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Research Article

Are Members of Long-Lived Families Healthier Than Their Equally Long-Lived Peers? Evidence From the Long Life Family Study

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Abstract

Background: The Long Life Family Study (LLFS) is a multicenter longitudinal study of exceptional survival among members of long-lived sibships (probands), their offspring, and spouses of either group. For these four "roles", we asked: Does membership in a long-lived family protect against disease?
Methods: We used 2008–2010 Beneficiary Annual Summary Files from the Centers for Medicare & Medicaid Services (CMS) to compare prevalences of 17 conditions among 781 LLFS participants in Medicare with those of 3,227 non-LLFS matches from the general Medicare population. Analyses accounted for nesting within LLFS families.
Results: Seven conditions were significantly less common among LLFS probands than their matches: Alzheimer's, hip fracture, diabetes, depression, prostate cancer, heart failure, and chronic kidney disease. Four diseases not strongly linked to mortality (arthritis, cataract, osteoporosis, glaucoma) were significantly more common for LLFS probands. Despite fewer people and less disease in those roles, LLFS offspring and LLFS spouses of either generation also had significantly lower risk for Alzheimer's, diabetes, and heart failure.
Conclusions: Common, severe mortality-associated diseases are less prevalent among LLFS probands and their offspring than in the general population of aging Americans. Quality-of-life-limiting diseases such as arthritis and cataract are more prevalent, potentially through more diagnosing of milder forms in otherwise healthy and active individuals. LLFS spouses are also relatively healthy. As the younger cohorts age into Medicare and develop more conditions, it will be important to see whether these tentative findings strengthen.

Key Words: Longevity—Genetics—Health Services—Morbidity—Resilience

Average life expectancy in the United States has been increasing fairly steadily since 1900; currently, men live on average 77 years and women 82 years (1). People surviving to age 65 are expected to live an average of 19.2 more years, 5 years longer than people age 65 in

1960 (2). From 2000 to 2010, the population aged more than 65 in the United States increased 15%, from 35 million to 40 million; it will increase another 36%, to 55 million, by 2020 (3). Unfortunately, chronic disease is common in this cohort, with 24% of people 65+ years old in the 2009–2010 National Health Interview Survey reporting cancer; 20%, diabetes; 30%, heart disease; and over 50%, arthritis (2).

The Long Life Family Study (LLFS) examines environmental and genetic factors that contribute to healthy longevity in people related—by genes or marriage—to an exceptionally long-lived sibship (4,5). The LLFS was founded in part because numerous studies demonstrate a strong familial component of survival in the nonagenarian years and an even greater effect for survival past age 100 years. For example, Perls and colleagues (6) described families demonstrating highly unusual clustering of extremely old siblings and noted markedly increased survival to age 100 among siblings of centenarians (7).

The LLFS is also interested in healthy aging, because survival to extreme old age can be associated with delayed onset of disability and morbidity (8–10). For instance, the LLFS cohort has lower age-adjusted prevalence of chronic diseases than other cohorts, such as the Framingham Heart Study and the Cardiovascular Health Study (11). Further, we know that healthy aging runs in long-lived families. In the New England Centenarian Study, centenarian offspring have significant delay in age of onset and markedly reduced risks of myocardial infarction, stroke, hypertension, and diabetes compared with members of their birth cohort whose parents were less long-lived (12,13). The Italian Centenarian Study also found that offspring with at least one centenarian parent had better functional status, reduced risk for common age-related diseases, and less medication use (14). In the Framingham Heart Study, offspring of parents surviving beyond the age of 85 years had half the mortality rate of age-matched participants whose parents died at younger ages (15). Therefore, we hypothesized that LLFS participants are healthier than similarly old Medicare enrollees in the general population and that disease rates differ between LLFS familial groups and general beneficiaries. To test this hypothesis, we compared disease rates determined from diagnoses that appear in 2008–2010 Medicare claims between LLFS participants and randomly selected Medicare enrollees who match them on age, sex, and ZIP code. The ZIP-code matching is intended to account for the nonrepresentative geographical distribution of LLFS study participants, addressing associated issues of nonrepresentative ancestry, environmental assets and insults, and socioeconomic characteristics.

