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Effect of Exceptional Parental Longevity and Lifestyle Factors on Prevalence of Cardiovascular Disease in Offspring

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Abstract

Offspring of parents with exceptional longevity manifest lower prevalence of cardiovascular disease (CVD) but the role of lifestyle factors in this unique cohort is not known. Our study tested whether individuals with exceptional parental longevity have lesser prevalence of CVD independent of lifestyle factors. Prevalence of CVD and CVD risk factors was assessed in a population of community dwelling Ashkenazi Jewish adults aged 65-94 years. Participants included offspring of parents with exceptional longevity (OPEL, n=395), defined as having at least one parent living past the age of 95 years, and offspring of parents with usual survival (OPUS, n=450), defined as having neither parent survive to 95 years. Medical and lifestyle information was obtained using standardized questionnaires. Socioeconomic status was defined based on validated classification scores. Dietary intake was evaluated with the Block Brief Food Frequency Questionnaire (FFQ 2000) in a sub-group of the study population (n=234). Our study found no significant differences in the prevalence of obesity, smoking, alcohol use, physical activity, social strata scores and dietary intake between the two groups. After adjustment for age and sex, the OPEL demonstrated 29% lower odds of having hypertension (95% CI 0.53-0.95), 65% lower odds of having had a stroke (95% CI 0.14-0.88), and 35% lower odds of having CVD (95% CI 0.43-0.98), compared with OPUS. In conclusion, exceptional parental longevity is associated with

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lower prevalence of CVD independent of lifestyle, socioeconomic status and nutrition; thus, highlighting the potential role of genetics in disease-free survival among individuals with exceptional parental longevity.

Keywords

Cardiovascular risk factors; Cardiovascular disease; Longevity; Aging; Diet

Individuals with exceptional longevity demonstrate a marked delay in the onset of age-related diseases and in many cases are spared from developing diseases altogether.[1-3] Thus, this group of individuals has served as a model of healthy aging, with many scientific efforts devoted to elucidating the mechanisms that allow these unique people to stay well as they age.[4] In humans, life span is at least in part heritable but the inheritance appears to be stronger for exceptional longevity, with several longevity-associated genes and genetic signatures identified.[5-8] A number of studies have demonstrated that the offspring of parents with exceptional longevity have lower incidence of cardiovascular disease (CVD) and lower prevalence of heart disease, stroke, and cancer compared to offspring of parents without exceptional longevity.[8-11] These observations suggest that the offspring are probably inheriting genetic factors from their parents that protect them from the effects of aging and diseases. While exceptional longevity has been associated with reduced CVD risk, numerous studies conducted in the general population have also demonstrated that physical activity, healthy dietary patterns, higher socioeconomic status and higher education are consistently related to better cardiovascular health.[12-14] However, to our knowledge, no studies have been conducted to date that compare the lifestyle factors of the offspring of parents with exceptional longevity with the offspring of parents without exceptional longevity. Thus, the present study tests the hypothesis that exceptional parental longevity is associated with lesser CVD prevalence independent of lifestyle factors, which if confirmed, would highlight the probable role of genetics on lifespan and health-span.

Methods

The subjects are participants of the LonGenity study, an on-going longitudinal study conducted at Albert Einstein College of Medicine, Bronx, NY since 2008. LonGenity focuses on identifying factors that contribute to protection from age-related diseases and extension of lifespan. All study participants are of Ashkenazi Jewish background, defined by all 4 grandparents being Ashkenazi Jewish, recruited from the Northeastern United States. This ensures relative genetic homogeneity of study subjects, thereby resulting in greater power to discover relevant genetic factors.[15] Two groups of participants were recruited based on the maximum lifespan achieved by their parents. Offspring of parents with exceptional longevity (OPEL) were defined as individuals with at least one parent living past the age of 95 years, about 20 years longer than the average life expectancy for the 1900 birth cohort.[2] These individuals are presumed to be enriched with longevity genotypes that they inherited from their parent with exceptional longevity. Offspring of parents with usual survival (OPUS) were defined as individuals whose both parents died before the age of 95 years. Both OPEL and OPUS were recruited through systematic searches of publicly available

voter registration lists, contacts at synagogues and community organizations, and advertisements in Jewish newspapers.[16] A subset of eligible subjects (n=85) were recruited from the Einstein Aging Study and were cross-enrolled. Potential participants were contacted by mail and then by telephone to assess interest and eligibility. Eligible participants were adults aged 65-94 years without baseline dementia, defined as a BLESSED score >8 and a score of >2 on the Eight-item Informant Interview to Differentiate Aging and Dementia (AD8) at the initial screening interview, who were also free of severe visual or hearing impairments and who did not have a sibling already enrolled in the study.

