Fertility History and Post-reproductive Longevity in a Long-living Population: Villagrande (1830 – 2013)

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Abstract

According to evolutionary theories of aging, there is a trade-off between fertility and post-reproductive longevity. Using data from Villagrande Strisaili, Sardinia, we have analyzed the relationship between the fertility pattern of mothers who survived past the age of 50 (n=522) and their overall lifespan. We found that, adjusting for potential confounders (year of mothers' birth, survival of spouse), delayed childbirth is associated with a reduced mortality risk (HR: 0.969), in particular, a 3-year delay in the average age at delivery is associated with a 10% reduction in mortality. In accordance with previous reports, these findings support the hypothesis that a delay in childbearing is favorable to a mother's survival although the underlying causes are likely population-specific. We also found that a higher proportion of male children decreases the mortality risk of the mother and that the survival of mothers whose average age at the birth of sons is > 35 is consistently better than among the group whose age falls below this value (p=0.005; log-rank test). Such results are in disagreement with other recent findings and we therefore suggest further investigation of the impact of the socio-cultural characteristics of the population under study.

Keywords: late maternity, post-reproductive longevity, sons, Sardinia

1. Introduction

The linkage between the timing of reproduction and longevity was first described by Buffon and Flourens (Robine 2009). Does the fertility history of mothers influence their post-reproductive longevity? This question has been addressed in the scientific literature largely since the pioneering work of Beeton et al. (1905) who demonstrated a positive correlation between the number of children and the survival of their mother beyond 50. Freeman (1935) reconsidered this statement and concluded that such an association was statistically weak. Perls (1997) demonstrated that middle-aged mothers live longer based on the New England Centenarian Study. More recent investigations show divergent results with a positive relation between the number of children and the post-reproductive longevity of mothers found in the Utah Population Database, as well as a negative relation in the BALSAC database of Université du Québec à Chicoutimi (UQAC) and in the Registre du Québec Ancien of the Université de Montréal (Gagnon et al. 2009). Reviewing a large collection of research results, Helle et al. (2005) reached the conclusion that only 39% of investigations found a positive relationship as predicted by the theory of trade-off between reproduction and longevity (Westendorp and Kirkwood 1998). Thus the question is still pending.

More consistent results have been found by analyzing the impact of the timing of fertility on the post-reproductive longevity of mothers. In these analyses the age at delivery of the first and last children is usually considered but so is the mean inter-birth interval and the mean age of mothers at delivery. Concordant results emerged showing the positive effects of late maternity (Smith et al. 2002, Mueller 2004, Gagnon et al. 2009, Smith et al. 2009) while no consistent results were found concerning the impact of the age at birth of the first child (Helle et al. 2005).

From a different viewpoint, the role of the gender of children born to a given mother was put in evidence by Helle et al. (2002b, 2002c) who demonstrated that the number of sons is unfavorably linked to the post-reproductive survival of women in the Finnish Sami population. However, Beise and Voland (2002) put this finding into question while Jasienska et al. (2006) found, in a rural Polish population, that the negative effect of the number of children on maternal longevity does not differ between sons and daughters. Analyzing data extracted from Umeå University database on Swedish Sami population, Cesarini et al. (2009) concluded that their findings failed to replicate Helle's result while Pham-Kanter and Goldman (2012) report the opposite result. More recently Helle and Lummaa (2013) reacted to the debate by bringing stronger statistical evidence for their findings. Their last contribution confirms that sons are detrimental to their mothers but their data show that no effect is observed when the number of sons surviving to adulthood is considered. According to evidence, such results warrant further replication in other populations and new results are needed.

The aim of this contribution is to revisit the relationships between the fertility history of mothers and their post-reproductive longevity in a population of particular interest. The population under study is living in Sardinia, in a region where mothers born up to the beginning of the XXth century exhibited a natural fertility regime, a later maternity pattern and, more recently, increased longevity.

2. Underlying theories: a short review of the literature

Because reproduction has a cost and resources are limited, individual maintenance and survival can increase only at the expenses of reduced fertility. These theories postulate that biological aging is a mere side effect of the balance between reproduction and self-maintenance as a result of an evolutionary adaptation. As outlined first by Williams (1957), inherited traits having harmful effects later in life accumulate progressively in post-reproductive life as natural selection declines with age (Medawar 1952). In the disposable soma (DS) theory, proposed in the 1970s by Kirkwood and Holliday (1979) and developed later by Kirkwood and Rose (1991), the trade-off between fertility and longevity is more general and it emphasizes the homeostatic balance and the costs required for maintaining high fertility levels. This theory predicts that mothers who allocate their lifelong resources more to reproduction than self-maintenance may experience premature deterioration in bodily conditions, with a subsequent rise in the risk of morbidity and mortality. On the opposite side, any reduction in an individual's fertility may lead to increased longevity, as is evident for late motherhood. Attempts to substantiate this hypothesis in model organisms gave controversial results, with a positive association reported in some studies (Stearns and Partridge 2001) but not in others (Le Bourg et al. 1988, Flatt 2011, Khazaeli and Curtsinger 2011, Wit et al. 2013). In humans, however, the trade-off between fertility and longevity, although extensively investigated in historical (Korpelainen 2000; Penn and Smith 2007; Westendorp and Kirkwood 1998) as well as contemporary (Hurt et al. 2006) populations, has produced conflicting results (Le Bourg 2007; Tabatabaie et al 2011). In particular, it is difficult to separate the effect of genetic from non-genetic factors on fertility, due to within-family correlations of socio-cultural, economic, influencing reproductive capacities, and family sizes (Kosova et al 2010). The causes for the large variability in reproductive timing are complex (Griskevicius et al 2010) and include emerging factors, such as psychology, behavior, economics, sociology, and many others related to life trajectories. From an evolutionary perspective, it has been proposed that aging individuals maintain a "reproductive value" through non-reproductive means, i.e. investing their resources in existing offspring rather than increasing the number of descendants (Gurven and Kaplan 2007). Finally, the study of the relationship between reproduction and lifespan is further complicated by potential methodological drawbacks, as pointed out by several authors (Beise and Voland 2002; Jasienska 2009), such as population size and heterogeneity, inappropriate control group selection, the effect of secular trend, the historical context, differences in socio-economic status of study populations, and even incomplete data collection. Taking into account these considerations, any study of the relationship between fertility and lifespan should ideally be carried out in a population that is both under the natural fertility regime and characterized by highly reliable and exhaustive data.

