takes place in the data. We performed a sensitivity analysis making the sample more homogeneous in terms of SES excluding those with low education and income (note that a small sample size restricts analyses focusing on individuals with lower SES only). The results of such analyses (see Tables S3 and S4 in Supplementary data) generally confirmed the observations shown in the paper).

Discussion

The results of these analyses indicate that a number of EPs measured in the LLFS have significant relationship with parental longevity. These include BG, BMI, SBP, FVC, INCOME and EDUC (with PP and FEV1 added to the list in the analyses of individuals with higher SES, see Table S3 in Supplementary data). The associations of each of the physiological indices listed above with longevity are well documented. Our recent studies of age related changes in mortality risks associated with blood glucose and BMI (see Kulminski et al., 2008a; Yashin et al., 2006; Yashin et al., 2009a; Yashin et al., 2009b and references therein) indicate an important role of dynamic mechanisms affecting these variables in aging organism, and their changing role in longevity determination. Studying longevity in the Japanese population, Kokaze et al. (2007) found that correlation of high level of FVC with longevity involves Mitochondrial DNA 5178 cytosine/adenine (Mt5178 C/A) polymorphism. Reed et al. (2003) confirmed that SBP together with a number of other factors is likely to contribute to the observed familial correlations in longevity. These results justify the need for a follow up study where measurements of EPs and life spans will be available for the same family members and more accurate estimates of respective connections will be possible to obtain. INCOME and EDUC are key social economical indices affecting longevity in humans (Clarkwest, 2008; Kim et al., 2004; Lynch et al., 2000).

Studying genetic effects on phenotypes affecting longevity in families may help generate insights concerning genetic pathways affecting life spans through heritable factors (endophenotypes). Data on multigenerational families, however, are often incomplete. The main result of this paper is that such incomplete data can be analyzed and respective connections between endophenotypes in offspring and parental life spans can be evaluated. The results suggest areas for further analyses. The fact that a number of offspring EPs measured in the LLFS have strong connections with the life spans of mothers in these families is consistent with maternal effects on life span in families. Experimental studies provide compelling evidence that maternal inheritance is responsible for a number of evolutionary outcomes, which are qualitatively different from those associated with Mendelian (nuclear) inheritance (Lande and Kirkpatrick, 1990). Mitochondria, and their DNA (mtDNA), are often considered as the genetic units of maternal inheritance. Maternal effects on longevity and stress

resistance have been observed in longevity studies of Drosophila (Golubovsky et al., 2006). Other factors may also contribute. These include the possibility that parents' life spans, which are ascertained by interview with probands, may have gender specific errors (e.g., the mothers' life spans may be better remembered than those of fathers). Furthermore, we have not controlled for such life style factors as smoking or work related exposures that may have played a more important role in determining the age at death of fathers than of the mothers. All these factors can be taken into account when more complete family data will be available.

Nevertheless, our results suggest that offspring characteristics are more predictive of mothers' than fathers' life spans. To test this hypothesis further we calculated correlations between life spans of parents and offspring using the original and offspring cohorts of the Framingham Heart Study data. We found that correlation between life spans of offspring and their fathers was about 0.08 and statistically not significant. The correlation between life spans of mothers and their offspring was about 0.22 and statistically significant (p-value less than 0.01). We also examined gender specific correlations in the life spans of parents and their offspring. We found correlations between fathers' and sons' life spans to be small (about 0.04) and not significant; between fathers and daughters the correlation was higher (0.15) but also not significant. In contrast, the correlations between the life spans of mothers and sons (0.21) and between mothers and daughters (0.23) were both statistically significant. Dependence between other variables in the original and offspring FHS cohorts deserves a separate study.

The data indicated the U-shape dependence of parental life span on BMI in offspring. Such dependence is not found for other EPs in this study. Note that in traditional epidemiological studies such effects were established using data on the same individuals (Boutitie et al., 2002; Okumiya et al., 1999; Protogerou et al., 2007).

