Endocrine and metabolic features of familial longevity : the Leiden Longevity Study

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Chapter 2: Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study

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Abstract

The aim of this study was to assess the risk of mortality of nonagenarian siblings compared to sporadic nonagenarians and to asses the prevalence of morbidity in the offspring compared to the partners thereof. We recruited 991 nonagenarian siblings derived from 420 Caucasian families, 1365 of their offspring and 621 of the partners thereof. In the Leiden 85-plus Study, 599 subjects aged 85 years were included of which 275 attained the age of 90 years (sporadic nonagenarians). All nonagenarians siblings (2.7 ± 1.4 years, mean ± SD) and sporadic nonagenarians (3.0 ± 1.5 years) were followed for mortality. Information on medical history and medication use was collected for offspring and their partners. Nonagenarian siblings displayed a 41% lower risk of mortality ($p<0.001$) compared to sporadic nonagenarians. Compared to their partners, the offspring of nonagenarian siblings displayed a lower prevalence of myocardial infarction (2.4% vs. 4.1%, $p=0.03$), hypertension (23.0% vs. 27.5%, $p=0.01$), diabetes mellitus (4.4% vs. 7.6%, $p=0.004$) and use of cardio-vascular medication (23.0% vs. 28.9%, $p=0.003$).

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.

Introduction

In Western societies, life expectancy has increased dramatically over the last century, but striking inter-individual differences in life expectancy remain [1]. Moreover, although rare examples of exceptional healthy longevity do exist, generally not all of the years that have been gained are spent in good health. Ample evidence has shown that healthy longevity is determined by a mix of genetic, environmental and chance elements. An increasing effort is currently being put in identifying the genetically determined pathways and mechanisms of healthy longevity in humans, as 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 rather modest (approximately 20-30%), but was shown to become increasingly important [2] and specific [3] at advanced ages. Studies aimed at understanding the genetics of human longevity have thus far preferentially studied the elite of exceptional longevity, such as centenarians or the even more elite "supercentenarians" that survive 110-plus years. In these studies, it was shown that compared to offspring of parents who had died at average age, offspring of centenarians displayed a lower prevalence [4] and incidence [5] of in particular cardiovascular disease (including hypertension and diabetes mellitus), as well as a later onset of these diseases [6] translating in a lower mortality risk [7]. Centenarians were also shown to have a healthier lifestyle compared to control groups, and may have transmitted part 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 is determined by either genetic or lifestyle factors. Comparable to the risk of developing common and rare diseases, such as breast cancer or hypercholesterolemia, the odds of exceptional longevity also runs in families [9].

We aim at identifying genetic determinants of healthy longevity in nonagenarians siblings enriched for heritable influences on morbidity and mortality. Therefore, we designed the Leiden Longevity Study in which we specifically recruited families based on proband siblings that both exhibit exceptional longevity [9] instead of the recruitment of families based on sporadic proband cases of exceptional longevity [10, 11]. Here, we compare the mortality risk of 991 nonagenarian siblings to that of 275 sporadic nonagenarians. Next, we assess disease prevalence in the offspring of nonagenarian siblings (n=1365) compared to the partners (n=621) thereof.

Materials and methods

Leiden Longevity Study

In the Leiden Longevity Study, 420 families were recruited consisting of long-lived Caucasian siblings together with their offspring and the partners thereof 9. In the Netherlands, there is no central registry of longevity. In 2002, only 0.5% the Dutch population was aged 89 years or older for males and 91 years or older for females. Long-living siblings fulfilling these age-criteria are even more rare and estimated to represent far less than 0.1% of the Dutch population. To recruit as much as possible long-living siblings within a fixed time window (July 2002-May 2006), we used the following strategy. A randomly chosen 80% (398 out of 496) of the municipalities in the Netherlands were approached and asked for the following information: names and addresses of all inhabitants aged 89 years or older for males and 91 years or older for females, as well as the names and birth dates of their parents. We received the requested information from 375 of the 398 municipalities. Next, by matching the inhabitants thus identified on the names and birth dates of both of their parents by means of a computer algorithm, we identified 2193 potential nonagenarian siblings. Approximately 1650 nonagenarian siblings were contacted and 991 nonagenarian siblings derived from 420 families of Caucasian descent agreed to participate and donate a blood sample (participation rate: app. 60%). Within the same time window, for each nonagenarian included in the Leiden Longevity Study, we also approached the offspring and the partners thereof for case control studies. Of the electable offspring cohort (n=2847), 1705 agreed to participate and donate a blood sample (participation rate: 60%) and of the app.1306 partners thereof, 760 agreed to participate and donate a blood sample (participation rate: app. 58%). There were no selection criteria on health or demographic characteristics. For all subjects, blood samples were taken at baseline for extraction of DNA, RNA and the determination of non-fasted serum and plasma parameters. Between November 2006 and May 2008, we collected additional information and biomaterials from the generation of offspring and partners, including self-reported information on life style, bodily measures, socio-economic 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 aged 85 years (birth cohort 1912-1914) and 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 years. 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 (CI)) are reported for transformed variables. All differences between offspring and partner categories were assessed with the use of linear regression, adjusted for sex, age, and correlation of sibling data using robust standard errors. Mortality analyses were performed with a sex-adjusted, left censored Cox proportional hazards model, to correct for late entry into the data set according to age. The Statistical Package for the Social Sciences (SPSS) program for Windows, version 14.0, and STATA version 10.0 were used for data analysis.

