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Longer Lived Parents: Protective Associations With Cancer Incidence and Overall Mortality

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Background. Children of centenarians have lower cardiovascular disease prevalence and live longer. We aimed to estimate associations between the full range of parental attained ages and health status in a middle-aged U.S. representative sample.

Methods. Using Health and Retirement Study data, models estimated disease incidence and mortality hazards for respondents aged 51–61 years at baseline, followed up for 18 years. Full adjustment included sex, race, smoking, wealth, education, body mass index, and childhood socioeconomic status. Mother's and father's attained age distributions were used to define short-, intermediate-, and long-lived groups, yielding a ranked parental longevity score (n = 6,055, excluding short–long discordance). Linear models (n = 8,340) tested mother's or father's attained ages, adjusted for each other.

Results. With increasing mother's or father's survival (>65 years), all-cause mortality declined 19% (hazard ratio [HR] = 0.81, 95% CI: 0.76–0.86, $p < .001$) and 14% per decade (HR = 0.87, 95% CI: 0.81–0.92, $p < .001$). Estimates changed only modestly when fully adjusted. Parent-in-law survival was not associated with mortality (n = 1,809, HR = 1.00, 95% CI: 0.90–1.12, $p = .98$). Offspring with one or two long-lived parents had lower cancer incidence (938 cases, HR per parental longevity score = 0.76, 95% CI: 0.61–0.94, $p = .01$) versus two intermediate parents. Similar HRs for diabetes (HR = 0.89, 95% CI: 0.84–0.96, $p = .001$), heart disease (HR = 0.88, 95% CI: 0.82–0.93, $p < .001$), and stroke (HR = 0.86, 95% CI: 0.78–0.95, $p = .002$) were significant, but there was no trend for arthritis.

Conclusions. The results provide the first robust evidence that increasing parental attained age is associated with lower cancer incidence in offspring. Health advantages of having centenarian parents extend to a wider range of parental longevity and may provide a quantitative trait of slower aging.

Key Words: Family history—Parental longevity—Cancer—Cardiovascular disease—Centenarian.

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THE children of exceptionally long-lived parents live longer themselves and have lower prevalence of cardiovascular disease compared with age-referent controls (1–4) However, it is unclear whether the wider "normal" range of parental survival is associated with incidence of cancer and other common diseases in the offspring.

With the large life expectancy differences between men and women and the rapid rise in life expectancies for both groups during the twentieth century, defining longer maternal or paternal survival is not straightforward. Most previous studies have chosen conventional (or arbitrary) definitions for classifying the length of parental survival (5,6), for example, Terry and colleagues focused on both mothers and fathers living to ages 85 years or more. Previous analyses have generally also not separated predominantly "premature" parental deaths (unlikely to be related to normal aging) from those that appear predominantly age related. It is therefore important to map the "normal" spectrum (7) of likely aging-related mortality and survival for mothers and fathers of study participants. This allows exclusion of premature parental deaths more likely to be caused by extrinsic factors including reproduction and accidents, which otherwise may obscure age-related effects in the offspring. This approach also provides empirical cut points for classification of relative parental longevity.

We aimed to estimate the effects of the complete range of normal aging-related parental survival on cancer and other common disease incidence plus all-cause mortality.

We used data from the Health and Retirement Study (HRS), a U.S. representative cohort of people aged 51–61 years followed up for 18 years. Questions on parental survival were asked at each follow-up, allowing a prospective analysis of mortality and incident disease in offspring, from middle age, with very high ascertainment of parental survival.

Methods

Cohort

The HRS recruited a representative multiethnic sample of Americans aged 51–61 years, as documented elsewhere (8). Baseline interviews were conducted in 1992 and repeat interviews biennially through 2010. For our analyses, we used data from all 10 HRS waves (1992–2010), collated in a single data set by the RAND Corporation (9).

Parental Survival

Respondents were asked at every wave about the age at death of their parents, or their current age if they were alive. There were 1,290 participants with parents (1,136 mothers and/or 282 fathers) recorded as living in the latest interview preceding the respondents' death, loss to follow-up, or current end-of-study period; these "living" parents were excluded from the main analyses because we cannot predict who will attain higher ages at death but have included them in a sensitivity analysis based on last reported attained age.

For a studied population, normal aging-related human survival is distributed symmetrically (10) around the mode (M), that is, the most frequent age at death. Consequently, we fitted a normal curve using nonlinear least square regression (7) around the mode for mapping the distribution of the normal survival of mothers and fathers, using the following formula: $f = a \times \exp\{-0.5 \times [(x - x_0)/b]^2\}$. The modal age at death for mothers is 84 ($SD = 7$ years); for fathers, estimates were 76 years ($SD = 11$ years). Based on these estimates, mothers were categorized as follows: short lived less than $M - 1$ *SD*, that is, 61–76 years; intermediate lived $M \pm 1$ *SD*, that is, 77–91 years; and long lived greater than $M + 1$ *SD*, that is, more than 91 years (Figure 1). Similarly, fathers were classified as follows: short lived less than $M - 1$ *SD*, that is, 46–64 years; intermediate lived $M \pm 1$ *SD*, that is, 65–87 years; and long lived greater than $M + 1$ *SD*, that is, more than 87 years. Mothers dying before 61 years and fathers dying before 46 years were classified as premature deaths, and respondents with prematurely dying parent(s) were not included in the parental longevity score (PLS). We then assigned a ranked "parental longevity score" to each participant based on parental attained age: (a) both parents short lived; (b) one parent short lived and the other intermediate lived; (c) both parents intermediate lived; (d) one parent intermediate lived and the other long lived; and (e) both parents long lived. Those offspring having one parent long lived and the other short lived (ie, a discordant status) were excluded from the analyses as they could not be classified into an ordinal rank.