An examination of prior literature shows that maternal and paternal effects on longevity differ from study to study. For example, strong paternal lineage of longevity was detected by Philippe (1978), Bocquet-Appel and Jakobi (1990). The maternal contribution outweighed the paternal component in studies by Abbott et al. (1974), Crawford and Rogers (1982), Brand et al. (1992), Korpelainen (1999; 2000), and Kemkes-Grottenthaler (2004). The presence of false paternity could produce difference in the effects, however, its exact contribution is difficult to evaluate without additional data. You et al. (2006) found a significant association between father's and son's and between mother's and daughter's longevity, but a weak, or insignificant association between the longevity of fathers and daughters and between mothers and sons. Several other studies have also shown that women's life span is more heritable than men's (Cournil and Kirkwood, 2001; Cournil et al., 2000; Kemkes-Grottenthaler, 2004). This variability in inheritance patterns of longevity by sex suggests the possibility of inheritance mechanisms other than nuclear genetic (Baldassarre et al., 2005). These mechanisms may include cultural, socio-economical, and other non-genetic factors that children can share with their parents. Studying such factors and mechanisms will contribute to better understanding heritable aspects of disease development as well.

The search for determinants of exceptional longevity involves the evaluation of effects of a host of potentially influential characteristics. Many of these factors may have weak effects on longevity *per* se and are thus thought to be unimportant. In addition, a comparison of effects of multiple EPs requires corrections for multiple testing, which further reduces the number of statistically significant characteristics. In this paper we demonstrated how information on multiple EPs can be combined and included in the analysis using cumulative indices. In the construction of these indices, we used the fact that mortality risk is a function of physiological state described by the values of physiological variables (Yashin et al., 2006). For a particular individual, the values of some of such physiological variables contribute to the increase in mortality risk, and the values of others contribute to the decline in this risk. The multivariate

evaluation of the effects of physiological variables in offspring on parental life spans using LLFS data did not produce significant results for many such variables, especially after correction for multiple comparisons. Therefore a one-dimensional indicator capable of characterizing the effect of deviation of the entire physiological state from its population mean might be useful. We hypothesized that the proportion of "unfavorable" deviations of physiological variables (measured in the LLFS) could be used as such measure for each individual. Note that similar cumulative measures characterizing frailty, comorbidity, and allostatic load are extensively used in studies of aging associated with declining health/well-being status (de Groot et al., 2003; Fried et al., 2001; Fried et al., 2009; Kulminski et al., 2008b; Puts et al., 2005; Rockwood and Mitnitski, 2007; Seeman et al., 2001). One remarkable property of such indices is that their effects on mortality risk show low sensitivity to modification of these indices (Rockwood et al., 2006). Such low sensitivity indicates that even in their simplest form (e.g., without using components' weights in constructing summary measures) cumulative indices capture some systemic aspects of aging related changes affecting mortality risk. These studies indicate the need in developing theoretical concepts explaining properties of such indices and their connection to aging.

The key step in further analyses is to consider the distribution of offspring with respect to constructed proportions, and compare the life spans of parents of offspring from different percentiles of this distribution. As described in the Data and Methods section, the dichotomous index PROPHALF assigns "1" to offspring which belong to the upper 50% percentile of this distribution and "0" to those who are from the lower percentile. It was constructed to provide a simple one-dimensional summary-measure of deviation of individual physiological state (represented by physiological variables measured in the LLFS study) from its population (age-specific) mean. The use of PROPTERT (when respective individuals belong to the lower and to the upper tertiles of respective distribution) and then PROPQUAR (when respective individuals belong to the lower and to the upper quartiles of respective distribution) makes the difference between compared groups of offspring more and more contrast. In the presence of hypothesized association, the difference in life spans of parents is expected to be larger in the groups constructed using PROPTERT than in the groups using PROPHALF, and in the groups using PROPQUAR than in the groups using PROPTERT dichotomous indices. The results of statistical analyses indicate the presence of such association with different effects on male and female parents.

With the use of cumulative indices we found that the greater the "distance" between offspring EP values (e.g., indices based on the tertiles and quartiles of respective EP distributions), the stronger the effect on parental longevity when measured by the absolute difference in average life spans of parents. The fact that only some of the EPs and indices based on them exhibited significant effects on parents' longevity may be an artifact of the relatively small sample size. With a larger sample size additional influential EPs are likely to emerge. Also note that although the use of indices of cumulative proportions allows us to combine information from several EPs, it also makes the results more difficult to interpret. Because many different mechanisms may now contribute to these associations, it becomes difficult to isolate the individual mechanisms involved. More insights can be gained by basing the cumulative indices on EPs that measure different aspects of a given health state, e.g., physiological status. Additional studies are needed to investigate properties of such indices used in characterizing integrative aspects of aging.