Methods

Study Population

The LLFS consists of one European site (Denmark) and three U.S. sites (Boston University, University of Pittsburgh, and Columbia University in New York City). This study relies on Medicare data and so excludes European participants. The Centers for Medicare & Medicaid Services (CMS) facilitated outreach by mail to Medicare enrollees (excluding those on hospice or receiving renal dialysis) age 80+ and within 3 hours' driving time of an LLFS site. Potential subjects (probands) returned a response card providing vital status data (including sex and dates of birth and death or current age) on all siblings. The Family Longevity Selection Score (FLoSS) was used to rank a potential proband sibship on their combined exceptionality of survival (4). A family's entry into LLFS required at least one living member of the proband sibship with "decisional capacity," a living offspring, and a proband sibship FLoSS of at least 7. The FLoSS is designed to be negative for families with less than average longevity, with higher scores representing increasingly exceptional longevity. For example, the FLoSS for a five-person sibship with each sib at the 91st percentile of longevity for his or her birth cohort is about 7; and if all five sibs were at the 98th percentile, its FLoSS would be nearly 15. As an indication of the exceptionality of LLFS sibships, fewer than 1% of families in the Framingham Heart Study sample have a FLoSS > 7 (4). Families were also recruited using local voter registration lists and other forms of outreach, such as local and national news articles that directed people to the LLFS and its website. Interested eligible U.S. families with particularly impressive longevity were enrolled even if geographically remote; consequently, proband sibships with FLoSS > 15 constitute about 10% of the U.S. LLFS sample. Phenotype data including sociodemographic, pedigree, medical, physical, and cognitive functional assessment data were collected in an initial in-person visit and augmented annually by telephone and mail. A slight majority (54%) of U.S. subjects allowed their social security number to be used to link to CMS data (11).

The U.S. sample comprises 463 families with 3,682 members; mean number of subjects per family was 8.0, and mean family FLoSS was 11.4. We obtained CMS Beneficiary Annual Summary File (BASF) data on 1,139 of these subjects in 2008, 1,163 in 2009, and 1,146 in 2010 (yearly changes were due to the offspring generation's "aging in" and mortality, Supplementary Appendix A). Over 90% of those whose records could not be found were either younger than 65 or had not shared their social security number.

Each LLFS participant occupied one of four positions (roles) in their family: proband, including members of the original long-lived sibship and half-siblings, proband spouse, proband offspring, and offspring spouse.

Non-LLFS Medicare Beneficiaries

Each LLFS beneficiary who was at least age 65 in 2008 and alive in 2009 was matched to four non-LLFS beneficiaries by age (or, when four exact-age matches were not available, to age within 1 year), sex, and ZIP code of residence (if fewer than four exact matches were available, we allowed adjacent ZIP codes) as of 2009. We used 4-to-1 matching because no more than four matches were available for some LLFS participants. Also, with a 4-to-1 match, the standard error for a difference in means between LLFS participants and matches is less than 12% greater than if the number of matches were arbitrarily large. (The standard error depends on the number of matches, k, mainly through the factor $\sqrt{(k+1)/k}$ and $\sqrt{5/4} < 1.12$.)

The most important limit on our ability to detect differences in disease rates between LLFS participants and their matches is the modest number of LLFS participants in several of the roles, with few instances of disease in any group for the least prevalent diseases studied, even after pooling evidence of disease from the 2008, 2009 and 2010 BASF files (Supplementary Appendix B).

Loss of Study Subjects Who Had No Informative Person-years

After matching, we examined the availability of usable data for each person in each year, retaining a person-year for the study only if he or she was enrolled for at least part of that year in the fee-for-service (FFS) Medicare benefit, and hence could have claims data for identifying medical conditions (Supplementary Appendix C). In this way, those 27% of LLFS subjects and 25% of matches who had been enrolled exclusively in the non-FFS Medicare Advantage program were lost for further analysis. Among retained subjects, average number of person-years per person was between 2.7 and 2.9 in

each of eight groups (LLFS subjects in 4 roles and their associated matches).