Covariates

Demographic variables in models were age, sex, and race. The socioeconomic and lifestyle variables (termed "environmental factors") include childhood environment of the participants represented by parental education; "job loss of several months experienced by respondent's father"; and "a time when family received financial help from relatives/friends because of financial difficulties" before the participants attained 16 years of age. Environmental factors affecting adult lives include smoking, alcohol consumption, education, body mass index (as proxy variable for diet), income, household wealth, health insurance, and exercise undertaken. Smoking status at baseline was coded to never smoked, exsmokers, and current smokers. Alcohol drinking at baseline was assessed using the CAGE instrument (11). The educational achievement of the respondents was categorized as 0 ≤ high school, 1 = high school, 2 = college, and 3 = higher/professional. Individual baseline income and household wealth were used in the analyses as continuous variables. Access to health insurance at baseline was coded to yes/no. Body mass index (kg/m^2) was calculated from self-reported weight and height at baseline and categorized into four natural groups (1 < 20, 2 = 20–24.9, 3 = 25–30, and 4 > 30). The exercise status at baseline was coded into a binary variable (yes/no) depending on vigorous exercises performed at least thrice a week.

Age-Related Diseases

Self-report of physician-diagnosed diabetes, heart disease, stroke, cancer (excluding nonmelanoma skin cancers), and arthritis was recorded as binary response (yes/no) in the first wave (1992). Incident diagnoses of heart disease, stroke, diabetes, arthritis, and cancer were recorded in each subsequent wave in answer to the question "Since we last talked to you, that is since [last interview date], has a doctor told you that you have ...." (12).

Ascertainment of Death

Death of participants was ascertained by linkage with National Death Index following each wave since 2000 (13), and their year of death was recorded. For 1.5% of respondents who died, the year of death is unknown, but the wave at which they were first reported as having died is recorded; for these, we have used the previous year as their year of death.

Statistical Analysis

Age at death of the offspring from all causes was used as the time-to-event outcome for survival analyses.

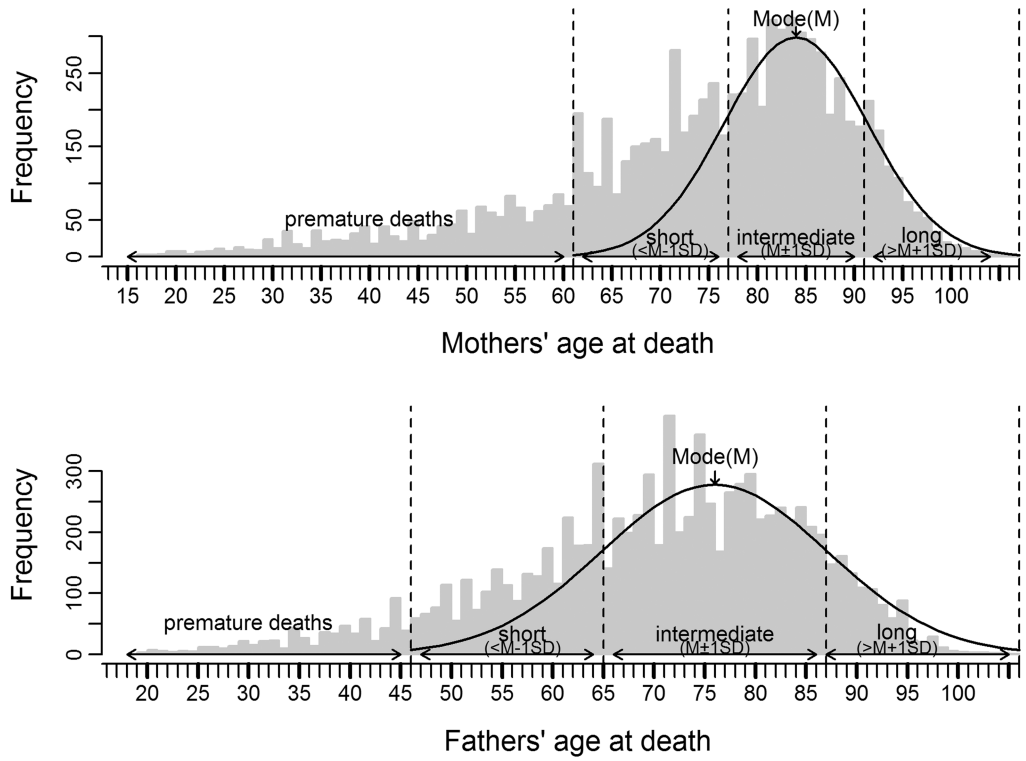

Figure 1. Frequency distribution of parental age at death (gray). The curve represents the normal distribution of aging-attributable parental deaths centered on their modal (most frequent) age at death. The normal distributions were modeled using nonlinear least square regression. (**A**) mothers and (**B**) fathers.

