ELSEVIER

Experimental Gerontology 38 (2003) 361–365

Experimental Gerontology

www.elsevier.com/locate/expgero

Have centenarians had younger parents than the others?

Jean-Marie Robine[a,*], Amandine Cournil[a], Nicolas Henon[b], Michel Allard[b]

[a]*INSERM Démographie et Santé, Université de Montpellier I et CRLC, Val d' Aurelle, 34298, Montpellier cedex 05, France*
[b]*Fondation Ipsen, Paris, France*

Received 4 April 2002; received in revised form 5 November 2002; accepted 6 November 2002

Abstract

This work, based on a matched case-control design, tests the assumption that centenarians were conceived by parents younger than the parents of individuals who had lifespan close to mean life duration. The centenarians are paired with controls of the same sex, born at the same place and at the same time in order to avoid traditional biases related to mortality peaks or secular trend of increase in life expectancy. The parental age at the time of the birth registration of 320 centenarians born in France between 1875 and 1890 and deceased between 1990 and 1999 is collected, as well as the one of 603 controls of the same sex whose births were recorded immediately before or after those of the future centenarians on the birth registers of the cities concerned. No difference is found between the parental age of parents of centenarians and of controls. In particular, no difference is found for females. Recent studies showed—from genealogical data—that the life expectancy of a female would be much reduced if her father was old at the time of her conception. Our study does not indicate a negative effect of a higher paternal age on the longevity of daughters.

Keywords: Centenarian; Human; Parental age; Case-control study; Longevity

1. Introduction

This study, based on a matched case-control design, aims at examining whether centenarians were conceived by parents younger than the parents of individuals who had lifespan close to the mean life durations. The impetus for this study is a finding showing a negative effect of a higher paternal age on the longevity of daughters, using data from European aristocracy genealogies (Gavrilov et al., 1996a,b, 1997; Gavrilov and Gavrilova, 1997). Beyond biological interest implicating the X chromosome in this specific relation, these results are relevant from a public health point of view in the current context of postponing procreation and lengthening of life span (Goldstein and Schlag, 1999). Some demographers have even begin to think of a world where after having raised a first child, still 'young' parents would conceive a second one…around the age of 50 years (Caselli and Vallin, 2001).

To study the influence of various familial characteristics on longevity, it is necessary to have information covering more than 100 years, from the birth of the parents to the death of the children. This explains the recourse to genealogies (Gavrilova et al., 1998; Westendorp and Kirkwood, 1999). The major problem arising from the use of genealogies is the under-registration of individuals and events (Post et al., 1997). As observed in many genealogical data (see for example Gavrilov et al., 1996a), females are frequently excluded from the genealogy, especially when they are not directly involved in the 'family line' (as a mother of a boy for example). This does not necessarily decrease the value of these studies, but illustrates the need for validation in general population to exclude potential bias of selection. The ideal protocol would be to have a register of historical populations like that in Quebec or Valserine (Desjardins and Charbonneau, 1990; Le Bourg et al., 1993; Cournil et al., 2000), allowing the prospective study of the relationship between the age of the parents at the birth of their children (parental age) and longevity of the children from all births occurring within a population and with control for confounding factors, such as social heterogeneity, peaks of mortality and secular trend in life expectancy increase.

An alternative design is to use a sample of long-lived subjects and to compare the parental age of their parents with those of controls. Studies relating to human longevity

* Corresponding author. Tel.: +33-467613043; fax: +33-467613047.
E-mail address: robine@valdorel.fnclcc.fr (J-M. Robine).

