

Nonagenarian Siblings and Their Offspring Display Lower Risk of Mortality and Morbidity than Sporadic Nonagenarians: The Leiden Longevity Study

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OBJECTIVES: To compare the risk of mortality of nonagenarian siblings with that of sporadic nonagenarians (not selected on having a nonagenarian sibling) and to compare the prevalence of morbidity in their offspring with that of the offsprings' partners.

DESIGN: Longitudinal (mortality risk) and cross-sectional (disease prevalence).

SETTING: Nationwide sample.

PARTICIPANTS: The Leiden Longevity Study consists of 991 nonagenarian siblings derived from 420 Caucasian families, 1,365 of their offspring, and 621 of the offsprings' partners. In the Leiden 85-plus Study, 599 subjects aged 85 were included, of whom 275 attained the age of 90 (sporadic nonagenarians).

MEASUREMENTS: All nonagenarian siblings and sporadic nonagenarians were followed for mortality (with a mean \pm standard deviation follow-up time of 2.7 ± 1.4 years and 3.0 ± 1.5 years, respectively). Information on medical history and medication use was collected for offspring and their partners.

RESULTS: Nonagenarian siblings had a 41% lower risk of mortality ($P < .001$) than sporadic nonagenarians. The offspring of nonagenarian siblings had a lower prevalence of myocardial infarction (2.4% vs 4.1%, $P = .03$), hypertension (23.0% vs 27.5%, $P = .01$), diabetes mellitus (4.4% vs 7.6%, $P = .004$), and use of cardiovascular medication (23.0% vs 28.9%, $P = .003$) than their partners.

CONCLUSION: The lower mortality rate of nonagenarian siblings and lower prevalence of morbidity in their middle-aged offspring reinforce the notion that resilience against disease and death have similar underlying biology that is determined by genetic or familial factors. *J Am Geriatr Soc* 57:1634–1637, 2009.

Key words: nonagenarian siblings; offspring; longevity; morbidity; familial

In Western societies, life expectancy has increased dramatically over the last century, but striking interindividual differences in life expectancy remain.¹ Moreover, although rare examples of exceptional healthy longevity exist, generally not all of the years that have been gained are spent in good health. Ample evidence has shown that a mix of genetic, environmental, and chance elements determines healthy longevity. An increasing effort is currently being put into identifying the genetically determined pathways and mechanisms of healthy longevity in humans, because these might provide targets for specific interventions aimed at preservation of disease-free longevity.

The contribution of genetic factors to healthy longevity has been estimated to be modest (~ 20 – 30%) but was shown to become increasingly important² and specific³ at advanced ages. Studies aimed at understanding the genetics of human longevity have thus preferentially studied the elite of exceptional longevity, such as centenarians or the even more elite “supercentenarians” who survive 110 years or longer. In these studies, it was shown that offspring of centenarians had a lower prevalence⁴ and incidence⁵ of, in particular, cardiovascular disease (including hypertension and diabetes mellitus), as well as a later onset of these diseases⁶ than offspring of parents who had died at average

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age, translating into a lower mortality risk.⁷ Centenarians were also shown to have a healthier lifestyle than control groups and may have transmitted some of these habits to their offspring.⁸ These results raise the question how much of the enhanced survival and health in elite cases of exceptional longevity genetic or lifestyle factors determine. Comparable with the risk of developing common and rare diseases, such as breast cancer and hypercholesterolemia, the odds of exceptional longevity also runs in families.⁹

This study aimed at identifying genetic determinants of healthy longevity in nonagenarian siblings enriched for heritable influences on morbidity and mortality. Therefore, the Leiden Longevity Study was designed, in which families were specifically recruited based on proband siblings that both exhibited exceptional longevity,⁹ instead of the recruitment of families based on sporadic proband cases of exceptional longevity.^{10,11} In the current study, the mortality risk of 991 nonagenarian siblings was compared with that of 275 sporadic nonagenarians. Next, disease prevalence in the offspring of nonagenarian siblings ($n = 1,365$) was compared with that of their partners ($n = 621$).