Respondents who were alive at 2010 and those who were lost to follow-up at intermediate waves were included as censored observations. Initial Cox models included parental attained age as continuous variables (termed Model 1). A smoothed hazard curve was fitted using a penalized spline function to plot the actual relationship between mortality risk in the offspring and mother's attained age, adjusted for gender, race and father's longevity. A second curve was fitted to plot the relationship with father's attained age with similar adjustments. Parental attained age more than 65 years was also modeled in decades rather than single years, to ease interpretation. We next estimated the effect of PLS on the mortality of participants' spouses/partners (hereafter termed "parent-in-law" longevity score) in a subsample (adjusting for their own PLS) where both age-eligible pairs were interviewed (n = 1,809) and had valid parent and parent-in-law longevity scores.

Survival curves and Cox models were then fitted with the PLS as the explanatory variable (termed hereafter as Model 2). The PLS was initially included as a continuous variable to estimate the hazards per PLS. It was then introduced as a categorical variable to compare the hazards with the middle category (PLS 3) used as the referent group as these participants were born to two intermediate-lived parents and hence are most likely to represent the normative aging-related parental mortality. The initial models were adjusted for race and gender (minimally adjusted) and then further adjusted for demographic and environmental covariates (fully adjusted).

Age at the self-reported incident diagnosis of age-related diseases, diabetes, heart disease, stroke, cancer, and arthritis, was then used as time-to-event outcome for disease-specific survival analyses, after excluding those diagnosed with prevalent conditions at baseline. To allow for more statistical power, in disease-specific analysis we collapsed five groups to three, combining groups PLS1 with PLS2 and PLS4 with PLS5 and compared these two new groups with PLS3.

Interaction between gender of offspring and PLS was tested. The complex multistage sampling design of the HRS was accounted for in the analyses and baseline sample weights were used. The graphs were fitted and drawn using *R* version 2.14.0, and other analyses were conducted using Stata, version 10.1.

Included Sample

At study baseline (1992), out of 9,764 age-eligible HRS participants, 4,746 (49%) had parent(s) still alive. After 18 years of follow-up, only 1,290 (13%) participants had parent(s) recorded as living.

The mean life span of mothers (n = 8,573) was 75 years (SD = 5.5) and fathers (n = 9348) was 71 years (SD = 14.6).

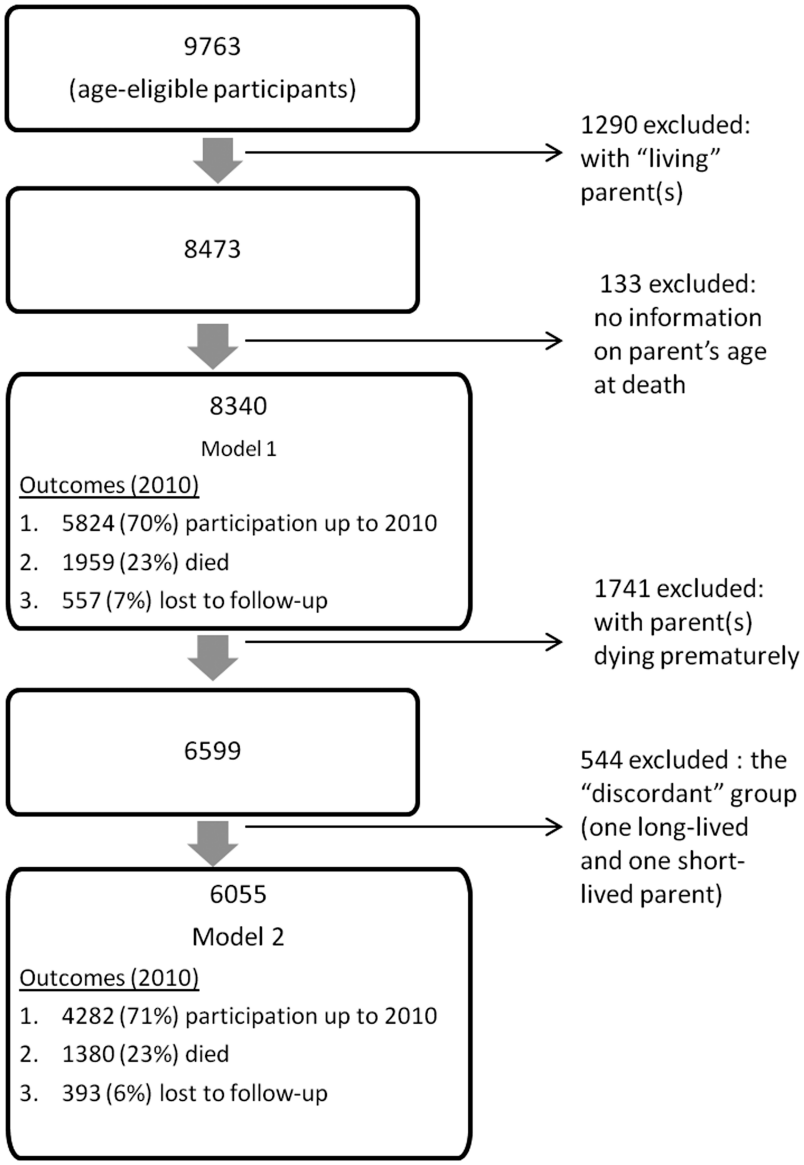

Figure 2. Flowchart of participants included in the analyses and their outcomes. Model 1 used parental attained age as a continuous variable, and Model 2 used parental longevity score to categorize the offspring in ordered ranks.