Results

Enrolment and baseline characteristics of participants

We previously recruited 420 families, consisting of 991 long-lived Caucasian siblings together with their offspring and the partners thereof in the Leiden Longevity Study. For 2465 of the offspring and their partners, non-fasted serum samples taken at baseline were available for the determination of endocrine and metabolic parameters. Between November 2006 and May 2008, for 2235 of the offspring and their partners, information on medical history was obtained from the participants' treating physicians (response: 90.7%). For 2255 of the offspring and their partners, information on the use of medication was obtained from the participants' pharmacist (response: 91.5%). For the present study, for a total of 1986 of the offspring and their partners, information on medical history and information on medication use were available (inclusion: 80.4%). Based on self-reported information from questionnaires, the offspring and partners did not differ for any major indicators of lifestyle, including current smoking (13.7% versus 15.6%, p=0.24), self-reported body mass index (BMI) (25.4 versus 25.6, p=0.26) and level of education (low level; 43.0 % versus 45.9 %, p=0.16; moderate level: 22.5 % versus 22.9 %, p=0.87; high level: 34.5 % versus 31.2 %; p=0.10).

Mortality characteristics of the long-lived siblings

After a mean (± standard deviation (SD)) follow-up of 2.65 (± 1.37) years, 43.1% of the nonagenarians with the familial longevity phenotype from the Leiden Longevity Study had died, while after a mean (SD) follow-up of 3.04 (± 1.51) years, 62.2 % of the nonagenarians with the sporadic longevity phenotype had died. At old age, the nonagenarian siblings displayed a 0.59

(95% Confidence Interval (CI): 0.45-0.71, p<0.001, **table 1** and **figure 1**) lower mortality risk compared to sporadic nonagenarians.

Table 1. Old age mortality in familial nonagenarians compared to sporadic nonagenarians

	Sporadic nonagenarians (n=275)	Familial nonagenarians (n=991)
Demographics		
Age, median (IQR)*	90 (90.0-90.0)	93.4 (91.5-94.9)
Females, No. (%)	199 (72.4%)	619 (62.5%)
Mortality		
HR (95% CI)†	1 (ref)	0.59 (0.46-0.71)

*Age is presented as median with interquartile range.

†Mortality risk is presented as hazard ratio (HR) with 95% confidence interval (CI).

Disease, medication use and anthropometric and metabolic characteristics in offspring and partners

In the group of 1986 subjects (**table 2**), a significantly lower disease prevalence was observed in the offspring compared to their partners for myocardial infarction (2.4% vs. 4.1%, p=0.03), hypertension (23.0% vs. 27.5%, p=0.01), diabetes mellitus (4.4% vs. 7.6%, p=0.004) and use of cardio-vascular medication (23.0% vs. 28.9%, p=0.003), including glucose lowering agents, anti-hypertensives and lipid lowering agents, but not anti-platelet agents (**table 2**).

Discussion

The majority of studies into human longevity have thus far focused on centenarians. Here, we show that selection for nonagenarian siblings leads to the inclusion of families that exhibit lower mortality rate at high ages and a better preservation of health at middle age compared to groups of 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/familial factors.

Table 2. Comparison of demographics, prevalence of disease and medication use between offspring and partners for males and females combined (n=1986)

	Offspring (n = 1365)	Partners (n = 621)	P-value
Demographics			
Age – yr	59.19 (54.97 - 64.02)	58.88 (54.31 - 63.63)	0.06
Females – no. (%)	732 (53.6)	354 (57.0)	0.16
Prevalence of disease			
Myocardial infarction – no. (%)	32 (2.4)	25 (4.1)	0.03
Stroke – no. (%)	47 (3.5)	19 (3.1)	0.87
Hypertension – no. (%)	307 (22.9)	168 (27.6)	0.009
Diabetes mellitus – no. (%)	59 (4.4)	46 (7.6)	0.004
Malignancies – no. (%)	115 (8.5)	44 (7.2)	0.43
Chronic obstructive pulmonary disease – no. (%)	49 (3.6)	25 (4.1)	0.50
Rheumatoid arthritis – no. (%)	21 (1.6)	4 (0.7)	0.06
Medication use			
Cardiovascular medication – no. (%)	316 (23.2)	180 (29.0)	0.004
-Glucose lowering agents – no.(%)	23 (1.7)	22 (3.5)	0.02
-Antihypertensive agents – no. (%)	223 (16.3)	142 (22.9)	<0.001
-Lipid lowering agents – no. (%)	107 (7.8)	69 (11.1)	0.01
-Acetylsalicylic acid – no. (%)	69 (5.1)	37 (6.0)	0.22
Thyroid medication – no. (%)	37 (2.7)	15 (2.4)	0.62
Growth hormone – no. (%)	0 (0.0)	0 (0.0)	-