3. The context and the choice of the population investigated

For a number of reasons, the population of Sardinia is an attractive subject for the study of possible interactions between the fertility history of mothers and their post-reproductive longevity; the in-land areas of the island are of particular interest:

(i) The fertility transition in Sardinia occurred very late and still in the 1950's, high level of marital fertility was recorded by researchers (Livi Bacci 1977, Bernardi and Oppo 2007). At that time, the province of Nuoro in the mountainous part of Sardinia showed the highest values for marital fertility among all Italian provinces.

(ii) Sardinia as whole, but more especially some in-land areas of the island mostly in the Nuoro province, were still recently characterized by late maternity (Astolfi et al. 2007, 2009).

(iii) Sardinia, and more specifically the Nuoro province, is also experiencing an extreme situation as far as the proportion of oldest olds and longevity are concerned. At the 1981 census, the Nuoro province presented the highest proportion of oldest olds (85+/60+), (Cantalini et al. 1990) and the highest male life expectancy (Salaris 2008). An area named *Longevity Blue Zone* composed of 15 municipalities located in the Ogliastra and the Nuoro provinces has been characterized by exceptionally high male longevity (Poulain et al. 2004).

(iv) Astolfi et al. (2007) suggested the existence of a possible relation between late maternity and higher longevity in Sardinia. Based on aggregated data on Sardinian municipalities, they observed that areas with persistent late maternity were also characterized by longer lifespans, suggesting that the extension of both the reproductive and post-reproductive period might be influenced by common determinants. More recently, Tentoni et al. (2011) argued that late maternity measured as the proportion of children born to mothers aged 35 years and older could be associated with a longer lifespan and correlated with the genetic structure of the local population. The similarity of the spatial patterns on maternal reproductive traits and longevity suggests the existence of this association at aggregated level in Sardinia and the Nuoro province was said to be a *candidate for studies on the association of the life longevity with reproductive longevity* (Astolfi et al. 2009). The *Longevity Blue Zone,* located in the same area, displays both the extremely late maternity and exceptional longevity; it accordingly represents the most interesting place for a more in-depth analysis of the relation between the two phenomena.

(v) More recently, Caselli et al. (2013) have investigated the relation between reproductive behavior of mothers and their longevity by considering Sardinian centenarians. Compared to women in the control group who died in their 60s and 70s, the preliminary results suggest that female centenarians seem to have fewer children on average, and apparently at an older age, particularly for their last child. These authors found that having a child at age 40 or older has a favorable effect on the mother's survival above age 80, while the total number of children, as well as the age at first childbirth, seem not to have a significant effect.

In the present study, we have selected the village of Villagrande Strisailli, which shows the highest value of the extreme longevity index of the *Longevity Blue Zone,* e.g. a larger proportion of newborns reaching age 100 compared to all other villages in Sardinia (Poulain et al. 2004).

4. Data used and methods

The village of Villagrande is located at 700 meters above sea level in the province of Ogliastra, but the altitude of its territory ranges from sea level to 1,834 meters at Punta La Marmora. On the 1st of January 2012, 3,373 inhabitants lived in Villagrande (ISTAT) where agro-pastoral activities and traditional life style are still prevalent. Despite the fact that until the 1960's this region was among the poorest within the island, recent economic developments brought the population of this area close to the average welfare standard of the Italian population.

Demographic genealogical data on the whole population of the village has been collected. The start and the end points of the database range from the beginning of the XIXth century up to 2013, as marked by earliest births, latest deaths and survival information included. For the purpose of this contribution, the families have been reconstructed for mothers born starting from 1815 until 1914. Data are based on parish records up to 1865 and on civil records starting from 1866 on. Civil records were satisfactory, crosschecked by information from parish records for the first decade of civil registration to ensure the exhaustive coverage of newborns at the beginning of the civil registration.