0531-5565/03/$ - see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0531-5565(02)00245-0

more and more often involve centenarians, now relatively numerous in developed countries with low mortality and good data quality (Blanché et al., 2001; Jeune and Vaupel, 1995, 1999; Perls et al., 1998a,b, 2001; Puca et al., 2001; Thatcher et al., 1998; Vaupel et al., 1998). A specific feature of most centenarian-based studies is to involve a control group, the choice of which is a key in the robustness of the approach. The definition and choice of controls for long-lived subjects for a variety of research objectives were the subject of an international protocol within the framework of Alliance for Research on Longevity and Exceptional Survival (ARLES). The cornerstone of the protocol is that in all instances, the control of a long-lived subject is the individual of the same sex born at the same place and at the same time as the long-lived subject or, failing this, the individual who complies with most of these criteria (Robine et al., 2002). Such a pairing in space and time makes it possible to avoid the major biases linked with geographical and temporal variations of the relationship studied.

Thus if having an old father has a deleterious effect on the longevity of females, centenarians who are almost all women should have had younger fathers compared to their non-centenarian' controls. This hypothesis is tested from a sample of 512 centenarians residing in France and for whom the age of at least one of the parents at the time of their birth is known. By excluding infant or early mortality for the controls, this study focuses on 'normal' longevity, corresponding to the age-group where most adult deaths occurred.

2. Materials and methods

2.1. Subjects

Nine hundred and ten subjects, born in 1890 or before, were examined in France in 1990, approximately a quarter of the French population of centenarians estimated to be 3500 at that time (Fondation Ipsen, 1991). Out of 910 subjects, 858 died after age 100, including 512 of them for whom a photocopy of the birth record (or its integral copy) was sent by the local civil registry office. Birth records provide the information of ages of the parents at the birth of the subject, taken as a proxy for parental age at conception, as well as other various information concerning the parents (name, address, occupation).

In 1999, these local registry offices were contacted again and requested to provide a photocopy of the birth record for two controls. Controls were chosen, according to the ARLES protocol, as children of the same sex whose births had been recorded immediately before and after that of the centenarian(s) of the commune.[1] Valid documents were obtained for 320 cases. Several cities misunderstood and sent again a photocopy of the centenarian's birth record. A significant number refused to provide the information since the identity of the searched persons was not mentioned.[2] Some cities made errors on pairing by sex. Finally some cities sent documents for one control only. In total, relevant information was gathered for 923 child-births, 320 future centenarians (284 females, 88.8% and 36 males, 11.2%) and 603 controls. The age of the mother was known for 313 centenarians (98% of the sample) and the age of the father for 294 (92%).

2.2. Study-design

Three separate analyses were carried out on different sub-samples of cases and controls (Table 1). The first analysis was performed using all data available. The aim of this first analysis was to test if centenarians, in general, have had parents younger than their controls. The second analysis was done on female centenarians and their controls who died between the age of 70 and 90. Controls who died before age 70 and after age 90 were excluded in the aim of focusing on normal longevity compared to exceptional longevity of centenarians. This age group was selected since, for the female cohort born in 1890 to which most controls belongs, the age-group 70–90 included (51%) of adult deaths (above 20), equally distributed at both sides of the model age at death of 84 years. Moreover, the age at death of the control is known from a report of the date of death in the margin of the birth record. However, this practice only became compulsory in 1945 and thus for the 1890-cohort, report of death before age 65 is under-reported. In contrast, the report of date of death after age 70 for this cohort is complete. In the third analysis, attention was focused on females who had reached the age of 105 and to their controls who died between 70 and 90 years, with the purpose of better separating long life from mean life durations.

2.3. Statistical analyses

Logistic regressions for matched case-control study with a variable number of controls by case were carried out using the procedure 'conditional (fixed effects) logistic regression (CLOG)' in Stata (StataCorp, 1999). Paternal and maternal ages were transformed to fit a normal distribution (Breslow and Day, 1980). The transformation $(\text{age}^{\lambda} - 1)/\lambda$ ($\lambda = -0.37$ for paternal age and $\lambda = 0.05$ for maternal age) was estimated using the BOXCOX procedure in Stata. In each analysis, univariate logistic regressions were carried out firstly separately for paternal age and maternal age. Then both paternal and maternal ages were included in multivariate regressions to estimate the age-effect of one parent when the contribution of the other parent's age on

[1] The communes were also asked to provide a third control if the date of death of any of the first two controls was not reported in the margin of his birth record but this part of the protocol became too cumbersome to be followed by register officers contacted by post.