At enrollment and at yearly follow-up visits, medical, lifestyle and socioeconomic information was obtained using detailed standardized questionnaires. Cardiovascular-related diseases and outcomes included hypertension (HTN), diabetes mellitus (DM), myocardial infarction (MI), congestive heart failure (CHF), percutaneous coronary interventions (PCI), coronary artery bypass graft surgery (CABG), and stroke. A composite outcome of CVD included a self-reported history of any one of the following conditions: MI, PCI, CABG or stroke. Data on anti-hypertensive medication use was also collected. Lifestyle assessments included a history of past or current tobacco use, alcohol use, and habitual physical activity. A physical performance questionnaire assessed self-reported walking endurance, number of blocks walked daily, number of stairs climbed daily, number of times strenuous physical activity undertaken weekly, and one's physical activity in the past year compared to people of similar age and sex. The nutritional information was obtained from a sub-group of the study population using the Block Brief Food Frequency Questionnaire (FFQ 2000) and the nutrient data was extracted from the questionnaires by Nutrition Quest, Berkeley, California. This validated questionnaire was developed based on a modified food frequency questionnaire by Block et al.[17] Socioeconomic factors included education and social strata score that was calculated based on the classification described by Hollingshead.[18] Physical assessments performed at baseline included measurements of height, weight, and waist circumference. Body mass index (BMI) was calculated as weight in kilograms/height in meters^2 and obesity was defined as a BMI of ≥30 kg/m^2. Abdominal obesity was defined as waist circumference of ≥102 cm and ≥88 cm for men and women, respectively. A written informed consent was obtained from all the participants. The study was approved by the Institutional Review Board at the Albert Einstein College of Medicine.

Baseline data collected at enrollment was analyzed for this study. Descriptive statistics were used to compare prevalence of medical conditions, lifestyle factors, socioeconomic factors and dietary intake between OPEL and OPUS. Continuous normally distributed data and non-parametric data was analyzed with parametric and non-parametric tests, respectively. Normality was assessed by visual inspection. The Chi-square test was used for analysis of categorical variables, with Fisher Exact test employed when appropriate. Odds ratios (OR) for disease prevalence were adjusted for age and sex in all models. Additional analyses adjusted for tobacco use, social strata score, weekly strenuous activity, and BMI. Weekly strenuous activity was dichotomized as none weekly vs. ≥1 times per week. Testing for interactions between the OPEL or OPUS status and tobacco use, social strata score, and weekly strenuous activity was performed in logistic models with CVD as the outcome of interest. Stratified analysis was also conducted in those considered to be at high risk and low risk for CVD. High-risk individuals were defined as having diabetes mellitus or at least 2 of

the following: obesity, HTN or history of tobacco use. Low risk individuals were defined as those with none of the above risk factors. About 20% (n=176) of the study subjects were married couples, with 77 OPUS-OPEL pairs and 11 OPUS-OPUS pairs. There were no statistically significant differences in smoking rates (p=0.15), weekly physical activity (p=0.19) or education (p=0.33) between couples and non-couples; thus, we pooled all subjects together and did not distinguish between coupled and non-coupled individuals in our final analysis. A p-value of <0.05 was considered to be statistically significant. Data analysis was performed using SPSS version 12.0 (SPSS Inc. Chicago, IL) and STATA software, version 12 (StataCorp LP, College Station, TX).