Disease Variables and Definitions

Each year's BASF contains demographic and enrollment data for Medicare beneficiaries, including indicators for 21 medical conditions as determined from CMS algorithms applied to diagnoses appearing in that year's claims (16) (Supplementary Appendix D). We examined the following 17 conditions: acute myocardial infarction, Alzheimer's disease (including related disorders or senile dementia), atrial fibrillation, cataract, chronic kidney disease, chronic obstructive pulmonary disease (COPD), depression, diabetes, female breast cancer, glaucoma, heart failure, hip or pelvic fracture, ischemic heart disease, osteoporosis, prostate cancer, rheumatoid arthritis or osteoarthritis, and stroke and transient ischemic attack (TIA). We do not report on the other four conditions in the CMS's Chronic Disease Warehouse, including three cancers (colorectal, endometrial, and lung), each present in less than 2% of both LLFS and matching study subjects, leading to models that did not converge; and "Alzheimer's disease [only]" because it substantially overlapped with the more-inclusive category of senile dementias.

Data Analysis

We examined LLFS beneficiaries and compared them descriptively with their non-LLFS matches. Initial descriptive comparisons used likelihood-ratio chi-squared tests for categorical variables and Student's *t*-tests for continuous variables. We examined: age and sex, race (white or nonwhite), mortality in each of 2009 and 2010, and the presence and absence of any fee-for-service (FFS) claims data in each study year.

The main analysis fitted hierarchical logistic regressions (a type of generalized linear mixed model, GLMM), using the GLIMMIX procedure in SAS 9.2, accounting for the nested structure of the data, where each LLFS participant belongs to an LLFS family and has matched non-LLFS beneficiaries (17). Indicators for presence of disease conditions, our primary outcomes, were identified from diagnoses in claims filed each year. Our primary explanatory variables of interest were captured with fixed-effect indicators for the 7 non-proband groups: proband spouse, offspring, offspring spouse, proband match, proband spouse match, offspring match, and offspring spouse match. These models also included random effects for each LLFS family and participants within a family and fixed effects for: time (2009 or 2010, compared with 2008), age (as of 2008), sex (female vs not), and race (white vs all others). Supplementary Appendices E and F give details of these models, as well as the estimates of the coefficients and random effects for each disease condition.

We used SAS Version 9.2 (SAS Institute, Cary, NC) for all analyses.

Results

The full study sample consisted of 1,070 LLFS beneficiaries and their 4,280 non-LLFS matches observed in 2008, 2009, and 2010. Mean age was about 90 years for probands, 85 for their spouses, and 70 for both offspring and their spouses (Table 1). Although numbers of men and women were similar for probands (46% were female) and for their offspring (56%), sex ratios were quite lopsided for spouses: the great majority of proband spouses (79%) were female, but only 28% of offspring spouses were. Matching criteria forced the near-equality of matches with LLFS participants on age and

Table 1. Demographics of LLFS Participants and Their Matches, by Role

	Proband		Offspring		Proband Spouse		Offspring Spouse	
	LLFS (n = 584)	Matches (n = 2,336)	LLFS (n = 317)	Matches (n = 1,268)	LLFS (n = 77)	Matches (n = 308)	LLFS (n = 92)	Matches (n = 368)
Female (%)	45.9	45.9	56.2	56.2	79.2	79.2	28.3	28.3
Age in 2008 (mean ± *SD*, range)	90.3 ± 5.9	90.2 ± 5.9	70.2 ± 4.6	70.3 ± 4.6	84.7 ± 6.2	84.7 ± 6.2	70.9 ± 4.7	70.9 ± 4.7
	65–106	65–107	65–88	65–88	65–96	65–97	65–89	65–89
Race, white (%)	99.1	96.0***	99.4	93.8***	100.0	96.4	100.0	92.9**
Any claims data (%)	75.9	77.6	69.1	71.8	70.1	78.9**	70.7	70.9
Deaths†, 2008 (%)	—	—	—	—	—	—	—	—
Deaths, 2009 (%)	8.4	16.5***	0.6	2.3	2.6	8.8	1.1	1.9
Deaths, 2010 (%)	9.5	18.9***	0.6	2.4*	8.0	9.6	0.0	1.9

Notes: LLFS = Long Life Family Study; *SD* = standard deviation.
†Study participants were selected from 2009 Medicare files.
Asterisks denote significant p values between cases and matches for likelihood-ratio chi-squared tests for categorical variables and Student's t-test for continuous variables where $^{*}p < .05$, $^{**}p < .01$, and $^{***}p < .0001$.