At first glance the use of cumulative indices introduces additional heterogeneity and non-specificity which could confound the discovery of genes influencing longevity. However, such non-specificity may manifest the effects of genetic pathways (rather than separate genes) involved in integrative regulation of aging related changes through the processes of compensatory adaptation and remodeling having heterogeneous manifestation. In this case the

results of genetic analyses will not only be the discovery of separate genes affecting longevity, but also detection of longevity regulating genetic pathways.

Finally, we should note that the results of our analyses do not characterize familial correlation in offspring EPs and parental longevity in the entire U.S. or the Danish populations. Because probands and their siblings in the LLFS must be exceptional survivors, they represent a selected population subgroup. Nevertheless our results provide important insights into potentially heritable factors identifiable in the offspring that are predictive of parental longevity. Further studies to identify additional EPs related to longevity by comparing offspring EPs and parental longevity in families with long lived members to that found in families with short or average life spans would be useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Estimates of the effect of individual (dichotomized) endophenotypes measured in offspring on parental longevity in the combined LLFS sample (Denmark and the United States)

Endophenotypes (EPs)	Means[1]						Tertiles[1]						Quartiles[1]					
	Fathers			Mothers			Fathers			Mothers			Fathers			Mothers		
	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]
Physiologic EPs																		
BG	239	411	−0.65	245	433	−2.75*	223	237	−0.49	227	242	−3.23*	175	186	−0.34	175	193	−3.21
BMI	295	356	−2.60*	302	375	−1.39	442	209	−1.75	469	208	−3.49#	340	311	−0.88	361	316	−3.99#
CHOL	306	349	2.28	321	362	−0.34	215	230	2.26	220	242	−0.83	164	165	1.34	168	175	−2.77
DBP	342	345	−0.17	355	359	0.05	244	225	−0.49	253	232	−0.82	191	175	−0.73	198	176	−2.29
SBP	326	361	−0.77	342	372	−2.01	242	224	−1.62	251	231	−3.17*	181	169	−1.83	186	174	−2.55
PP	322	365	−1.35	335	379	−2.29	240	217	−1.61	246	228	−2.73	179	165	−1.0	187	173	−3.16
FEV1	301	288	1.15	317	294	−0.95	197	186	1.01	208	190	−2.71	147	138	−1.15	154	141	−3.14
FVC	314	275	−0.23	327	284	−2.33	196	177	0.44	206	186	−3.08	145	137	0.45	153	145	−4.76#
PR	318	368	0.11	332	381	−0.7	232	243	0.19	244	250	−1.81	178	193	0.88	187	198	−2.22
HCT	316	317	−0.2	329	327	1.25	216	236	−0.73	225	244	0.5	161	170	−0.84	169	178	0.32
Physical & Cognitive Func.																		
GRIP	339	344	−0.05	358	350	0.84	240	249	−0.75	259	250	0.61	189	183	−0.19	207	184	1.0
MMSE	266	399	1.32	271	418	1.12	266	272	2.12	269	284	1.29	193	203	1.71	196	211	0.27
SES & lifestyle																		
INTACT	480	123	0.3	492	130	0.35	480	123	0.3	492	130	0.35	480	123	0.3	492	130	0.35
MODACT	467	226	−0.79	494	228	0.27	467	226	−0.79	494	228	0.27	467	226	−0.79	494	228	0.27
INCOME	113	566	−3.29*	118	588	−2.12	113	566	−3.29*	118	588	−2.12	113	566	−3.29*	118	588	−2.12
EDUC	184	514	0.31	188	538	−4.42#	184	514	0.31	188	538	−4.42#	184	514	0.31	188	538	−4.42#
Disease History																		
HYPERT	346	349	−1.49	359	363	1.08	346	349	−1.49	359	363	1.08	346	349	−1.49	359	363	1.08
CANCER	233	466	−0.99	248	479	0.72	233	466	−0.99	248	479	0.72	233	466	−0.99	248	479	0.72
PROPHALF[4]	319	388	−1.8	335	403	−2.59*	369	337	−1.02	390	347	−3.83#	354	351	−1.37	370	365	−3.23#