[2] In theory request by mail is only possible for an identified person, not an anonymous control.

Table 1
Characteristics and size of the samples available for each analysis

	Cases	Controls	Together
First analysis	All centenarians	All controls	
	$n = 320$	$n = 603$	$n = 923$
Number of fathers	294	514	808
Number of mothers	313	590	903
Second analysis	Female centenarians	70–90 years old controls	
	$n = 284$	$n = 230$	$n = 514$
Number of fathers	164	194	358
Number of mothers	173	219	392
Third analysis	Females 105 and over	70–90 years old controls	
	$n = 71$	$n = 58$	$n = 129$
Number of fathers	45	53	98
Number of mothers	46	56	102

the longevity of the child is taken into account. Multivariate approach is particularly important in case of correlated variables, as observed for paternal and maternal ages.

3. Results

The first analysis, using all the data, shows that the paternal or the maternal age does not appear to have a significant effect on the future longevity of the child (Table 2, Figs. 1 and 2). Taking into account the age of the other parent in the multivariate model does not change the results. The second analysis, focusing on female centenarians and using controls who died between the ages of 70 and 90 years, produces almost identical results showing that the parental age appears to have little effect on the longevity of the daughter (Table 2). Finally, the third analysis confirms the previous results when focusing on cases of exceptional longevity with females having reached the age of 105 years (Table 2).

4. Discussion

The objective of this study was to test whether differences in parental ages at birth could play a role in

Table 2
Parental age of parents of children who became centenarians and of controls born in France during the period 1875–1890

		Cases	Controls	p-value[a] (univariate)	p-value[b] (multivariate)
First analysis		All centenarians	All cases		
Paternal age	Mean	33.8	33.8	0.986	0.592
	(± SD)	(± 6.9)	(± 7.1)		
	min–max	20–67	20–61		
Maternal age	Mean	28.5	28.2	0.320	0.362
	(± SD)	(± 5.9)	(± 5.9)		
	min–max	15–45	15–45		
Second analysis		Females 100 +	70–90 years old		
Paternal age	Mean	34.4	34.5	0.873	0.966
	(± SD)	(± 7.2)	(± 7.7)		
	min–max	21–67	21–61		
Maternal age	Mean	29.0	28.9	0.856	0.864
	(± SD)	(± 5.9)	(± 6.2)		
	min–max	17–42	17–45		
Third analysis		Females 105 +	70–90 years old		
Paternal age	Mean	34.7	35.1	0.744	0.668
	(± SD)	(± 6.7)	(± 8.7)		
	min–max	23–47	24–61		
Maternal age	Mean	28.9	29.3	0.801	0.726
	(± SD)	(± 6.3)	(± 6.4)		
	min–max	19–44	17–43		

[a] p-value for the effect of parental ages from univariate logistic regressions.
[b] p-value for the effect of parental ages from multivariate logistic regression. Each parental age effect is estimated when taking into account the effect of the other parent.

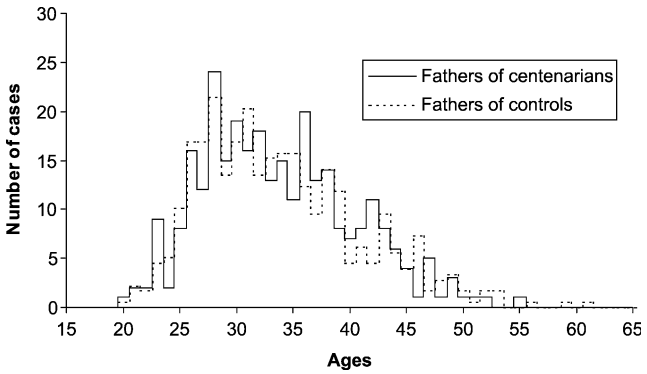

Fig. 1. Paternal ages at the birth of 294 future centenarians and 514 controls, France 1875–1890. (Scale for the number of cases: 1 control equals to 294/514 cases).