As mentioned by Van Poppel et al. (2012) in a population experiencing demographic transition, the relationships between fertility and mortality can be hard to follow and diverse results might appear due to the changes in both patterns. Particularly, with a declining average age at last childbirth in parallel to the decrease in mortality, the relationship between late maternity and longevity could be biased. The data presented in Table 1 show that the characteristics of fertility remain relatively stable for selected mothers born during the whole of the XIXth century and up until 1914, while the longevity of these mothers has continuously improved with a gain of about 15 years over a 100-year period. Accordingly, the population of mothers under study has been limited to the extinct birth cohorts 1815-1914 whose reproductive life occurred under a still prevailing natural fertility regime, and the birth cohort of mothers was included as a control covariate.

The total number of women born between 1815 and 1914 who had at least one child and all their children born in Villagrande was 927. The number of children born to these mothers was 5,320. Women born outside of the village as well as those whose exact date of death was unknown were excluded in this analysis. Notwithstanding, the completeness of death data was very high ensuring that 868 from the total number of 882 women born in Villagrande could be effectively included (98.4%). Among these, 193 women died before reaching age 50 and 675 survived above age 50. Finally, 136 women were excluded because their last husband died before the end of the fertility period of their wife, and 17 additional women because they had only one child. As a result of the described selection procedure, the final analysis includes 522 mothers born between 1815 and 1914 that had at least two children, were potentially childbearing during the complete fertility period and survived up to age 50. None of these mothers were surviving in June 2013. Their survival after age 50 has been investigated by considering various characteristics of their reproductive history. For a specific analysis on the impact of the gender of children, the female dataset was further limited to 485, having at least one boy and one girl.

We use survival analysis to assess the relative mortality risks of mothers in different generations associated with the characteristics of their reproduction history. The data were analyzed using the Statistical Package for Social Science (SPSS, version 16.0, Chicago, IL, USA). Total and partial bivariate Pearson correlation analysis was performed to assess any association between the quantitative variables. A series of multivariate Cox proportional hazard models were constructed with the women's age at death as the outcome variable. Hazard ratios (HRs) and their 95% confidence intervals were computed, and the Wald test was used or model testing. Kaplan–Meier (KM) curves were also plotted, and a log-rank test was performed to identify potential variables linked to the reproduction history of mothers that are capable of influencing their later survival.

5. Results

The outcome variable is the number of years spent after reaching 50 years of age. As mentioned above, in correspondence with mortality improvement, the mean survival of mothers above 50 improved largely for the successive generations of mothers with a linear increase of 15 years during a 100-year period from 1815 to 1914 (Table 1). Considering this linear trend, the year of birth of mothers has been included as a covariate to adjust for the improvement of survival of the successive generations of mothers. In addition to the years of birth of mother, the survival of a woman's last spouse after she reached the age of 50 was introduced in the analysis, as the survival of spouse is a well-known contributor to individual survival (Helle et al. 2005, Alter et al. 2007). Table 1 presents the mean values of the outcome variable and the different covariates per decade of birth of selected mothers (1815-1914).

The following covariates (all considered as continuous variables in the survival analysis) have been considered to describe the fertility history of mothers:

1. The number of deliveries
2. The age at first child
3. The age at last child
4. The mean age at delivery for each mother
5. The mean interval between successive deliveries
6. The number of sons
7. The number of daughters
8. The proportion of sons born (the number of sons divided by the total number of children).
9. The mean age of mothers at delivery of their sons
10. The mean age of mothers at delivery of their daughters.

The bivariate Pearson correlation between these variables, adjusted by the year of birth of the mother and the survival of her last spouse, are reported in Table 2. The variables showing the strongest correlations with the survival of women above 50 are the mean age at delivery (r = +0.117), the mean age at delivery of sons (+0.117) since no correlation is observed with daughters (+0.010), the age at last child (r = +0.094) and the age at first child (r = +0.091). The number of deliveries and the mean interval between successive births show a weak negative correlation with the survival of mothers, which is not is statistically significant.

Among the variables describing the fertility history of mothers, the age at the first child is weakly correlated with the age at last child (r = +0.164), which means that mothers starting their fertility history earlier do not stop it systematically earlier. The mean interval between successive births is correlated neither with the age at first child nor with the age at last child. The total number of deliveries is the most correlated trait with the age at first child, a factor that largely determines the number of children of a given mother.

Generally spoken all these variables are poorly correlated the results are significant only because of a large size of the database. Only a tiny part of the variance is explained as, for instance, r = 0.117 represents only 1% of the total variance.

Table 1. Descriptive statistics: mean values of the outcome variable and the different covariates per decade of birth of mothers selected in the analysis (1815-1914).