Results

The demographics, lifestyle and socioeconomic factors of the study population are presented in Table 1. The study included 845 participants, with 47% being OPEL. There were no significant differences in any of the lifestyle or socioeconomic factors between OPEL and OPUS. Despite having similar physical activity rates, the OPEL demonstrated greater walking endurance compared to OPUS. Physical characteristics and disease prevalence for the two groups are depicted in Table 2. There were no significant differences in BMI, blood pressure, or obesity between the two groups; however, OPUS were more likely to use antihypertensive medication than OPEL (p<0.01). In models adjusted for age and sex, OPEL were found to be 29% less likely to have been hypertensive, 65% less likely to have had a stroke, and 35% less likely to manifest CVD overall, compared to OPUS. Although OPEL were also less likely to have had DM, MI, CHF, PCI, or CABG than OPUS, these differences did not persist after adjustment. Additional adjustment for BMI did not change the results. Age and sex adjusted logistic regression analysis, stratified on CVD risk, did not identify significant differences in the odds of CVD between OPEL and OPUS who were at low risk for CVD (n=498) [OR 0.87 (0.49-1.54); p=0.63]. However, among individuals at high risk for CVD, the OPEL had a lower prevalence of CVD compared to OPUS (n=341), [OR 0.45 (0.24-0.85); p=0.01]. Significant interaction was noted between the OPEL/OPUS group status and history of tobacco use in models of CVD as the outcome, with p=0.04 for the interaction term. Subsequent logistic regression analysis stratified by OPEL/OPUS status and adjusted for age, sex, BMI, tobacco use, social strata score and weekly strenuous activity revealed that tobacco use was not significantly associated with increased odds of CVD among the OPEL, [OR 0.66 (0.33-1.33), p=0.24]. On the other hand, tobacco use was nearly significantly associated with increased odds of CVD among the OPUS [OR 1.56 (0.96-2.55), p=0.07], although the power for detecting significant associations was substantially reduced in the stratified analysis. No significant interactions were identified between the OPEL/OPUS status and social strata scores or weekly strenuous activity.

The subject characteristics and nutritional intake for the subgroup who completed the Block FFQ 2000 (n=234) is presented in Table 3. The total daily caloric intake and the percentage of total daily kcal derived from carbohydrates, proteins, fats, including saturated fats, poly-unsaturated fats, and trans-fats, sweets and desserts was similar between OPEL and OPUS. While the percentage of total daily kcal derived from alcohol was significantly higher in the OPEL, it represented a very low consumption overall in both groups. Consumption of sodium and long chain (n – 3) fats was similar between OPEL and OPUS. There were also

no significant differences between the two groups in the intake of the number of daily servings of fruits, vegetables, grains, eggs, meats, dairy, fats, sweets and sodas.

Discussion

Our study found that exceptional parental longevity is associated with a 35% reduction in the prevalence of CVD among the offspring of parents with exceptional longevity compared to controls. Previous studies conducted by our group and others have observed lower prevalence of HTN, MI, and strokes, as well as, lower incidence of DM, MI, strokes and mortality among individuals with exceptional parental longevity.[8,9,11] The current study expands on this knowledge by demonstrating that the reduced prevalence in CVD in families with exceptional longevity cannot be explained by differences in lifestyle, socioeconomic status, and diet. Therefore, our results support the hypothesis that exceptional longevity and protection from age-related diseases, such as CVD, are at least partly influenced by genetics.

It has been well documented that obesity and sedentary lifestyle are risk factors for CVD.[19] Studies have also shown that a non-smoking status and physical activity predict 5-year mortality and cardiovascular disease-free survival at older ages.[13,20] In our study, however, despite similarities in their rate of obesity, participation in physical activities, and tobacco use, the OPEL had a lower prevalence of CVD compared to OPUS. These findings are similar to a prior study, which found that the lifestyle, BMI, physical activity and dietary patterns were similar among individuals with exceptional longevity and those with usual life-spans from the same birth cohort.[21] In addition to lifestyle and nutritional risk factors, lower levels of education and low income have been associated with increased disease risk.[13,20,22] Our study found no differences in the socioeconomic factors between OPEL and OPUS, although on average, both groups were highly educated and had social strata scores in the highest category.[18]

The importance of diet on CVD risk has been well documented. In 2012, about 45.4% of deaths from heart disease, stroke and type 2 diabetes mellitus in the United States were attributed to sub-optimal intake of nutrients[23], which included high intake of sodium, processed meats and sugary beverages and low intake of nuts, seeds, seafood omega-3 fats, vegetables, fruits and whole grains. Furthermore, increased consumption of fruits, vegetables, whole grains, poly-unsaturated fats, which are contained in seafood and olive oil, low-fat dairy products, and reduced intake of salt and refined sugars have been shown to prevent cardiovascular diseases.[12,24] Our study demonstrated no differences in the dietary patterns between the OPEL and OPUS. These findings further reinforce the idea that dietary practices are less likely to induce adverse effects among individuals with exceptional parental longevity.