Table 2. Adjusted Odds Ratios (95% Confidence Intervals) for Conditions, LLFS versus Matches, by Role

Condition	Proband	Offspring	Proband Spouse	Offspring Spouse
Number of LLFS: men, women	243, 200	103, 116	11, 43	44, 21
Number of Matches: men, women	983, 830	406, 504	43, 200	185, 76
Alzheimer's and related disorders	**0.36 (0.30, 0.42)**	**0.21 (0.09, 0.46)**	**0.19 (0.10, 0.34)**	**0.34 (0.13, 0.90)**
Hip fracture	**0.58 (0.36, 0.95)**	1.79 (0.46, 6.93)	1.68 (0.52, 5.44)	1.98 (0.18, 21.99)
Diabetes	**0.62 (0.52, 0.74)**	**0.70 (0.54, 0.90)**	**0.30 (0.17, 0.53)**	**0.56 (0.35, 0.89)**
Depression	**0.64 (0.52, 0.78)**	1.05 (0.78, 1.41)	0.87 (0.53, 1.41)	1.28 (0.76, 2.16)
Breast cancer*	0.68 (0.36, 1.29)	0.90 (0.47, 1.73)	0.20 (0.03, 1.59)	3.79 (0.23, 63.01)
Acute myocardial infarction	0.70 (0.42, 1.19)	—	—	—
Prostate cancer†	**0.72 (0.53, 0.99)**	0.49 (0.23, 1.01)	**5.63 (1.81, 17.59)**	1.83 (0.95, 3.51)
Heart failure	**0.77 (0.67, 0.89)**	**0.53 (0.36, 0.78)**	**0.36 (0.22, 0.60)**	**0.41 (0.20, 0.84)**
Chronic kidney disease	**0.82 (0.70, 0.96)**	**0.52 (0.35, 0.77)**	**0.47 (0.25, 0.86)**	1.50 (0.86, 2.60)
Stroke and TIA	0.84 (0.64, 1.09)	0.55 (0.29, 1.05)	—	—
COPD	0.87 (0.71, 1.06)	**0.36 (0.23, 0.58)**	0.81 (0.46, 1.46)	0.60 (0.31, 1.16)
Ischemic heart disease	1.00 (0.87, 1.14)	**0.62 (0.48, 0.78)**	**0.33 (0.21, 0.51)**	0.67 (0.45, 1.01)
Atrial fibrillation	1.11 (0.94, 1.32)	**0.55 (0.34, 0.89)**	0.80 (0.46, 1.38)	0.82 (0.41, 1.67)
Arthritis (RA or OA)	**1.26 (1.09, 1.46)**	1.26 (0.97, 1.62)	1.08 (0.72, 1.62)	1.31 (0.85, 2.02)
Cataract	**1.38 (1.19, 1.61)**	**1.57 (1.28, 1.93)**	1.42 (0.95, 2.13)	**1.59 (1.10, 2.29)**
Osteoporosis	**1.48 (1.24, 1.76)**	0.98 (0.73, 1.31)	1.05 (0.69, 1.61)	1.63 (0.94, 2.84)
Glaucoma	**1.76 (1.47, 2.09)**	0.78 (0.57, 1.07)	0.82 (0.49, 1.39)	1.03 (0.58, 1.83)

Notes: 2008–2010 data on 781 unique LLFS cases and 3,227 matches (10,936 person-years) with at least 1 month of Medicare FFS data. Bold values indicate a statistically significant finding ($p < .05$). Odds ratios are from multivariable models (see Supplementary Appendices E and F) and express risk among LLFS participants compared with matches. The rows are ordered by increasing odds ratio (most to least favorable) for probands. A dash (—) indicates that the role could not be included in the final model. COPD= chronic obstructive pulmonary disease; TIA = transient ischemic attack; LLFS = Long Life Family Study; RA= rheumatoid arthritis; OA=osteoarthritis.