explaining mortality differences at late ages. This hypothesis had been suggested by recent results involving genealogical data, finding that having an old father strongly reduced longevity of daughters. Our study, based on a matched case-control design, showed no difference between the parental age of parents of centenarians and of controls. Controls were born at the same time and in the same place as the centenarians ensuring a perfect control for possible geographical or temporal variations in the relationship studied.

One limitation of our dataset is the lack of relevant information on the causes of death preventing us from formally disentangling ageing-related causes of death from the unrelated ones. Several authors made such a partitioning, opposing intrinsic to extrinsic mortality (Bourgeois--Pichat, 1952; Carnes and Olshansky, 1997). To overcome this limitation we fixed a limit age for the choice of the controls and we developed an approach relying on the criteria of specificity and sensitivity largely used in epidemiological studies. In this study, age at death is taken as an indicator of ageing-related cause of death. In the first analysis where all the controls are kept the sensitivity is 100% since all ageing-related deaths are included. But as all ageing-unrelated causes of death are also retained, the specificity is minimal. In the second analysis where the controls dead before 70 years are excluded, the sample of controls contains in proportion much more lifespans which were ended by an ageing-related cause of death, although we recognise that it does not include all ageing-related deaths. Thus our design was a trade off in favour of a high specificity versus sensitivity to ageing-related or intrinsic deaths. The fact that the results do not change in the first analysis which includes all ages at death compared to the second analysis focusing on age-group 70–90, where the specificity to ageing-related death is higher, suggests a stability of the results for the different age groups.

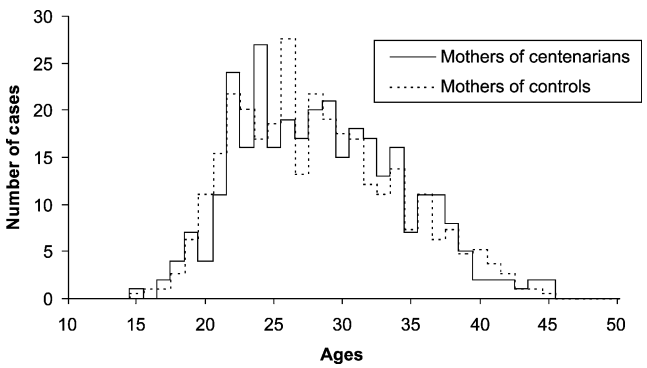

Fig. 2. Maternal ages at the birth of 313 future centenarians and 590 controls, France 1875–1890. (Scale for the number of cases: 1 control equals to 313/590 cases).

The second and the third analysis focused specifically on females because male centenarians were too few to allow a separate analysis. Our study does not confirm the previous results of a negative effect of a higher paternal age on the normal longevity of daughters. If such an effect did exist then centenarians who are almost all women, should have had, on average, fathers less old than their non-centenarian controls. The assumption remains that the 'exceptional' longevity of the centenarians could be due to specific factors (genetics or way of life), which would have nothing to do with the factors affecting normal longevity, to which the age of the father might belong. However, this assumption is unlikely since the study of the distribution of lifespan shows that centenarians clearly constitute the higher tail of a normal distribution of the lifespans (Kannisto, 2001). When excluding infant mortality, for which parental age effect is well known (Abernethy et al., 1990), it is still possible to consider a paternal effect on the life durations ending before the age of 70 years. Many life durations ended in this range in the past, 40% in the French female 1890 cohort. Most of these deaths were premature due to infectious diseases, accidents or maternal mortality. Some of course constitute the lower tail of the normal longevity but in the current life table no more than 13% of the deaths occur between the ages of 1 and 70 years.[3] Thus one can consider that a higher paternal age might have an effect on premature mortality, decreasing for example the resistance to infectious diseases, and thus decreasing the total life expectancy. But this is not the topic of the present study dealing with normal and exceptional longevity.