Short-lived fathers (46–65 age group, n = 1,528) had a mean age of 58.1 years (SD = 0.14); intermediate (66–85 age group, n = 3,831) had a mean age of 76.21 (SD = 0.093); and long lived (≥87 years age group, n = 696) had a mean age of 90.83 (SD = 0.13). Short-lived mothers (61–76 age group, n = 2,058) had a mean age of 69.46 years (SD = 0.10); intermediate (77–90 age group, n = 3,256) had a mean age of 83.56 (SD = 0.06), and long-lived mothers (≥91 years age group, n = 741) had a mean age of 94.24 years (SD = 0.11).

The participants were aged 51–61 years at 1992 (mean = 55.5, SD = 3.2) and those interviewed in 2010 were aged 69–79 years (mean = 73.4, SD = 3.1). The samples included in the models are presented in Figure 2.

Results

Baseline Characteristics (1992)

Offspring with higher PLS had mothers with slightly more years of education (p = .05; Table 1) and were less likely to be born to families receiving financial help (p = .006) although trends were modest. Higher PLS offspring at HRS baseline (in middle age) were less likely to be current smokers (19% in PLS5 vs 30% in PLS1), were better educated, were less obese, had higher mean household wealth, and had higher personal incomes.

All-Cause Mortality (1992–2010)

In penalized smoothing spline regression models of each parent's continuous attained age (adjusted for

Table 1. Distribution of Demographic and Environmental Factors and Prevalence of Age-Related Diseases at Baseline (1992)

	Total (n = 6055)	PLS1 (n = 638)	PLS2 (n = 2310)	PLS3 (n = 1865)	PLS4 (n = 1047)	PLS5 (n = 195)	p*
Demographic variables							
Age	56 (3.2)	56 (3.3)	56 (3.2)	56 (3.1)	56 (3.1)	56 (3.1)	.79
Sex (%)							
Male	2844 (47)	308 (48)	1076 (47)	862 (46)	516 (49)	82 (43)	.27
Female	3211 (53)	330 (52)	1234 (53)	1003 (54)	531 (51)	113 (57)	
Race (%)							
White	4965 (82)	517 (81)	1835 (80)	1585 (85)	862 (82)	166 (85)	.01
African American	874 (14)	100 (16)	392 (17)	224 (12)	138 (14)	20 (11)	
Others	216 (4)	21 (3)	83 (4)	56 (3)	47 (4)	9 (4)	
Environmental factors related to childhood							
Mother's education (y)	9 (5)	9 (5)	9 (5)	9 (4)	10 (4)	10 (5)	.05
Father's education (y)	8 (6)	8 (6)	8 (6)	8 (6)	9 (5)	8 (6)	.49
Father losing job (%)	952 (20)	102 (23)	369 (21)	288 (19)	163 (18)	30 (17)	.08
Family receiving financial help (%)	545 (11)	58 (12)	223 (12)	178 (11)	71 (7)	15 (8)	.006
Environmental factors related to adulthood							
Household wealth	89,000 (17,5200)	75,000 (141,150)	83,750 (168,500)	98,100 (183,247)	92,000 (200,200)	128,000 (257,200)	<.001
Annual income	15,000 (30,000)	14,280 (30,000)	13,500 (29,200)	15,000 (31,000)	17,000 (32,500)	15,000 (30,150)	.005
Smoking (%)							
Never	2282 (38)	215 (34)	831 (36)	738 (40)	418 (40)	80 (41)	.001
Ex	2182 (36)	229 (36)	829 (36)	660 (35)	386 (37)	78 (40)	
Current	1591 (26)	194 (30)	650 (28)	467 (25)	243 (23)	37 (19)	
Drinking assessment, CAGE (%)							
Not excess	5227 (86)	536 (84)	1992 (86)	1615 (87)	907 (87)	177 (90)	.17
Excess	828 (14)	102 (16)	318 (14)	250 (13)	140 (13)	18 (10)	
Vigorous activity (%)							
≥3/wk	4864 (80)	529 (83)	1837 (80)	1518 (81)	824 (79)	156 (81)	.15
0–2/wk	1191 (20)	109 (17)	473 (20)	347 (19)	223 (21)	39 (19)	
Body mass index, kg/m^2 (%)							
<20	222 (4)	25 (4)	84 (4)	66 (4)	36 (3)	11 (6)	.05
20–24.9	1962 (32)	187 (29)	723 (31)	621 (33)	366 (35)	65 (33)	
25–29.9	2465 (41)	257 (40)	930 (40)	760 (41)	439 (42)	79 (41)	
≥30	1406 (23)	169 (26)	573 (25)	418 (22)	206 (20)	40 (20)	
Education (%)							
<High school	1514 (25)	188 (29)	646 (28)	431 (23)	212 (20)	37 (19)	<.001
High school	3262 (54)	331 (52)	1246 (54)	1028 (55)	562 (54)	95 (49)	
College	814 (13)	79 (12)	265 (11)	254 (14)	177 (17)	39 (20)	
Mast/Prof	465 (8)	40 (6)	153 (7)	152 (8)	96 (9)	24 (12)	
Health insurance (%)							
No plan	1724 (29)	191 (30)	699 (31)	506 (27)	276 (27)	52 (27)	.005
1–4 plans	4275 (71)	440 (70)	1611 (69)	1359 (73)	762 (73)	141 (73)	
Prevalence of age-related diseases (%)							
Diabetes	609 (10)	84 (13)	278 (12)	159 (9)	73 (7)	15 (7)	<.001
Heart disease	764 (13)	99 (16)	342 (15)	203 (11)	102 (10)	22 (9)	<.001
Stroke	161 (3)	23 (4)	72 (3)	41 (2)	18 (2)	7 (3)	.04
Cancer	324 (5)	36 (6)	134 (6)	95 (5)	50 (5)	9 (5)	.7
Arthritis	2282 (38)	254 (40)	910 (40)	687 (37)	360 (34)	71 (36)	.05