*Breast cancer was based on 380 unique LLFS cases and 1,610 matches (5,433 person-years) in females only (including just 21 offspring spouses).

†Prostate cancer was based on 401 unique LLFS cases and 1,617 matches (5,503 person-years) in males only (including just 11 proband spouses).

sex distributions within each role. The availability of fee-for-service claims data (for detecting disease when present) was similar, with between 69% and 79% of each group having at least some coverage over the 3 years.

Table 2 pertains to the analytic subset of those with at least some claims data available, and shows odds ratios from the models for each chronic condition, comparing LLFS participants with matches by role. These models were based on 781 unique LLFS cases and 3,227 matches, totaling 10,936 person-years or 2.73 observed years per person.

Compared with their matches, the LLFS probands were significantly less likely to have claims indicating Alzheimer's, hip fracture, diabetes, depression, prostate cancer, heart failure, and chronic kidney disease; they were more likely to have claims for arthritis, cataract, osteoporosis, and glaucoma.

Compared with their matches, LLFS offspring were significantly less likely to have claims for Alzheimer's, diabetes, heart failure, chronic kidney disease, COPD, ischemic heart disease, and atrial fibrillation; they were more likely to have claims for cataract.

Among the (mostly female) proband spouses, LLFS participants were significantly less likely than their matches to have claims for Alzheimer's, diabetes, heart failure, chronic kidney disease, and ischemic heart disease. The "finding" in prostate cancer, although highly statistically significant, appears to be an anomaly, based on observing 5 cases among just 11 LLFS subjects.

Among the (mostly male) offspring spouses, LLFS participants had significantly less Alzheimer's, diabetes, and heart failure, and more cataracts, than their matches.

Table 3 shows the crude prevalence of each disease by role, where a person is counted as having a condition if he or she had claims data supporting its presence in any year.

Discussion

For several of the most common diseases, we found differences in prevalence (as measured by the presence of diagnoses in claims) between LLFS participants and matched non-LLFS Medicare beneficiaries. LLFS probands and their offspring had significantly less Alzheimer's disease, diabetes, heart failure, and chronic kidney disease. Indeed, all four LLFS groups were significantly less likely to have Alzheimer's, diabetes, and heart failure than their matches. Previous studies have also shown a relation between delay in onset of age-related diseases and disability and extreme survival (9,18,19). In contrast, LLFS probands had more arthritis, cataracts, osteoporosis and glaucoma, with somewhat similar patterns for other LLFS participants. This may be due to *healthy* older people being more likely to have mild forms of such conditions identified and treated than elders with multiple debilitating morbidities.

Prevalence of most conditions was lower for LLFS offspring than for their matches, suggesting a possible genetic effect on health and longevity, although lower rates of several conditions in LLFS spousal roles suggest a household effect as well. Small numbers prevent definitive judgments on the extent to which LLFS spouses share the lower risk profile of probands and their offspring, perhaps because familial social and environmental factors also cluster in families. Indeed, others have found that, although the mother's age of death strongly predicted her children's ages of death in families with unexceptional life expectancy, the association was partially mediated by nongenetic risk factors, such as years of education, socioeconomic status, tobacco and alcohol use, diet, and access to health care (20). Some studies suggest that genetic factors play a stronger role with increasingly old survival ages (7,21,22). If so, the LLFS families, with so many very old probands, may be potent subjects for discovering both rare and common genetic variants associated with increased

Table 3. Prevalence of Conditions and Adjusted Odds Ratios for LLFS versus Matches, by Role