Although favorable lifestyle factors have a role in reducing the risk of CVD irrespective of the genetic risk, it must be appreciated that the beneficial effect of lifestyle is diminished in individuals with low genetic risk, such that the risk of coronary events in those with high genetic risk and favorable lifestyle is similar to those with low genetic risk and unfavorable lifestyle.[14] Similar findings were reflected in our study where among all subjects who had major risk factors for CVD, OPEL clearly demonstrated lower prevalence of CVD compared

to OPUS. While this highlights the importance of the interactions between genes and environment, it also points to the power of protective genes. Identification of genes that protect from the negative impacts of environment can lead to the development of drugs that have the capacity to modulate the interactions between genes and the environment.

Numerous studies have identified genetic markers that may contribute to human longevity and resilience to disease, including genotypes in the somatotropic axis, thyrotropic axis, insulin signaling pathway, lipid metabolism and adiponectin, several of which have been associated with protection from CVD.[4] Identification of these genotypes in our subjects has facilitated further investigations in translational cardiovascular medicine. The cholesteryl ester transfer protein inhibitor, Anacetrapib, has been shown to increase high density lipoprotein cholesterol and reduce low density lipoprotein cholesterol levels and is currently being tested in a phase 3 trial for its ability to reduce CVD in combination with atorvastatin.[25] In a phase 2, randomized, placebo-controlled trial, apolipoprotein c-III inhibitor significantly lowered triglyceride levels.[26] These examples demonstrate the importance of unraveling the mechanisms of healthy aging that may enable the potential development of novel therapies for CVD.

The strengths of this study include a large cohort consisting of a genetically, demographically and culturally homogeneous population. Additionally, the analyses of lifestyle, socioeconomic and dietary habits of OPEL and OPUS were performed using the same tools; thereby allowing for direct comparison between the two groups. Previous studies have demonstrated similar life-span extension and morbidity reduction in Ashkenazi Jewish centenarians compared with Caucasian centenarians from other backgrounds.[2] Therefore, our findings can be generalizable to other populations. Our study also has several limitations that are common to observational studies. The cross-sectional design does not permit causal inferences. The dietary analysis was performed on a sub-group of the total sample; however, no meaningful differences were appreciated between the total cohort and the subgroup in terms of age, sex or BMI; thus, we believe that the sub-group is representative of the cohort as a whole. Also, the Block Brief FFQ 2000 used in this study is a brief questionnaire that has been shown to provide a lower estimate of macronutrient intake.[17] As dietary recall and report of medical history are dependent on self-report, they are subject to recall bias. However, since our study compared measures between the two groups, both of whom were studied using the same research tools, these limitations are not likely to have affected the responses of the groups differentially and to have influenced the conclusions.

Based on our study, we conclude that exceptional parental longevity is associated with reduced CVD prevalence independent of lifestyle, socioeconomic background and nutrition. The OPEL may possess genetic determinants that protect them from the hazardous effects of the environment. These results, together with data from other studies that showed protective effects of exceptional parental longevity on the development of other age-related diseases, highlight the strengths of such studies and their value in helping to identify the mechanisms of healthy aging.

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Table 1
Subject characteristics, socioeconomic and lifestyle factors

Characteristic	OPEL (n=395)	OPUS (n=450)	p-value
Female	59%	50%	<0.01
Age (years)	75±6	76±7	<0.01
Married, currently	65%	62%	0.46
Married, ever	97%	98%	0.45
Education (years)	17±3	17±3	0.55
Social strata score	56 (28-66)	56 (28-66)	0.76
Smokers, ever	55%	54%	0.80
Smokers, current	3%	3%	0.94
Smoking pack-years	12 (3-20)	15 (5-36)	0.12
Alcohol use in past year	90%	88%	0.32
Drinks/week in past year	2 (0.5-4)	1 (0.2-4)	0.35
Drinks/week at age 20-50 years	2 (2-3)	2 (2-3)	0.91
Drinks/week at age >50 years	2 (2-3)	2 (2-3)	0.43
Walking endurance			
<5 minutes	1%	4%	
5-30 minutes	21%	26%	
>30 minutes	77%	70%	0.05
Blocks walked daily (number)	11 (3-20)	12 (3-20)	0.68
Strenuous physical activity (times/week)	3 (0-4)	3 (0-4)	0.71
Flights of stairs per day	4 (1-10)	4 (1-10)	0.67
Physical activity compared to peers			
Less active	11%	15%	
More active	35%	30%	
Similar	54%	54%	0.18