Note: PLS = parental longevity score; continuous variables: median (inter-quartile range) and categorical variables: numbers (percentage).
*p values for continuous variables obtained through Kruskal–Wallis and for categorical variables through chi square test.

gender, race, and other parent's attained age, n = 8,340), age of parental death more than 65 years was associated with offspring mortality (Figure 3), with an approximately linear reduction in hazard ratio (HR) with increasing parental attained age for both mothers and fathers. This association was stronger for mother's attained age: for every additional decade of mother's (n = 6,584) and father's (n = 5,848) survival beyond 65, the minimally adjusted HR in the offspring was 0.76 (95% CI: 0.72–0.80) and 0.83 (95% CI: 0.78–0.88), respectively, that is, representing a central estimate of 19% and 14% reductions in offspring mortality per mother's and father's attained decade more than 65 years, respectively. After full adjustment, the HRs were slightly attenuated to 0.81 (95% CI: 76–0.86, p < .001) for mothers and 0.86 (95% CI: 0.81–0.92, p < .001) for fathers (Supplementary Table 2). An interaction term between parents' survival and offspring gender was not significant in the Cox models.

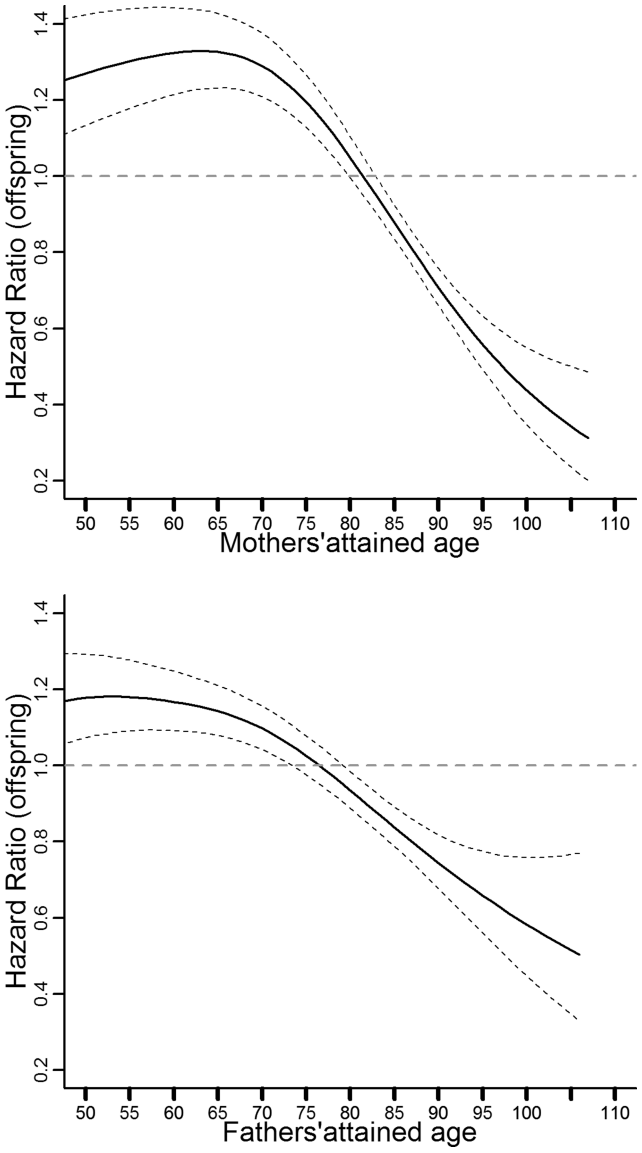

Figure 3. Relationship between parental ([**A**] mothers and [**B**] fathers) attained age and risk of mortality from all causes in the offspring during follow-up (1992–2010) using penalized smoothing spline graphs (adjusted for gender and race and other parent's attained age; n = 8,340).