P-values were calculated using a linear regression model, adjusted for age and sex. Age is presented as median with interquartile range. Diabetes mellitus is defined as reported by the general practitioner. Glucose lowering agents are defined as insulins and analogues, oral blood glucose lowering drugs. Antihypertensive agents are defined as diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system. Lipid lowering agents are defined as fibrates, niacin, bile acid sequestrants, HMG-COA reductase inhibitors. Thyroid medication is defined as thyroid hormones, anti-thyroid preparations, iodine therapy.

Previously [9], we showed that standardized mortality ratios compared with the general Dutch population were app. 30% lower for all first degree family members of the proband siblings from the first 100 families that were included in the Leiden Longevity Study. Here, we extend those findings by showing that the survival benefit observed earlier is maintained up to the highest age categories (89-104 years) in the complete cohort of nonagenarian siblings (derived from 420 families) as compared to the survival of sporadic nonagenarians from the Leiden 85-plus Study using prospective survival analysis. This result is in line 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 status, life styles 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 years in the nonagenarian siblings), strongly suggests that genetic factors could play a role in longevity in these families.

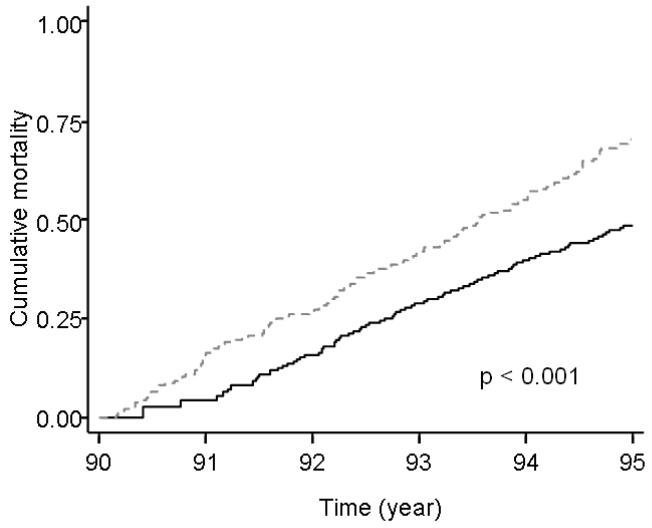

Figure 1. Cumulative mortality from age 90 through age 95 among familial nonagenarians (n=991) and sporadic nonagenarians (n=275) for males and females combined. *Solid line indicates familial longevity, dashed line indicates sporadic.*

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 years have a lower prevalence of diseases when compared to control subjects from the same birth cohort whose parents died at younger ages [6]. However, when comparing offspring from one or two parents who survived to 'old' age to offspring of parents who died at '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.[14] Likewise, centenarians were also shown to generally 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, we [9] have deliberately chosen to compare offspring from long-lived cases to their partners. Although the amount of cohabitation may have been variable, the lack of differences between these two groups in major indicators of lifestyle, including estimates for body mass index, current smoking, and prevalence of COPD, a smoking related disease, may be explained by the shared adult environment of the couples.

The decreased prevalence of myocardial infarctions, diabetes mellitus and hypertension in the offspring of nonagenarian siblings as compared to their partners is thus more likely to be due to genetic influences rather than environmental differences between the two groups. This result is in line with those of another study, in which significant lower prevalence was observed for diabetes mellitus and myocardial infarction in 180 offspring from Ashkenazi Jewish centenarians as compared to 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 for subjects with 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, as these might provide targets for specific interventions aimed at preservation of disease-free longevity in the population at large.

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Author contributions: RGW and PES conceived and directed the project. DvH contributed to the design and conduct of the project, to the data analysis and drafted the manuscript, MP contributed to the conduct of the project, performed the data analysis and drafted the tables and figures, MF, GJB contributed to the design and conduct of the project, MB and BT contributed to the design of the project, SPM contributed to the conduct of the project, AJdC contributed to the design and conduct of the project and to the data analysis. All authors contributed to the interpretation of the data, critically reviewed the report and approved the final version.

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