Table 2
Subject physical characteristics and disease prevalence

Characteristic	OPEL (n=395)	OPUS (n=450)	p-value	OR (95% CI)[a]
Body mass index (kilogram/meters^2)	27.5 ± 4.9	27.8 ± 4.7	0.34	
Obese[b]	26%	27%	0.84	
Abdominal obesity[c]	48%	48%	0.95	
Systolic blood pressure (mmHg)	129 ± 17	129 ± 17	0.78	
Diastolic blood pressure (mmHg)	74 ± 9	74 ± 10	0.92	
Antihypertensive use	39%	49%	<0.01	
Diabetes mellitus	7%	11%	0.10	0.70 (0.43-1.15)
Hypertension	42%	51%	<0.01	0.71 (0.53-0.95)
Myocardial infarction	5%	7%	0.12	0.77 (0.42-1.42)
Congestive heart failure	1%	2%	0.14	0.43 (0.09-2.10)
Percutaneous coronary intervention	9%	11%	0.24	0.96 (0.59-1.56)
Coronary artery bypass graft surgery	3%	7%	0.03	0.61 (0.29-1.29)
Stroke	2%	5%	<0.01	0.35 (0.14-0.88)
Cardiovascular disease[d]	12%	20%	<0.01	0.65 (0.43-0.98)

Data are expressed as mean ± standard deviation, median (interquartile range) or as percentage.

[a] Odds ratio of disease in OPEL compared to OPUS, adjusted for age and sex (further adjustment for BMI did not make significant difference).

[b] Defined as a BMI ≥ 30 kg/m^2

[c] Defined for males as waist circumference of 102cm or greater and for females as waist circumference of 88cm or greater.

[d] Includes a self-reported history of any of the following conditions: myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery or stroke.

Table 3
Subject characteristics and dietary intake

Characteristics	OPEL (n=89)	OPUS (n=145)	p-value	Adjusted p –value[a]
Females	65%	57%	0.19	
Age (years)	74.6±5.3	79.0±6.9	<0.01	
Body mass index (kilogram/meters^2)	27.8±5.1	28.7±4.7	0.16	
Daily caloric intake				
Total calories (kcal)	1119 (906 – 1520)	1218 (940 – 1553)	0.29	0.83
Daily proportion of kilocalories				
Total carbohydrates kcal	49% ± 11%	51% ± 9%	0.04	0.28
Total protein kcal	17% ± 4%	16% ± 3%	0.14	0.65
Total fat kcal	34% ± 7%	34% ± 7%	0.83	0.71
Total alcohol kcal	2% (0.4% – 7%)	1% (0.2% – 4%)	0.01	0.02
Total sweet, dessert kcal	8% (4% – 17%)	12% (5% – 19%)	0.12	0.23
Saturated fat	10.2% (8% – 15%)	11% (8% – 15%)	0.87	0.18
Poly-unsaturated fat	6.8% (4.6% – 9.9%)	6.5% (4.8% – 9.5%)	0.94	0.73
Trans-fat	0.9% (0.7% – 1.3%)	1% (0.8% – 1.3%)	0.39	0.46
Daily food serving intake (number of servings)				
Vegetables	3.2 (1.7 – 4.5)	3.4 (2 – 4.8)	0.38	0.66
Fruits	1.7 (1.2 – 2.6)	2.1 (1.3 – 2.8)	0.04	0.42
Grains	2.6 (1.5 – 3.7)	2.6 (1.7 – 3.8)	0.44	0.35
Meat and eggs	1.3 (0.7 – 1.9)	1.1 (0.7 – 1.1)	0.25	0.28
Dairy	1.1 (0.6 – 1.9)	1.2 (0.7 – 1.8)	0.14	0.81
Fats, Sweets, Sodas	1.6 (1 – 2.6)	2 (1.3 – 2.8)	0.03	0.15
Dietary components (grams/day)				
Sodium	1.3 (1 – 1.9)	1.5 (1 – 1.9)	0.14	0.45
Long-chain (n-3) fat[b]	0.08 (0.04 – 0.1)	0.05 (0.04 – 0.08)	0.01	0.32

Data are expressed as mean±standard deviation, median (interquartile range) or as percentage.

[a]Adjusted for age and sex;

[b]Includes eicosapentaenoic acid and docosahexaenoic acid.