Decades of birth of mothers	***Number of mothers selected***	***Mean age at death of mothers surviving at 50***	***Mean number of deliveries per mother***	***Mean age at first child***	***Mean age at last child***	***Mean age at delivery (*)***	***Mean intergenesic interval (in years)***	***Proportion of sons***	***Mean survival of last spouse (**)***
1815-1834	**36**	**69.70**	**6.97**	**25.19**	**42.40**	**33.52**	**2.93**	**0.429**	**10.7**
1835-1844	**34**	**73.28**	**5.74**	**27.19**	**41.04**	**33.74**	**3.00**	**0.525**	**13.4**
1845-1854	**26**	**72.31**	**6.19**	**27.77**	**42.08**	**34.38**	**2.88**	**0.583**	**13.4**
1855-1864	**45**	**73.16**	**6.93**	**25.57**	**42.18**	**33.32**	**2.95**	**0.495**	**14.5**
1865-1874	**63**	**75.58**	**7.00**	**25.06**	**41.66**	**32.96**	**2.93**	**0.538**	**15.8**
1875-1884	**67**	**78.99**	**6.58**	**27.44**	**42.14**	**34.42**	**2.75**	**0.526**	**18.1**
1885-1894	**85**	**81.55**	**6.72**	**26.40**	**41.66**	**33.59**	**2.78**	**0.485**	**21.5**
1895-1904	**67**	**82.94**	**6.42**	**27.02**	**41.33**	**33.79**	**2.74**	**0.507**	**23.5**
1905-1914	**99**	**84.50**	**5.86**	**28.56**	**41.34**	**34.60**	**2.72**	**0.542**	**24.8**
1815-1914	**522**	**78.69**	**6.48**	**26.83**	**41.69**	**33.86**	***2.82***	***0.515***	***21.8***

(*) The number of deliveries considers the occurrence of multiple births

(**) The survival of the last spouse is considered starting when mother reaches 50 years of age.

In the survival analysis, all models include the year of birth of mothers and the number of years survived by the last spouse after woman reached age 50 years as control covariates. When each covariate is considered separately (Table 3), the mother's age at the birth of the first child and at the birth of the last child, as well as the mean age at deliveries, present a statistically significant with relative mortality risk, which suggests that the mortality risk decreases when these ages increase. In Model 1, the mother's age at first and last child as well as the mean interval between successive births were included, considering the limited correlation found between these variables. In Model 2, the mother's age at first and last child were replaced by the mean age at delivery. The results confirm that this covariate characterizing the timing of fertility shows a stronger association with the post-reproductive survival of the mother than the age at birth of the first and last child. A 3-year delay in the mean age at delivery is associated with a 10% reduction of the relative mortality risk above 50 years of age.

As far as the gender of children is concerned, in Model 3 we have included the proportion of sons born to a given mother with the mean age of women at delivery. The results suggest that having a higher proportion of sons is favorable for the post-reproductive survival of the mother but that effect is not statistically significant. To further test this hypothesis we built Model 4 with the number of sons and the number of daughters as covariates and find a stronger negative, but still not statistically significant effect, of the number of daughters on their mother's survival and no effect of sons.

Finally, considering that the mean age at childbearing has a stronger impact on the post-reproductive survival compared to the number of deliveries, we included the mean age at childbearing of sons and daughters as covariates in Model 5. Despite the fact that the gap between these mean ages is very small (33.68 versus 33.61), late delivery of sons has a statistically significant positive effect on the mother's survival even and no similar effect was found for daughters. To confirm this gender difference we compared KM survival curves related to mothers who delivered their sons before and after age 35 on average, and the same considering daughters (Figure 2). The results prove that having sons at above age 35 on average results in more than three years of advantage in terms of prolonged survival of mother after 50, while no significant impact was found in the case of daughters.

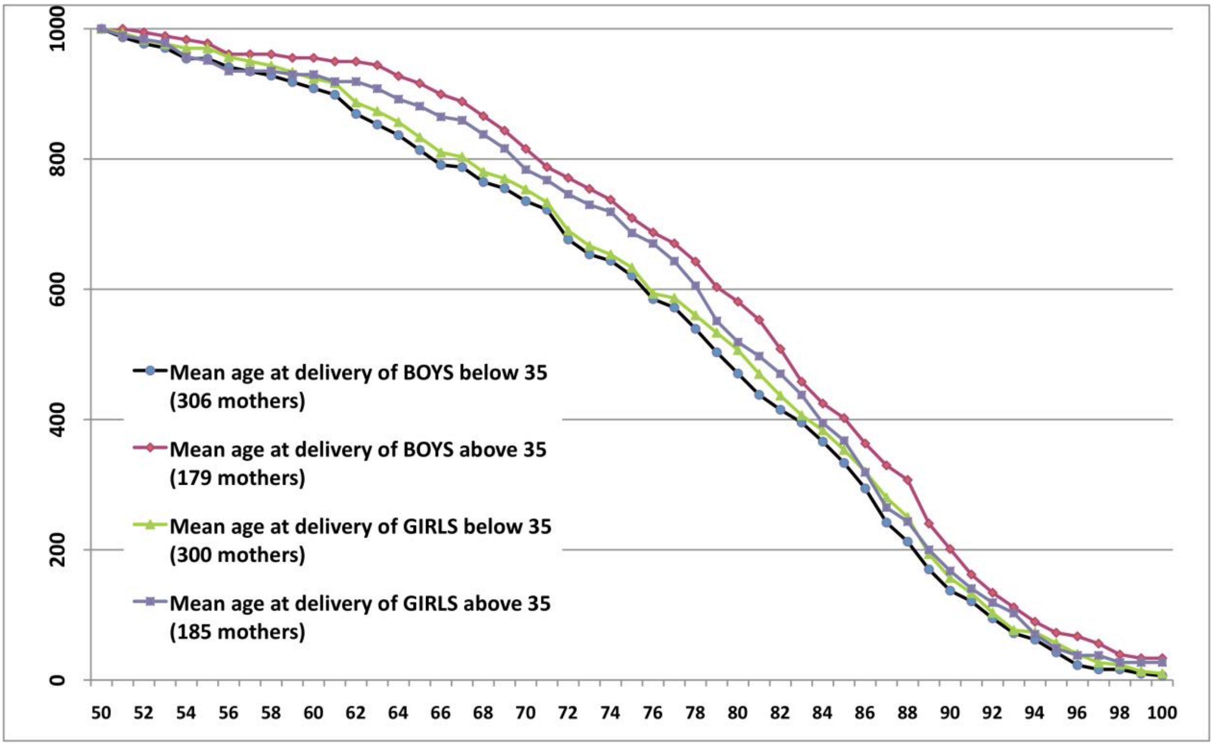
Table 2. Bivariate Pearson correlation between the outcome variable and selected covariates controlled by the year of birth of mothers and corresponding p-values.