METHODS

Leiden Longevity Study

In the Leiden Longevity Study, 420 families consisting of long-lived Caucasian siblings together with their offspring and the offsprings' partners were recruited.⁹ In the Netherlands, there is no central registry of longevity. In 2002, only 0.5% of Dutch men were aged 89 and older, and only 0.5% of Dutch women aged 91 and older. Long-lived siblings fulfilling these age criteria are even rarer and are estimated to represent far less than 0.1% of the Dutch population. To recruit as much as possible long-lived siblings within a fixed time window (July 2002–May 2006), the following strategy was used. A randomly chosen 80% (398/496) of the municipalities in the Netherlands were approached and asked for the following information: names and addresses of all men aged 89 and all women aged 91 and older, as well as the names and birth dates of their parents. The requested information was received from 375 of the 398 municipalities. Next, by matching the inhabitants thus identified on the names and birth dates of both of their parents using a computer algorithm, 2,193 potential nonagenarian siblings were identified. Approximately 1,650 nonagenarian siblings were contacted; 991 derived from 420 families of Caucasian descent agreed to participate and donate a blood sample (participation rate ~ 60%). Within the same time window, the offspring of each nonagenarian included in the Leiden Longevity Study and the offsprings' partners were also approached for case control studies. Of the electable offspring cohort ($n = 2,847$), 1,705 agreed to participate and donate a blood sample (participation rate 59.9%), and of the 1,306 of their partners, 760 agreed to participate and donate a blood sample (participation rate 58.2%). There were no selection criteria on health or demographic characteristics. For all subjects, blood samples were taken at baseline for extraction of deoxyribonucleic acid and ribonucleic acid and the determination of nonfasting serum and plasma parameters. Between November 2006 and May 2008, additional information and biomaterials were collected from the generation

of offspring and partners, including self-reported information on lifestyle, bodily measures, socioeconomic status, perceived health, physical activity, number of children, and dietary intake. Information on medical history was requested from the participants' treating physicians, and information on medication use was requested from the participants' pharmacist. The Medical Ethical Committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all subjects.

The Leiden 85-Plus Study

In the Leiden 85-Plus Study, a prospective, population-based study of all individuals 85 years old (birth cohort 1912–1914) living in Leiden, the Netherlands, 599 subjects were enrolled between September 1997 and September 1999.¹² Of the Leiden 85-Plus cohort, 275 subjects survived to the age of 90. The Medical Ethical Committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all subjects.

Statistical Analysis

Distributions of continuous variables were examined for normality and logarithmically transformed, when appropriate. Geometric means (with 95% confidence intervals (CIs)) are reported for transformed variables. All differences between offspring and partner categories were assessed using linear regression, adjusted for sex, age, and correlation of sibling data using robust standard errors. Mortality analyses were performed using a sex-adjusted, left-censored Cox proportional hazards model to correct for late entry into the data set according to age. SPSS for Windows, version 14.0 (SPSS, Inc., Chicago, IL) and STATA, version 10.0 (StataCorp, College Station, TX) were used for data analysis.

RESULTS

Enrollment and Baseline Characteristics of Participants

Four hundred twenty families consisting of 991 long-lived Caucasian siblings together with their offspring and the partners of the offspring had previously been recruited in the Leiden Longevity Study. For 2,465 of the offspring and their partners, nonfasting serum samples taken at baseline were available for the determination of endocrine and metabolic parameters. Between November 2006 and May 2008, information on medical history was obtained for 2,235 of the offspring and their partners from the participants' treating physicians (response rate 90.7%). For 2,255 of the offspring and their partners, information on the use of medication was obtained from the participants' pharmacist (response rate 91.5%). For the present study, information on medical history and medication use were available for 1,986 of the offspring and their partners (inclusion rate 80.4%). Based on self-reported information from questionnaires, the offspring and partners did not differ on any major indicators of lifestyle, including current smoking (13.7% vs 15.6%, $P = .24$), self-reported body mass index (BMI) (25.4 vs 25.6, $P = .26$), and level of education (low level: 43.0% vs 45.9%, $P = .16$; moderate level: 22.5% vs 22.9%, $P = .87$; high level: 34.5% vs 31.2%; $P = .10$).