Endophenotypes (EPs)	Means[1]						Tertiles[1]						Quartiles[1]					
	Fathers			Mothers			Fathers			Mothers			Fathers			Mothers		
	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]
PROPTERT[4]	80	111	−1.43	84	116	−1.31	112	102	−1.42	123	108	−2.75	116	125	−2.31	122	126	−5.32[#]
PROPQUAR[4]	16	50	1.39	17	56	0.0	42	39	−0.94	44	42	−4.32	38	57	0.99	42	57	−5.61

[*] $0.01 \le p < 0.05$;

[#] $0.001 \le p < 0.01$; for other estimates $p \ge 0.05$

[1] **Means, Tertiles, Quartiles:** method of dichotomization of respective EPs based on the observed deviation of values measured in offspring from the average age trajectories of the EPs in the sample (see section "**The creation of dichotomous indices**")

[2] **N1, N0:** numbers of offspring having values of dichotomized EPs "1" (worse health) and "0" (better health), respectively

[3] **Diff:** difference between mean life spans of parents (fathers or mothers) whose offspring have values of EPs "1" (worse health) and "0" (better health) as defined by the respective dichotomization

[4] **PROPHALF, PROPTERT, PROPQUAR:** indices based on cumulative proportions of dichotomized EPs (see section "**The creation of indices based on cumulative proportions**")

Abbreviations: BG - fasting blood glucose, BMI - body mass index, CHOL - total cholesterol, DBP (SBP, PP) - diastolic (systolic, pulse) blood pressure, FEV1 - forced expiratory volume in 1 second, FVC - forced vital capacity, PR - pulse rate, HCT - hematocrit, GRIP - grip strength, MMSE - total MMSE score, INTACT - no intensive physical activity, MODACT - no moderate physical activity, INCOME - low income, EDUC - low education, HYPERT - hypertension

Table 2

Results of Cox regression model applied to individual endophenotypes measured in offspring and parental longevity in the combined LLFS sample (Denmark and the United States)

Covariate	Fathers						Mothers					
	Daughters		Sons		All		Daughters		Sons		All	
	β	N	*β*	N	*β*	N	*β*	N	*β*	N	*β*	N
BG	−0.0025	355	0.0042	295	0.0005	650	0.0043*	374	0.0008	304	0.0021	678
BMI	0.0048	359	0.0416#	292	0.0154	651	0.0141	374	0.0153	303	0.0153	677
CANCER	0.231*	389	−0.0364	310	0.1049	699	0.0763	408	−0.0362	319	0.0368	727
CHOL	−0.0018	357	−0.0009	298	−0.0011	655	0.0025*	376	0.0008	307	0.0016	683
DBP	−0.0022	381	−0.0022	306	−0.0025	687	0.0083*	399	−0.0034	315	0.0039	714
EDUC	0.0914	389	−0.0178	309	0.0693	698	0.284#	408	0.2058	318	0.2438#	726
FEV1	0	317	0.0001	272	0	589	−0.0003*	332	−0.0003#	279	−0.0002*	611
FVC	0.0001	317	0.0001	272	0	589	−0.0003*	332	−0.0003#	279	−0.0001*	611
GRIP	−0.0125	379	0.0098	304	−0.0034	683	−0.0181*	395	−0.0034	313	−0.004	708
HCT	0.0008	346	−0.0183	287	−0.0098	633	−0.0104	362	−0.0126	294	−0.0099	656
HYPERT	−0.0758	387	0.2202	308	0.0602	695	−0.0354	405	0.0312	317	−0.0289	722
INCOME	0.2134	376	0.1015	303	0.2025	679	0.057	394	0.2123	312	0.0934	706
INTACT	−0.1823	325	0.1883	278	0.0697	603	0.1913	334	−0.1849	288	−0.0156	622
MMSE	−0.002	372	0.0046	293	−0.0009	665	−0.0037	389	−0.0272	300	−0.0108	689
MODACT	−0.0814	383	0.1106	310	0.0304	693	−0.0229	403	−0.0838	319	−0.0498	722
PP	0.0032	381	−0.0013	306	0.0021	687	0.0032	399	0.005	315	0.0034	714
PR	−0.0089*	380	0.004	306	−0.0034	686	0.002	398	0.0083	315	0.0042	713
SBP	0.0016	381	−0.0013	306	0.0008	687	0.0037*	399	0.002	315	0.0029*	714