	Number of deliveries	Age at first child	Age at last child	Mean age at delivery	Mean interval between successive deliveries	Proportion of boys among mother's children	Number of sons	Number of daughters	Mean age at delivery of sons	Mean age at delivery of daughters
Age at death of mothers	**-.029**	**.091**	**.094**	**.117**	**-.026**	**.028**	**.004**	**-.040**	**.117**	**.010**
	.515	***.037***	***.033***	***.008***	***.553***	***.518***	***.935***	***.375***	***.010***	***.827***
Number of deliveries		-.759	.351	-.466	-.330	.008	.719	.661	-.373	-.343
		.000	***.000***	***.000***	***.000***	***.856***	***.000***	***.000***	***.000***	***.000***
Age at first child			.164	.862	-.020	-.063	-.541	-.474	.744	.615
			.000	***.000***	***.653***	***.155***	***.000***	***.000***	***.000***	***.000***
Age at last child				.529	.040	-.024	.255	.238	.447	.401
				.000	***.369***	***.580***	***.000***	***.000***	***.000***	***.000***
Mean age at delivery					-.008	-.082	-.330	-.262	.797	.780
					.847	***.061***	***.000***	***.000***	***.000***	***.000***
Mean interval between successive deliveries						.139	-.225	-.280	-.012	.087
						.001	***.000***	***.000***	***.796***	***.056***
Proportion of boys among mother's children							.671	-.696	-.033	-.015
							.000	***.000***	***.475***	***.737***
Number of sons								-.023	-.272	-.257
								.612	***.000***	***.000***
Number of daughters									-.237	-.236
									.000	***.000***
Mean age at delivery of sons										.343
										.000

Table 3. Summary results of the survival analysis (the outcome variable is the age at death of mothers surviving at age 50)

Covariates (all continuous)	Each covariate separately	Model 1	Model 2	Model 3	Model 4	Model 5
522 mothers having at least two deliveries						
Age at first child	0.983*	0.985				
Age at last child	0.976	0.981				
Mean age at delivery	0.967**		0.969**	0.968**		
Number of deliveries	1.026					
Mean intergenesic interval	1.047	1.051	1.046			
Proportion of sons	0.738			0.729		
Number of sons	1.000				1.002	
Number of daughters	1.049				1.049	
485 mothers having at least one boy and one girl						
Mean age at delivery of boys	0.976*					0.974*
Mean age at delivery of girls	0.994					1.004
Control variables						
Year of birth of mother	0.983	0.983	0.983	0.983	0.983	0.983
Survival of last spouse	0.993	0.993	0.993	0.993	0.994	0.994

Figure 2. KM survival curves from 50 to 100 years by groups of mothers considering average age at delivery of boys and girls before or after age 35 years.



Mean age of mothers at birth of their sons (below of above age 35)	Mean survival above age 50	Mean age of mothers at birth of their daughters (below of above age 35)	Mean survival above age 50
< 35 (N = 306)	27,472	< 35 (N = 300)	28,350
> 35 (N = 179)	30,793	> 35 (N = 185)	29,251
Logrank = 0.005	+ 3, 321	Log rank : 0.546	+ 0.801

6. Discussion

The relationship between fertility and post-reproductive survival has long attracted the attention of researchers and has become the subject of intensive investigation. In this study we have analyzed the survival of women after age 50 in a homogeneous population characterized by a remarkably stable reproductive history over more than a century, and a 15% gain in lifespan during the same period. The overall aim of this study was to test the hypothesis that a longer post-reproductive survival is specifically associated with the ability to maintain reproductive capacity later in life.

6.1. Reproductive characteristics of Villagrande women

Compared with other populations investigated for the relationship between the fertility history of mothers and their post-reproductive longevity, the fertility of mothers in Villagrande shows levels similar to those observed in populations like the Finnish Sami (Table 4). Delayed childbearing ages have been found in both settings with a slightly higher parity in Villagrande, which could be the result of shorter birth intervals. The higher parity levels observed in North-American populations, as reported in the comparative analysis by Gagnon et al. (2009), are explained both by the earlier age at first child and shorter birth intervals. These comparisons indicate that the mothers in Villagrande followed a natural fertility regime far later than most Western European populations.