Lastly, our study relies on high quality data from the French civil registration system. Dates of birth and dates of death of the centenarians and their controls as well as the age of their parents at the time of their birth, were recorded at the time of their occurrence, which is a source of exactness. It is likely that old genealogies do not provide the same degree of data quality. However, Gavrilov and Gavrilova recently confirmed their results, for fathers aged from 35 to 55 years old, with a broadened sample of European aristocratic genealogies (Gavrilov and Gavrilova, 2001), although no significant relationship was found

[3] In the life table for the year 1999, less than 0.5 of the deaths occurs during the first year of life, 13% between the ages of 1 and 70 years, 56% between the ages of 70 and 90 years and 31% at the age of 90 or over.

between the paternal age and the longevity of daughters using genealogical data from the British aristocracy (Westendorp and Kirkwood, 2001).

Acknowledgements

We wish to thank Leonid and Natalia Gavrilov as well as our colleagues from the Alliance for Research on Longevity and Exceptional Survival for our scientific exchanges on the questions tackled in this study. We also wish to thank Andrew Kramar for his advice on the statistical analysis, France Meslé who provided us with the female life table of the cohort born in 1890, and two anonymous referees for helpful comments on the manuscript.

References

Abernethy, V., Hip, R., 1990. Parent characteristics and sex differential infant mortality: the case in Tennessee. Hum. Biol. 62 (2), 279–290.

Blanché, H., Cabanne, L., Sahbatou, M., Thomas, G., 2001. A study of French centenarians: are ACE and APOE associated with longevity? CR Acad. Sci. Paris, Sci. de la vie/Life Sci. 324, 129–135.

Bourgeois-Pichat, J., 1952. Essai sur la mortalité biologique de l'homme. Population 7 (3), 381–394.

Breslow, N.E., Day, N.E., 1980. Statistical methods in cancer research. World Health Organization (WHO) and International Agency for Research on Cancer (IARC), Lyon.

Carnes, A.B., Olshansky, S.J., 1997. A biologically motivated partitioning of mortality. Exp. Gerontol. 32 (6), 615–631.

Caselli, G., Vallin, J., 2001. Demographic trends: beyond the limits? Popul.: Engl. Sel. 13 (1), 41–72.

Cournil, A., Legay, J.-M., Schächter, F., 2000. Evidence of sex-linked effects on the inheritance of human longevity: a population-based study in the Valserine valley (French Jura), 18–20th centuries. Proc. R. Soc. London B Biol. Sci. 267, 1021–1025.

Desjardins, B., Charbonneau, H., 1990. L'héritabilité de la longévité. Population 3, 603–616.

Fondation Ipsen, 1991. 100 tableaux pour 100 ans. Fondation Ipsen, Paris.

Gavrilov, L.A., Gavrilova, N.S., 1997. When fatherhood should stop. Science 277, 17–18.

Gavrilov, L.A., Gavrilova, N.S., 2001. Biodemographic study of familial determinants of human longevity. Population, 197–222.

Gavrilov, L.A., Gavrilova, N.S., Evdokushkina, G.N., Semyonova, V.G., Gavrilova, A.L., Evdokushkina, N.N., Lapshin, E.V., 1996a. Determinants of human longevity: parental age at conception and offspring longevity. Longevity Rep. 10 (54), 7–15.

Gavrilov, L.A., Gavrilova, N.S., Kroutko, V.N., Evdokushkina, G.N., Semyonova, V.G., Gavrilova, A.L., Lapshin, E.V., Evdokushkina, N.N., Kushnareva, Yu.E., 1996b. Specific decrease in longevity of daughters conceived by old fathers. Longevity Rep. 10 (56), 4–5.