In analyses based on PLS, the divergence in survival between offspring groups is evident from approximately 57 years of offspring age (Figure 4). The minimally adjusted HR for all-cause mortality per increasing PLS (n = 6055) was 0.75 (95% CI: 0.71–0.80, $p < .001$). Controlling for the full model variables attenuated the HR to 0.8 (95% CI: 0.77–0.86, $p < .001$; Supplementary Table 3). Dose–response trends were evident compared with the referent middle category of PLS3; the fully adjusted HR for PLS4 was 0.76 (95% CI: 0.62–0.94, $p = .01$) and for PLS5 was 0.68 (95% CI: 0.47–0.97, $p = .03$). The fully adjusted HR for PLS2 was 1.27 (95% CI: 1.13–1.43, $p < .001$) and for PLS1 was 1.41 (95% CI: 1.18–1.67, $p < .001$).

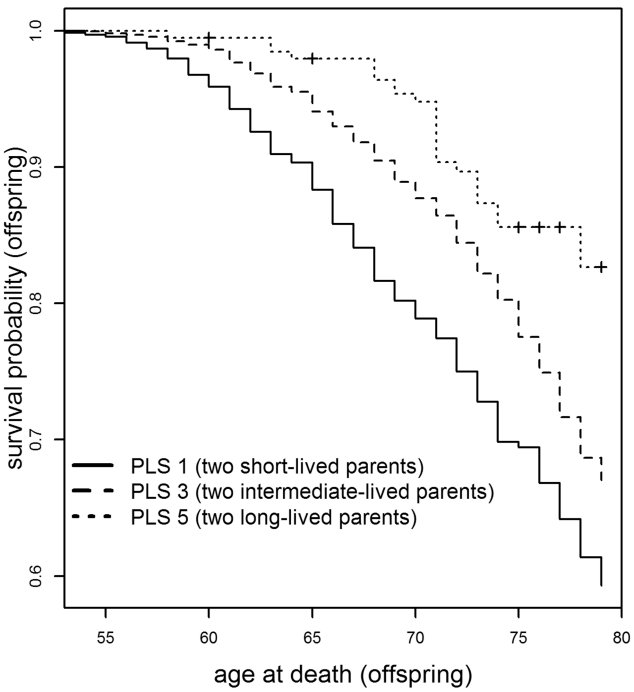

Figure 4. Survival curve in three offspring groups (categorized by parental longevity score) for all causes of mortality during follow-up (1992–2010), adjusted for gender and race (n = 6,055).

Parent-in-law Effects

We also examined the effects of parent-in-law longevity scores on available spouse/partners in the HRS subsample (n = 1,809). For all-cause mortality, HR (fully adjusted) per parent-in-law longevity score was 1.00 (95% CI: 0.90–1.12, $p = .98$), whereas HR per PLS (the effect of participants' own parents) in the subsample was 0.82 (95% CI: 0.73–0.91, $p < .001$), which was similar to the overall sample estimate.

Incident Disease (1992–2010)

Increasing PLS was associated with significantly lower incidence of cancers (HR per PLS = 0.93, 95% CI: 0.88–0.98, $p = .01$; Figure 5 and Supplementary Table 3). Participants with at least one long-lived parent had 24% lower incidence of cancer (HR = 0.76, 95% CI: 0.61–0.94, $p = .01$) compared with those having two intermediate-lived parents. There was no significant difference in cancer incidence between offspring of short and intermediate-lived parents. In Cox models, increasing PLS was also associated with reduced hazard of incident diabetes, (HR = 0.89, 95% CI: 0.83–0.95, $p = .001$), heart disease (HR = 0.88, 95% CI: 0.82–0.93, $p < .001$), and stroke (HR = 0.86, 95% CI: 0.78–0.95, $p = .002$) with clear dose–response relationships for most of these (Figure 5 and Supplementary Table 3), with the exception of arthritis, for which no trend was apparent.