The fertility history of Villagrande mothers who had at least two children, whose husband had not died prematurely, and who survived past 50 years, can be characterized essentially by three basic variables. They are (i) the age at first birth, (ii), the age at last birth, and (iii) the mean interval between two successive live births. Comparing the range of variability of these three variables, two main findings have emerged, i.e. the intergenesic interval appears tightly compressed around the mean (2,82 years, 95% CI 2.75 – 2.88), and the variability of age at first birth (mean 26.8, 95% CI 26.3 – 27.3) is twice as wide as that of the age at last birth (mean 41.7, 95% CI 41.4 – 41.9). A weak but statistically significant direct relationship was detected between age at first and last birth (r = +0.164), whereas the correlation between age at first and last child and the average interval between successive births was not statistically significant (r= +0.040 and -0.020 respectively), likely due to the narrow range of variation of the latter variable.

These primary variables were used to create secondary (derived) variables such as the number of deliveries, or parity (mean 6.48 children, 95% CI 6.26 – 6.69), and the mean age at delivery (33.86 years, 95% CI 33.5 – 34.2). Taking into account the relative uniformity of the intergenesic interval, it is not surprising to find an inverse correlation between parity and the age at first birth, as well as a direct correlation between parity and age at last child (r = -0.829 and r = +0.416, respectively). Besides, the evidence of a significant inverse relationship between parity and the intergenesic interval (r = -0.330) indicates that the mothers with a smaller number of children were also those who experienced longer post-delivery intervals. In general, however, the relative uniformity of the intergenesic interval among Villagrande women suggests that extensive birth-spacing strategies for family limitation have hardly been adopted before the era of modern contraception.

Table 4. Comparison of the fertility characteristics in Villagrande compared to other populations where the relationship between fertility history and post-reproductive longevity has been investigated.

Reference	Selected mothers	Number of mothers	Mean Age at first child	Mean Age at last child	Mean age at childbearing	Number of children or deliveries	Mean intergenesic interval	Mean age at death of mothers
Old Quebec (Gagnon et al. 2009)	Mothers born 1599-1729	5,477	23.4	41.1	?	10.0	2.12	71.4
Saguenay (Gagnon et al. 2009)	Mothers born 1809-1869	1,610	23.5	41.5	?	9.8	2.15	74.4
Utah (Gagnon et al. 2009)	Mothers born 1753-1870	11,395	21.7	40.5	?	8.7	2.62	76.0
Sami (Finland) (Helle et al. 2005)	Mothers born 1679-1839	306	27.2	41.8	33.9	5.7	3.12	72.2
Sardinia (Caselli et al. 2013)	Female centenarians born 1895-1904	106	26.7	38.5	32.7	5.4	?	-
	Controls born 1895-1904	186	26.7	37.8/38.0	31.2/32.1	5.6	?	-
Villagrande	Mothers born 1815-1914	522	26.8	41.7	33.9	6.5	2.82	78.7

The fertility life of Villagrande mothers selected for this study could be summarized by saying that, owing to the relatively narrow variability of the age at last birth and intergenesic interval, the duration of reproductive life span, the parity, and the average age at delivery are largely determined by the age at first birth.

6.2. Impact of reproductive life of Villagrande mothers on their post-reproductive survival

This paper explores the impact on post-reproductive survival of mothers through their fertility history, by fitting Cox proportional hazards models with mother's age at death as the response variable. In the first step we considered each covariate, separately adjusting for mother's year of birth and (last) spouse survival. In line with earlier studies carried out in pre-industrial populations, the first selected predictor was **mothers' parity**. Cox regression shows that each additional child increases the hazard risk of death of 2.6% (HR = 1.026). However, as this finding is not statistically significant, it cannot be taken as supporting evidence for a detrimental effect of parity on a mother's overall life span, as reported earlier (Gagnon et al. 2005). It is rather more consistent with findings in historical Sami women (Helle et al. 2005) whose parity is much closer to that of Villagrande women than with populations of Quebec and Utah. Thus, the number of children appears to have a very limited role in the post-reproductive survival of Villagrande mothers.

The mother's **age at first child** is a significant predictor of post-reproductive life expectancy of women in the population under study. This result seems in contrast with the findings in the Old Quebec and Saguenay populations, where age at first birth is negatively correlated with mother's survival, whereas it is in accord with similar findings in the Utah and Sami populations. Considering that the ages at first child in the Sami population and in Villagrande are very similar (age 27.2 and 26.8 respectively) and are about 3 years later compared to the value recorded in the other historical populations, this finding may support the hypothesis that having first birth later indeed has a protective effect on a mother's late survival. This seems to be further confirmed by the significant correlation found in Villagrande between the age at first birth and mother's survival. Also, the **age at last child** was a positive predictor of survival, a finding consistent with data reported in other populations, including Sami, and fits well with the hypothesis that late motherhood may favor the survival of women beyond their reproductive age.