	Proband				Offspring				Proband Spouse				Offspring Spouse			
	LLFS	Matches	OR	*p* value	LLFS	Matches	OR	*p* value	LLFS	Matches	OR	*p* value	LLFS	Matches	OR	*p* value
Number of people	443	1813			219	910			54	243			65	261		
Observation-years per person	2.81	2.72			2.69	2.71			2.78	2.78			2.78	2.73		
	Percent				Percent				Percent				Percent			
Alzheimer's and related disorders	**27.3**	**44.4**	**0.36**	**<.0001**	**2.3**	**6.0**	**0.21**	**<.0001**	**14.8**	**37.0**	**0.19**	**<.0001**	**3.1**	**10.0**	**0.34**	**.029**
Hip fracture	**4.3**	**6.4**	**0.58**	**.029**	1.4	0.8	1.79	.402	7.4	4.1	1.68	.387	1.5	0.8	1.98	.578
Diabetes	**21.0**	**27.8**	**0.62**	**<.0001**	**20.5**	**24.4**	**0.70**	**.006**	**14.8**	**32.1**	**0.30**	**<.0001**	**23.1**	**28.7**	**0.56**	**.014**
Depression	**20.5**	**27.4**	**0.64**	**<.0001**	17.4	16.8	1.05	.744	22.2	29.2	0.87	.563	20.0	15.7	1.28	.355
Acute myocardial infarction	3.6	4.7	0.70	.188	0.5	1.5	—	—	5.6	3.7	—	—	0.0	1.5	—	—
Heart failure	**40.2**	**45.7**	**0.77**	**.000**	**8.7**	**14.2**	**0.53**	**.001**	22.2	**40.3**	**0.36**	**<.0001**	**6.2**	**16.1**	**0.41**	**.014**
Chronic kidney disease	**31.6**	**34.4**	**0.82**	**.013**	**8.2**	**14.2**	**0.52**	**.001**	14.8	**25.5**	**0.47**	**.015**	12.3	14.2	1.50	.150
Stroke/TIA	13.5	14.1	0.84	.183	3.7	6.0	0.55	.068	5.6	13.6	—	—	4.6	8.4	—	—
COPD	19.4	20.7	0.87	.176	**5.9**	**12.4**	**0.36**	**<.0001**	16.7	21.0	0.87	.489	12.3	17.2	0.60	.128
Ischemic heart disease	56.7	56.3	1.00	.959	**23.3**	**32.1**	**0.62**	**<.0001**	31.5	54.7	0.33	<.0001	29.2	36.4	0.67	.059
Atrial fibrillation	27.5	26.0	1.11	.211	**5.5**	**8.5**	**0.55**	**.015**	14.8	23.9	0.80	.418	9.2	10.7	0.82	.591
Arthritis (RA or OA)	**43.3**	**39.1**	**1.26**	**.002**	**28.8**	**22.1**	**1.26**	**.079**	46.3	44.0	1.08	.695	27.7	24.9	1.31	.216
Cataract	**42.9**	**34.3**	**1.38**	**<.0001**	**50.2**	**41.2**	**1.57**	**<.0001**	48.1	43.2	1.42	.0891	**56.9**	**41.8**	**1.59**	**.0137**
Osteoporosis	**31.8**	**25.4**	**1.48**	**<.0001**	21.5	21.2	0.98	.874	40.7	42.8	1.05	.8074	23.1	14.9	1.63	.0843
Glaucoma	**26.2**	**17.7**	**1.76**	**<.0001**	13.7	15.3	0.78	.122	18.5	23.9	0.82	.4670	13.8	13.4	1.03	.9124
Single-sex diseases*																
Breast cancer	4.5	4.9	0.68	.235	6.9	5.8	0.90	.758	2.3	6.0	0.20	.129	4.8	1.3	3.79	.352
Prostate cancer	**11.5**	**15.2**	**0.72**	**.046**	5.8	9.6	0.49	.055	**45.5**	**9.3**	**5.63**	**.003**	15.9	10.3	1.83	.070

Notes: Prevalence is defined as (number of people in the group for whom the disease was present in at least 1 year)/(number of distinct people in the group). Bold values indicate a statistically significant finding ($p < .05$), based on the adjusted odds ratio (shown in Table 2 and repeated here). Observation-years per person ranges from 2.7 to 2.9 in each group, except for the 11 male LLFS proband spouses, where it is 2.45. A dash (—) indicates that the role could not be included in the final model. COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; LLFS = Long Life Family Study; RA = rheumatoid arthritis; OA = osteoarthritis.