Mortality Characteristics of the Long-Lived Siblings

After a mean \pm standard deviation follow-up of 2.6 ± 1.4 years, 43.1% of the nonagenarians with the familial longevity phenotype from the Leiden Longevity Study had died, whereas after a mean follow-up of 3.0 ± 1.5 years, 62.2% of the nonagenarians with the sporadic longevity phenotype had died. At old age, the nonagenarian siblings displayed a 0.59 (95% CI = 0.45–0.71, $P < .001$, Table 1 and Figure 1) lower mortality risk than sporadic nonagenarians.

Disease, Medication Use, and Anthropometric and Metabolic Characteristics of Offspring and Partners

In the 1,986 subjects (Table 2), a significantly lower prevalence was observed in the offspring than in their partners for myocardial infarction (2.4% vs 4.1%, $P = .03$), hypertension (23.0% vs 27.5%, $P = .01$), diabetes mellitus (4.4% vs 7.6%, $P = .004$), and use of cardiovascular medication (23.0% vs 28.9%, $P = .003$), including glucose-lowering agents, antihypertensives and lipid-lowering agents, but not antiplatelet agents (Table 2).

DISCUSSION

The majority of studies of human longevity have focused on centenarians. The current study showed that selection for nonagenarian siblings leads to the inclusion of families who exhibit lower mortality rate at older ages and a better preservation of health at middle age than age- and sex-matched controls. This observation indicates that resilience against disease and death may have similar underlying biological mechanisms that are influenced by genetic or familial factors.

It has previously been shown that standardized mortality ratios compared with the general Dutch population were approximately 30% lower for all first-degree family members of the proband siblings from the first 100 families included in the Leiden Longevity Study.⁹ The current study extends those findings by showing that the survival benefit observed earlier is also observed in the age range of 89 to 104 and in the complete cohort of nonagenarian siblings (derived from 420 families), compared with the survival of sporadic nonagenarians from the Leiden 85-plus Study using prospective survival analysis. This result is consistent with that of another study, showing that the survival advantage of siblings of centenarians persists into the highest age categories.^{2,13} In the first phase of life, siblings share many environmental factors, including socioeconomic sta-

Table 1. Demographics and Old-Age Mortality in Familial and Sporadic Nonagenarians

Characteristic	Sporadic Nonagenarians (n = 275)	Familial Nonagenarians (n = 991)
Demographic		
Age, median (interquartile range)	90 (90.0–90.0)	93.4 (91.5–94.9)
Female, n (%)	199 (72.4)	619 (62.5)
Mortality risk, hazard ratio (95% confidence interval)	1.00 (reference)	0.59 (0.46–0.71)

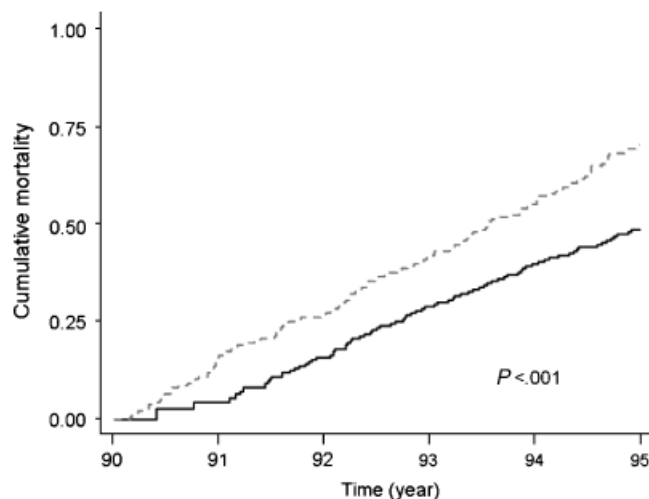


Figure 1. Cumulative mortality from age 90 through age 95 in familial nonagenarians (n = 991) and sporadic nonagenarians (n = 275) for men and women combined. Solid line indicates familial longevity; dashed line indicates sporadic longevity.

tus, lifestyle, and region of residence, but these are likely to diverge as they grow older. Because the influence of genetic factors has been shown to become increasingly important at advanced ages, the observation that the survival advantage extends up to the highest age category (89–104 in the nonagenarian siblings) strongly suggests that genetic factors play a role in longevity in these families.