In a subsequent analysis, **both age at first and last birth** were imputed together as covariates in Cox regression (Model 1). Since they correlate only minimally with each other, the redundancy of their explanatory power is limited. Both variables display a not statistically significant, positive effect on post-reproductive survival of mothers (HR=0.985 and 0.981, respectively) when adjusting for the intergenesic interval. Accordingly, Villagrande women who had their children later in life experienced longer survival after age 50 than women who delivered their children earlier. The effect is stronger for the age at last birth, despite its lower statistical significance. Considering the wider variability of the age at first birth as compared to the age at last birth, as well as the limited correlation between these two variables, it can be postulated that a mother who begins her reproductive life earlier do not necessarily stop earlier and *vice versa*. Consistent with this hypothesis, the population of Villagrande mothers should actually be viewed as rather heterogeneous as far as their reproductive timing is concerned. However, when interpreting the effect of fertility timing on survival, two potential sources of bias should be taken into account. First, the exclusion of mothers who did not survive until age 50 may lead us to underestimate the impact of early motherhood, since the earlier the birth of first child takes place, the greater the cumulative risk of dying in childbirth before attaining age 50. Second, age at last child might be overestimated, since late motherhood obviously entails a higher risk of maternal mortality. To assess the impact of these possible confounding effects, we tested for differences of the average age at first and last child in all mothers and those selected for the study. No difference was found in the case of first birth (26.2 vs 26.8) while a 3-year difference was observed for last birth (38.6 vs 41.7). Although we are aware of the potential bias arising from these minor discrepancies, the strict selection criteria adopted in our study were considered necessary to ensure that the age at last child is determined by the end of the fertile period of the mother and is not affected by the premature death of the spouse. Besides, stringent selection criteria are usually applied in the majority of researches in this field. Overall, our results on the impact of late ages at first and last child confirm their favorable role for the survival of mothers reported in previous studies.

To overcome possible biases resulting from the variable gap between the ages at first and last child, we decided to replace these covariates in the model with an alternative variable i.e. the **mean age at delivery** (Model 2). We accurately verified that the assumption of linearity between this new variable and the response variable was not violated and imputed this variable in the regression models adjusting for the intergenesic interval. We find that the effect of the mean age at delivery on mother's survival is stronger than that found with ages at first and last birth taken separately: the hazard mortality risk decreases by 3.3% for each additional year (HR = 0.969; p = 0.008). As observed for parity, the mean age at delivery clearly displays a significant correlation with age at first (r = +0.862) and last child (r = +0.529). Indeed, it shows an inverse correlation with parity itself (r = -0.466). As far as we know, no previous study has considered this variable in relation with survival, with the exception of Caselli et al. (2013) who reported that, on average, Sardinian centenarians have an older age at delivery. Our findings are similar and confirm that mean age at delivery is a major predictor of late survival. This can be viewed as supporting the favorable effect of a *forward-shifted timing* of motherhood on late survival. Mean age at delivery might reflect the extent and direction of this shift better than the time at first or last child, thus displaying a much more powerful effect than the mere ages at first and last child.

Another point addressed in our study is how the differential cost of producing sons and daughters affects mother's survival. It has been suggested that it is more demanding for a mother producing sons than daughters in terms of energy cost. In order to compare with previous findings (Cesarini et al. 2009 ; Helle and Lummaa 2013) we tested the effect of the **number of sons and the number of daughters** on mother's survival and we found no effect of the number of sons and negative effect of the number of daughters but not statistically significant (HR = 1.002 and 1.049 respectively). These findings therefore suggest that producing sons and daughters has different consequences on mother's post-reproductive survival. However, we find that daughters are more unfavorable, a conclusion opposed to that provided by Helle et al. (2002a) and Helle and Lummaa (2013) in the historical Sami population where every new son shortened the post-reproductive lifespan of their mother, whereas producing daughters had the opposite effect. Our results suggest that male children may provide mothers with more benefits appearing later in their life. In Villagrande, a set of context-dependent conditions rooted in the socio-cultural background of the local population and in particular in its matrilocal character might explain this divergent finding. One may even speculate that this family system is highly male-biased since sons help strengthen their parents in everyday economic activity. Overall, we support the statement of Beise and Voland (2002) who explained that these gender effects *are modulated decisively by yet unknown factors, probably of a socio-cultural nature.* They considered that life-history studies of historical populations *although fruitful in many aspects, sometimes suffer from a lack of information concerning influential covariates*.

To investigate the role of children gender more deeply we tested the hypothesis that the gender ratio (M/F) among the offspring of mothers who died before age 50 should be more male-biased than for women who survived up to age 50. Instead, our data show that a reverse tendency, with 1.054 sons per daughter among women who died before age 50 versus 1.064 for those women who survived age 50. This difference, though not significant, suggests that producing more male children helps mothers to reach age 50, while the opposite was expected. Thereafter, we considered the **intergenesic interval** related to offspring gender to assess whether male children extend the birth spacing more than females or not. Concretely, when we tested for the difference between the intervals preceding the birth of sons and daughters separately, only a positive difference as short as 10 days was found in favor of sons. This suggests that the women's average physiological status before conception has no substantial effect on the gender of the next child. In addition, the interval following a birth is totally independent on the child's gender, which is in contrast with the hypothesis of a male-biased superior investment (e.g. related to breastfeeding). Furthermore, when the **proportion of sons** was imputed into the survival analysis as a covariate, a higher proportion of male children appeared to increase the likelihood of the mother to survive past age 50 (HR= 0.738) although with no statistical significance. Finally, the **mean age at birth of sons** (HR: 0.974, p

= 0.029) tends to have a greater impact on long-term survival of mothers than the average age at birth of daughters (HR: 1,004, p = 0.746) what is confirmed by the comparison of the KM survival curves of mothers who delivered their sons or daughters before or after age 35 on average. This finding reinforces the previous results and supports the idea that a larger number of sons born from aged mothers might be an important resource for their late survival and does not show negative consequences on a mother's post-reproductive survival as found by Helle and Lummaa (2013). Thus, the gender-specific costs of reproduction for maternal longevity may not only be related to biological factors but also to socio-cultural ones explaining why mothers benefit from their sons later in their life.