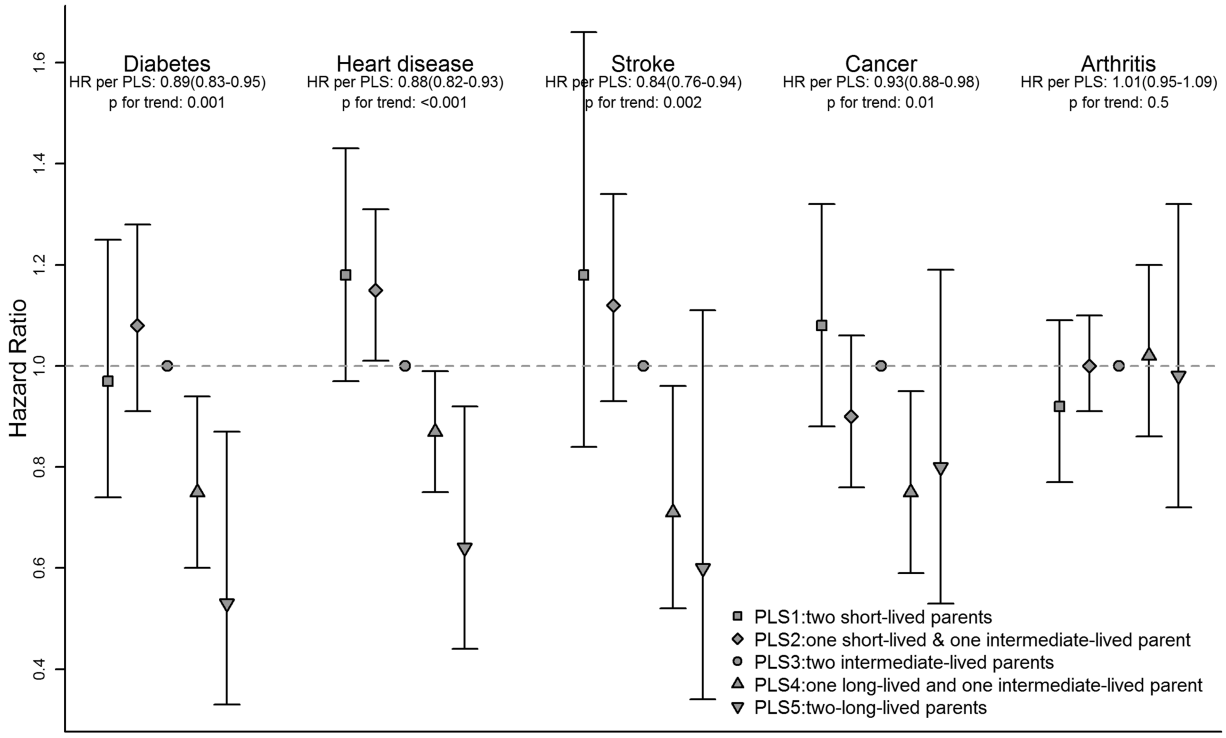

Figure 5. Hazard ratios (fully adjusted) for incident disease during follow-up (1992–2010) in offspring categorized by parental longevity score.

Sensitivity Analyses

For a sensitivity analysis, we included the 1,290 participants with living parents (178, 726, and 386 attaining short-lived, intermediate-lived, and long-lived status, respectively) with their last known "living" parental age in models. Their inclusion changed the estimates only modestly (Supplementary Table 4).

The group with discordant parents (one long lived and one short lived) compared with group 3 (two intermediate-lived parent) had estimates around the null value for all-cause mortality, incident heart disease cancer, stroke, and diabetes, with 95% CI always crossing null values.

Discussion

We aimed to estimate the association between parental survival and offspring survival, as well as incident cancer and other common diseases, in a large U.S. population cohort. We found that a wide range of increasing parental attained ages (>65 years) were associated with progressively lower mortality and incidence rates of diabetes, stroke, and heart disease (but not arthritis) among offspring aged 51–61 years at baseline (1992) and followed up for 18 years. We have also shown, for the first time, that there are robust associations between parental attained age and cancer incidence in offspring.

Our study finding of an association between parental survival and cancer incidence in offspring was minimally modified on adjusting for measured environmental factors. We did not observe this association at baseline (as others) (6) perhaps because of differential response to study invitations. An association between extreme parental life span and cancer was suggested by only one previous study (to the best of our knowledge), which included 295 offspring of centenarians and 276 age-matched controls, with 32 incident cancer cases (3) and with no adjustment for environmental confounders such as smoking. Although we have studied 938 cases of cancer, data are not available to allow separate analyses by cancer subtype. This information was not collected in HRS interviews, and the HRS linked Medicare records (for those aged 65 plus) can provide only a small data set for a minority of the follow-up period for our participants (who were 51–61 years old at baseline). It is unlikely that known hereditary cancer syndromes of breast, ovary, colon, and retina could account for the association we found as these are relatively rare and affect younger groups. Also important is that our finding of reduced cancer incidence was clearest in the comparison of longer lived versus normal or modal parental survival and is not attributable to parents who died young. It is therefore more likely that longer parental life span representing the broader decelerated aging phenotype has protective effects on common forms of "sporadic" cancers in later life.

The offspring of longer lived parents also had higher overall survival, better cardiovascular health, and less diabetes at baseline, and they continued to experience the

same health advantages as they aged. These findings from a population sample, and studying the effects of a wide range of parental survival confirm and extend previous observations substantially (14) as many of the earlier studies were either cross sectional (4,15) or focusing on exceptionally long-lived groups (3,16) or only reported effects on male offspring (17).

The effect sizes for overall mortality of having longer lived parents in our study may appear somewhat smaller than previously reported ones although this may be due to our use of a comparison group of parents who attained "normal" or intermediate survival. This comparison group was designed to avoid possible effects of the usual comparisons with short-lived groups, who might have specific susceptibilities for early mortality not related to "normal" aging. If we compare the two extreme groups (two short-lived parents vs two long-lived parents, the HRs in reference to PLS3 is 1.41 [95% CI: 1.18–1.67] vs 0.67 [95% CI: 0.47–0.97], with regards to all-cause mortality), the effect sizes would appear to be comparable (if not larger) than those reported in other studies. To our knowledge, this is also the first study to demonstrate that parental attained age of only 65 years appears to be the threshold after which a steep linear reduction in mortality rates is evident in offspring. Previous studies reported attainment of 80 years or more was necessary for parental attained age–associated survival benefits to appear in offspring (18,19) and exceptional life span, mainly more than 95 years has been the focus of many research studies (2,20–22).