*Numbers of males in the four roles (LLFS & Matches), respectively, are: 243 & 983; 103 & 406; 11 & 43; 44 & 185. Numbers of females, respectively, are: 200 & 830; 116 & 504; 43 & 200; 21 & 76.

healthy life expectancy. Continuing to follow LLFS spouses and offspring and their age–sex–ZIP code-matched cohorts in Medicare claims data should help tease out the role of nongenetic factors.

Our findings in the LLFS offspring, of lower prevalence of several life-threatening common chronic diseases, but not some less-threatening ones, are broadly consistent with those of Dutta and coworkers, who, using Health and Retirement Study data, found a protective effect of long-lived parents on diabetes, heart disease, stroke, and cancer, but not arthritis (20).

Newman and colleagues reported LLFS disease prevalence rates that differ from ours, most notably a 17.7% prevalence of heart disease in probands in contrast to our 56.7% (11). However, their article identifies heart disease from self-report confirmed by medication use, whereas we use presence, over a 3-year period, of at least one ICD-9 code in a substantially more inclusive list of conditions that map to "heart disease" in CMS's Chronic Disease Warehouse. Thus, the difference in reported prevalence is not surprising and does not present a problem for either study. Our claims-based definition enables equitable prevalence *comparisons* between LLFS and non-LLFS Medicare beneficiaries.

This study has several limitations. The LLFS is essentially a convenience sample of families with unusually exceptional survival; thus, it is likely (especially in its early years) to reflect healthy-volunteer bias, in which those who volunteer for a study are healthier than the general population. Also, the requirement that at least 1 living member of the proband sibship have "decisional capacity" may have reduced the prevalence of Alzheimer's disease and other dementias in probands. Further, many LLFS participants could not be tracked in the Medicare data, most commonly because they did not share their social security number. However, as of fall 2014, the LLFS subjects who shared their SSN had higher mortality than those who did not (see Supplementary Appendix A, Table S3), suggesting that the protective effects of LLFS cohort membership may be even larger than reported here. Some genetic protective factors may be rare and specific to particular families or even to one family. Some gene–environment interactions that are conducive to exceptional survival might be specific to certain ethnicities or races, and Caucasians predominate in the LLFS sample to an even larger extent than in their matches. The aim of this study, however, was not to discover factors associated with exceptional survival, but rather to examine whether LLFS probands are, as hypothesized, a healthy aging cohort relative to general Medicare beneficiaries of the same gender, age, and geographic location, and whether their offspring and spouses are also healthier than average.

Another limitation is that the study could only identify conditions in CMS's Beneficiary Annual Summary File (16), and this identification relied entirely on Medicare claims data, which do not give a full picture of a person's health. However, the data source is the same for LLFS participants and their matches, eliminating the reporting or recall bias present in studies that rely on self-report (8).

Also, we addressed bias arising from modest differences in missing claims data associated with enrollment in managed care by including only person-years for which some claims data could be expected. Although we had no information on socioeconomic factors that may play a role in disease rates, matching on ZIP codes addresses some of these issues.

Our use of CMS's condition definitions embodied in the BASF (16) is also a strength. Through matching, we equalized age-, sex-, and geography-related factors for LLFS participants and their comparators. Future studies should more closely examine sex differences in age of onset for chronic diseases, to try to understand the mechanisms behind the observation that, although many more women than men live to older ages, men who survive into their late nineties are typically much healthier than similarly old women (23).

We have confirmed that LLFS subjects are typically healthier than general populations with the same age–sex mix. We have further shown (by matching on ZIP code of residence) that the atypical geographic mix of LLFS participants is not responsible for this finding, and we have some evidence that spousal participants may be also be much healthier than their peers.

Much interest focuses on discovering and investigating factors that predispose to age-related diseases and disabilities. Relatively recently, however, with the emergence of substantial numbers of extremely old individuals who markedly delay onset of many age-related diseases relative to the average aging population, researchers have a new model of healthy aging from which to delineate the absence of disease-related factors and the presence of longevity-associated or protective factors. The LLFS provides such an opportunity, as well as opportunities to discover those protective factors, both genetic and nongenetic, that might be family-specific and relatively rare.

Supplementary Material

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

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