Previous studies have shown that the offspring of centenarians, as well as offspring from one or two parents who survived to the age of 85, have a lower prevalence of diseases than control subjects from the same birth cohort whose parents died at younger ages,¹⁴ although when comparing offspring from one or two parents who survived to “old” age with offspring of parents who died at a “young” age, significant differences were observed in major cardiovascular risk factors between these groups, including years of education and current smoking, which complicates disentangling the precise contribution of genetic, behavioral, and lifestyle factors to the observed longevity phenotype.¹⁵ Likewise, centenarians were also shown generally to avoid bad lifestyle habits, and their offspring may have copied their behavior.⁸

As a strategy to minimize the potential confounding effects of differences in (adult) environment, it was deliberately decided to compare offspring from long-lived cases with their partners.⁹ Although the amount of cohabitation may have been variable, the shared adult environment of the couples may explain the lack of differences between these two groups in major indicators of lifestyle, including estimates for BMI, current smoking, and prevalence of chronic obstructive pulmonary disease, a smoking-related disease.

Genetic influences are thus more likely than environmental differences to be the cause of the lower prevalence of myocardial infarctions, diabetes mellitus, and hypertension in the offspring of nonagenarian siblings than in their partners. This result is consistent with that of another study, in which a significantly lower prevalence was observed for diabetes mellitus and myocardial infarction in 180 offspring

Table 2. Comparison of Demographics, Prevalence of Disease, and Medication Use of Offspring and Partners (N = 1,986)

Characteristic	Offspring (n = 1,365)	Partners (n = 621)	P- Value*
Demographic			
Age, median (interquartile range)	59.2 (55.0–64.0)	58.9 (54.3–63.6)	.06
Female, n (%)	732 (53.6)	354 (57.0)	.16
Prevalence of disease, n (%)			
Myocardial infarction	32 (2.4)	25 (4.1)	.03
Stroke	47 (3.5)	19 (3.1)	.87
Hypertension	307 (22.9)	168 (27.6)	.009
Diabetes mellitus [†]	59 (4.4)	46 (7.6)	.004
Malignancies	115 (8.5)	44 (7.2)	.43
Chronic obstructive pulmonary disease	49 (3.6)	25 (4.1)	.50
Rheumatoid arthritis	21 (1.6)	4 (0.7)	.06
Medication use, n (%)			
Cardiovascular medication	316 (23.2)	180 (29.0)	.004
Glucose-lowering agent [‡]	23 (1.7)	22 (3.5)	.02
Antihypertensive agent [§]	223 (16.3)	142 (22.9)	<.001
Lipid-lowering agent	107 (7.8)	69 (11.1)	.01
Acetylsalicylic acid	69 (5.1)	37 (6.0)	.22
Thyroid medication [#]	37 (2.7)	15 (2.4)	.62
Growth hormone	0 (0.0)	0 (0.0)	—

* P-values were calculated using a linear regression model adjusted for age and sex.

[†] As reported by participant's general practitioner.

[‡] Insulins and analogues, oral blood glucose-lowering drugs.

[§] Diuretics, beta-blockers, calcium channel blockers, agents acting on the renin-angiotensin system.

^{||} Fibrates, niacin, bile acid sequestrants, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.

[#] Thyroid hormones, antithyroid preparations, iodine therapy.

from Ashkenazi Jewish centenarians than 75 of their partners in the absence of differences in BMI and percentage of body fat between these two groups.¹⁰

In conclusion, by recruiting nonagenarian siblings in the Leiden Longevity Study, the current study was enriched with subjects who have a familial predisposition for longevity. Early features of healthy longevity appear already at middle age in these families, setting the stage for further analyses on how to live healthier for longer. Future research in this study population will focus on unraveling the genetic determinants and biochemical pathways and mechanisms that contribute to healthy longevity, because these might provide targets for specific interventions aimed at preservation of disease-free longevity in the population at large.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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