Our analyses found little evidence for a larger than expected or "elite" health advantage in the offspring of exceptionally long-lived parents, instead trends for offspring mortality, for example, appeared linear through parental attained ages more than 100 years (n = 160 offspring with at least one parent aged ≥100 years) although our power to detect smaller deviations from linear effects is limited.

We have also demonstrated that parental survival has comparable effects on survival of offspring irrespective of offspring gender although previous studies have reported the contrary (23,24). Our analysis has shown that mortality differentials associated with parental survival are apparent in offspring from as early as 57 years old, in contrast to one previous study reporting this threshold as 70 years (15). This suggests that the aging process can be studied in offspring from middle age (25). Offspring included in most related studies were already relatively old (3,4,22,26), which may have obscured (27,28) effects due to comorbidities, multiple treatments, and the loss of valid control groups.

Familial longevity has two broad components: intrinsic and "environmental" (29). Some environmental factors may be "inherited" from the previous generation such as education, wealth, diet, and smoking, which may be consistent with our findings as some of these attributes were differentially distributed in offspring across PLS groups. However, controlling for these factors changed the effect sizes of the parental survival associations only modestly, suggesting that the parental survival health advantage is not primarily a socioeconomic or "extrinsic" construct. This was reinforced when we found that survival of parents-in-law or partner's parents had no effect on mortality despite partners generally sharing adult environments for substantial periods. Given these results, the beneficial effect of longer lived parents on their offspring is likely to be transmitted predominantly through intrinsic factors such as genetic variants or epigenetic markers. Our results do not claim to contradict the well-established and stronger influence of individual environmental factors (often referred to as "nurture" variables) on variability in human life span and age-associated disease incidence. It only suggests that the protective influence of having long-lived parents is likely to be primarily due to inherited intrinsic factors (often referred to as "nature" variables). Parental attained age may be a powerful quantitative trait for the study of intrinsic mechanisms underlying lower incidence of age-related disease and lower mortality risks, which might be termed "slower aging."

The major strength of our study is the design of HRS, which ascertained offspring and parental deaths simultaneously for 18 years. Rosengren and colleagues (17) using a Swedish population study also collected follow-up data on middle-aged offspring, but only baseline data on parental attained age. They noted that almost 46% of the parents (predominantly mothers) with average age of 82 years were still alive at baseline as the mean age difference between generations is approximately 30 years (6). Other notable studies in this field perhaps faced similar limitations (15,24). Only 13% of HRS respondents were recorded as having living parent(s) as per their last available records. Inclusion of these respondents in the sensitivity analyses with their last recorded parental "living" age as parental survival only marginally modified the estimates.

Another strength of our study is the use of cohort and sex relevant cut points to classify parental survival, in contrast to arbitrary (or life expectancy based) and/or gender-neutral cut points used in most previous studies (5,6,17,30–35) despite very different gender-specific life span. We were able to estimate the distribution of normative aging-related life span of the HRS parents and empirically establish sex-specific parental survival or "longevity" cut points, which helped distinguish predominantly prematurely dying parents (unrelated to aging) from predominantly "normally" aging parents (10).

While assessing the results, it should be noted that the chronic disease data were from self-report of physician-diagnosed conditions. The self-reported health data in HRS was benchmarked against the National Health Interview Survey and demonstrated a high degree of similarity between prevalence estimates (12). Our most striking result, namely of a parental survival association with cancer incidence, seems unlikely to have been affected by poor self-reporting as a diagnosis of cancer would be a very major and easily recalled life event for respondents. Also note that as

HRS does not record dates of birth for parents, detailed classifications were not possible for mother's or father's relative survival within narrow birth cohorts or other key groupings (eg, race and education). However, the limited misclassification arising from this is unlikely to bias analyses against offspring outcomes. Our parental longevity ranked categories are unweighted, implying that the effects of father's and mother's attained ages are similar; as noted in the linear models, the strengths of associations for these with offspring survival were a little different, so our simplified categories may also contribute to a small misclassification. There is inevitably limited information available on exposures or preventive treatments relevant to specific diseases, for example, access to mammograms for breast cancer. However, only factors affecting both parents and offspring could explain the parent offspring health associations we report.

Future studies of specific forms of cancer should explore the effects of parental survival as individual cancer subtypes are mostly too rare to be studied in population-representative studies. Also, studies of causation might examine genetic and biomarker differences between offspring of long-lived parents versus intermediate or shorter lived parents to identify the "nature" variables influencing variability in individual life span and risk of age-associated diseases. The potential for use of parental longevity as a clinical tool alongside family history of specific diseases should also be explored.

Conclusion

Our analysis has demonstrated for the first time that middle-aged offspring of relatively longer lived parents experience substantially lower incidence of cancer, other common diseases, and all-cause mortality compared with contemporaries born of intermediate-lived or shorter lived parents. This protective association between parental attained age and offspring health status altered only modestly after accounting for early and midlife environmental factors. The health advantages associated with having a centenarian (or nonagenarian) parent extend proportionately to a wide range of parental longevity and may provide a quantitative trait to identify novel mechanisms of slower aging.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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Conflict of Interest

There were no conflicts of interest for any author.

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