Gavrilov, L.A., Gavrilova, N.S., Kroutko, V.N., Evdokushkina, G.N., Semyonova, V.G., Gavrilova, A.L., Lapshin, E.V., Evdokushkina, N.N., Kushnareva, Yu.E., 1997. Mutation load and human longevity. Mutat. Res. 377, 61–62.

Gavrilova, N.S., Gavrilov, L.A., Evdokushkina, G.N., Semyonova, V.G., Gavrilova, A.L., Lapshin, E.V., Evdokushkina, N.N., Kushnareva, Yu.E., Kroutko, V.N., Andreyev, A.Yu., 1998. Evolution, mutations, and human longevity: European royal and noble families. Hum. Biol. 70, 799–804.

Goldstein, J.R., Schlag, W., 1999. Longer life and population growth. Popul. Dev. Rev. 25 (4), 741–747.

Jeune, B., Vaupel, J.W., 1995. Exceptional Longevity: from Prehistory to the Present, Odense University Press, Odense, Odense Monographs on Population Aging; 2.

Jeune, B., Vaupel, J.W., 1999. Validation of Exceptional Longevity, Odense University Press, Odense, Odense Monographs on Population Aging; 6.

Kannisto, V., 2001. Mode and dispersion of the length of life. Popul.: Engl. Sel. 13 (1), 159–172.

Le Bourg, E., Thon, B., Légaré, J., Desjardins, B., Charbonneau, H., 1993. Reproductive life of French–Canadians in the 17–18th centuries: a search for a trade-off between early fecundity and longevity. Exp. Gerontol. 28, 217–232.

Perls, T.T., 2001. Genetic and phenotypic markers among centenarians. J. Gerontol. 56A (2), M67–M70.

Perls, T.T., Bubrick, E., Wager, C.G., Vijg, J., Kruglyak, L., 1998a. Siblings of centenarians live longer. Lancet 351, 1560.

Perls, T.T., Alpert, L., Fretts, R.C., 1998b. Middle-aged mothers live longer. Nature 389, 133 Scientific Correspondence.

Post, W., van Poppel, F., van Imhoff, E., Kruse, E., 1997. Reconstructing the extended kin-network in the Netherlands with genealogical data: methods, problems and results. Popul. Stud. 51, 263–278.

Puca, A.A., Daly, M.J., Brewster, S.J., Matisse, T.C., Barret, J., Shea-Drinkwater, M., Kang, S., Joyce, E., Nicoli, J., Benson, E., Kunkel, L.M., Perls, T., 2001. A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4. PNAS 98 (18), 10505–10508.

Robine, J.-M., Jeune, B., Poulain, M., 2002. The Paris protocol for case-control studies of the lifespan of ancestors of very long-lived people. In: Jeune, B., Vaupel, J.W. (Eds.), Longlived Kin: Does Longevity Run in Families, Odense University Press, Odenses, in press.

StataCorp, 1999. Stata Statistical Software: Release 6.0. College Station, TX, Stata Corporation.

Thatcher, A.R., Kannisto, V., Vaupel, J.W., 1998. The Force of Mortality at Ages 80 to 120, Odense University Press, Odense.

Vaupel, J.W., Carey, J.R., Christensen, K., Johnson, T.E., Yashin, A.I., Holm, N.V., Iachine, I.A., Kannisto, V., Khazaeli, A.A., Liedo, P., Longo, V.D., Zeng, Y., Manton, K.G., Curtsinger, J.W., 1998. Biodemographic trajectories of longevity? Science 280, 855–860.

Westendorp, R.G., Kirkwood, T.B.L., 1999. Human longevity at the cost of reproductive success. Nature 396, 743–746.

Westendorp, R.G., Kirkwood, T.B.L., 2001. Maternal and paternal lines of familial longevity. Popul.: Engl. Sel. 13 (1), 223–236.