*$0.01 \le p < 0.05$;

#$p < 0.01$; for other estimates $p \ge 0.05$

β denotes the estimates of respective regression parameters; **N** signifies the sample size

Abbreviations: BG - fasting blood glucose, BMI - body mass index, CHOL - total cholesterol, DBP (SBP, PP) - diastolic (systolic, pulse) blood pressure, EDUC - low education, FEV1 - forced expiratory volume in 1 second, FVC - forced vital capacity, GRIP - grip strength, HCT - hematocrit, HYPERT – hypertension, INCOME - low income, INTACT - no intensive physical activity, MMSE - total MMSE score, MODACT - no moderate physical activity, PR - pulse rate

Table 3

Estimates of the combined effect of 10 physiological variables (i.e., cumulative indices based on respective dichotomized endophenotypes) measured in offspring on parental longevity in the combined LLFS sample (Denmark and the United States) excluding parents with life spans less than 60 years

Cumulative Index	Fathers									Mothers								
	Daughters			Sons			All			Daughters			Sons			All		
	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]	N1[2]	N0[2]	Diff[3]
Means[1]																		
PROPHALF[4]	174	160	0.94	146	137	−0.37	320	297	0.34	194	167	−1.0	147	138	−2.27	341	305	−1.55
PROPTERT[4]	71	92	1.24	58	72	1.48	129	164	1.35	83	93	−3.80*	58	74	−2.87	141	167	−3.40#
PROPQUAR[4]	38	54	−0.91	33	42	0.3	71	96	−0.37	40	56	−4.33	31	45	−3.64	71	101	−4.03*
Tertiles[1]																		
PROPHALF[4]	185	131	0.17	178	96	1.7	363	227	0.9	205	137	−1.98	175	99	−4.64§	380	236	−3.15§
PROPTERT[4]	100	72	−0.15	91	42	1.16	191	114	0.42	113	76	−3.28	89	46	−3.19	202	122	−3.23*
PROPQUAR[4]	72	46	0.63	55	22	2.16	127	68	1.14	78	46	−3.14	54	22	−4.79	132	68	−3.66*
Quartiles[1]																		
PROPHALF[4]	159	117	−0.39	147	93	1.92	306	210	0.71	173	126	−3.86#	144	97	−4.35#	317	223	−4.08†
PROPTERT[4]	97	75	−0.93	78	57	3.74*	175	132	1.1	107	78	−4.71#	80	56	−3.02	187	134	−3.99#
PROPQUAR[4]	75	51	−1.72	56	31	2.55	131	82	−0.05	77	54	−4.11	56	31	−3.47	133	85	−3.84*

*$0.01 \le p < 0.05$;

#$0.001 \le p < 0.01$;

§$0.0001 \le p < 0.001$;

†$p < 0.0001$; for other estimates $p \ge 0.05$

10 endophenotypes included in calculation of cumulative indices: fasting blood glucose; body mass index; total cholesterol; diastolic, systolic, and pulse pressure; forced expiratory volume in 1 second; forced vital capacity; pulse rate; hematocrit

[1]**Means, Tertiles, Quartiles:** method of dichotomization of respective EPs based on the observed deviation of values measured in offspring from the average age trajectories of the EPs in the sample (see section "**The creation of dichotomous indices**")

[2]**N1, N0:** numbers of offspring having values of dichotomized EPs "1" (worse health) and "0" (better health), respectively

[3] **Diff:** difference between mean life spans of parents (fathers or mothers) whose offspring have values of EPs "1" (worse health) and "0" (better health) as defined by the respective dichotomization

[4] **PROPHALF, PROPTERT, PROPQUAR:** indices based on cumulative proportions of dichotomized EPs (see section "**The creation of indices based on cumulative proportions**")