6.3. Implications in the light of underlying theories

The results obtained in our study should be "interpreted" in the framework provided by current theories on aging. The first theoretical implication is related to the age at first birth. The so-called *disposable soma* (DS) theory states that if parents invest their resources early in reproduction, they must sustain a certain "cost" that can lead to a shorter life expectancy. In the case of Villagrande, it is evident that our findings are not in contrast with this theory: we have found that mothers who started their reproductive life earlier did also show a significantly worse survival record above age 50. In general, the more a mother delays her reproductive life, the more her survival is improved. Age at first birth is tightly linked to the age at marriage, thus any in-depth analysis of the factors modulating the inter-individual variability of this parameter is welcome. It is possible that some context-dependent socio-cultural factors deserving further investigation may be responsible for women marrying earlier or later, and that the same factors may affect their lifespan. Accordingly, the relationship found in our study between age at first child and mother's survival may not necessarily be due to a biological mechanism predicted by the DS theory but, more simply, the result of a selection process acting upon the age at marriage and likely related to socio-cultural and anthropological factors.

The role of age at last child on survival is usually explained by assuming that it is a proxy of age at natural menopause. Despite contrasting reports in literature, the overall trend tends to support a link between late menopause and longer survival (Yonker et al. 2011). In the case of Villagrande, mother's age at last birth is distributed as a rather narrow gaussian curve, so that up to 69% of mothers selected (361) had their last child between 39 and 44 years of age. Unfortunately, under these conditions it is quite difficult to establish a statistically meaningful relationship between age at last child and survival.

Aside from the effect of maternal age at birth of first and last child, the existence of a potential "trade-off" between reproduction and survival should be tested considering the rather uniform intergenesic interval as well as the influence of child gender. In Villagrande, the reproductive life of mothers does not seem to decisively support the existence of such a "trade-off". Having the last child later may be associated with more success by the mother in keeping most of her soma resources, and in turn this may explain her better survival. It is obvious that mothers of the same chronological age, but who have the possibility to reproduce later, may bear a lighter burden as the residual soma is large enough to optimize its maintenance. In the current state of knowledge, variability of age at natural menopause is the favorite biological explanation, although many other non-biological factors could determine the end of reproductive life as well (voluntary decision to stop having children, nutritional constraints and other factors).

Giving birth to many male children is often considered to be highly demanding and conducive to exhaustion of soma resources, therefore it is expected to compromise longevity of mothers. In addition, although energy costs of pregnancy and lactation would apparently be heavier for sons than for daughters actually, both are "expensive" *per se* in terms of physiological costs, whereas the gender of child is involved only marginally. From a different perspective, having more boys than girls may be a sign that the soma resources of the mother were constitutively stronger and may consequently increase the chance of attaining longevity. We suspect that the modest survival advantage observed among mothers who had more sons than daughters would not be linked to any differential reproductive cost related to the child gender (an hypothesis not strongly supported by evidence), but rather attributable to long-term benefits of male children on the overall life of the mother.

The investigation carried out in this study has certain **strengths and limitations**. First, in our study a set of stringent selection criteria have been adopted purposely, thus reducing the number of women eligible for the analysis to nearly 50% as compared to their original number. This restriction is comparable to that adopted in the ancient Québec and Saguenay studies, whereas is lacking in the Utah study. Most studies do not even report the number of mothers before selection whereas this was a major concern in our study. As pointed out by Gavrilova and Gavrilov (2005), this research field requires extremely careful data handling (data quality control and adjustment for important predictor variables). Second, the population selected in this study displays a remarkable ethnic and socio-cultural homogeneity, hardly found elsewhere, as well as a reproductive history very stable over more than a century, which contributes to reducing the confounding effect of changes in the reproductive pattern. Third, the Villagrande population has a well-documented history of longevity that may help to highlight important relationships between fertility and longevity, although the size of our population similar to the one studied by Helle and Lummaa (2013) is smaller than that of the historical populations studied previously in North America, which may entail a small risk of false positive results. Moreover, the influence of biological factors on the age at first childbirth may hypothetically depend on several socio-cultural factors specific to the population in concern. In particular, the number and gender of children already born and surviving may be a crucial factor for their mother’s survival, but even so, this potential relationship has been much less investigated and deserves to be further analyzed by means of anthropological surveys. In any case, both biological and socio-cultural components are interacting with each other and it is *a priori* difficult to weigh their relative roles. We support the statement of Le Bourg (2007) claiming that *the relationship between fertility and longevity, when it does exist, is more dependent upon the specificity of the population under study than on a general mechanism linking these variables*.

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