Exploring Sardinian Longevity and its Association with Reproductive Behaviors and Infant Mortality

Graziella Caselli¹, Rosa Maria Lipsi², Enrica Lapucci¹, James W. Vaupel³

Abstract

This paper aims at investigating the interaction between longevity and Fertility, and longevity and infant mortality. Research questions are: has fertility a protective effect on maternal survival at advanced ages? Have long-lived women been doubly favored, due to their lower fertility being distributed over a greater proportion of their fertility period? And, at the same time, is maternal longevity associated with lower infant mortality in her offspring? The wealth of information gathered in the AKeA2 survey, concerning family genealogies of the Sardinian centenarians and control groups have been used to study various hypotheses about longevity by applying a Logistic Regression Model and a Logistic Random-Intercept Model. As regards the first interaction, long-lived women having had the last child at advanced ages (e.g. 45 years or more) shows a protective effect on mother's survival. With respect to the relationship between longevity and infant mortality, the most interesting result concerns the significantly lower mortality in the first year of life among children of centenarian women.

¹Sapienza University of Rome, Department of Statistical Sciences, Italy.

²National Institute of Statistics (ISTAT), Italy.

³Max Planck Institute for Demographic Research, Rostock, Germany.

Corresponding author: Graziella Caselli; e-mail: graziella.caselli@uniroma1.it

1. Background and Research Questions

The relationship between longevity and fertility has been tackled in various articles (Behr and Small 1997; Westendorp and Kirkwood 1998; Vinogradov 1998; Lycett et al. 2000; Doblhammer 2000; Müller et al. 2002; Doblhammer and Oeppen 2003; Yi and Vaupel 2004; Larke and Crews 2006; McArdle et al. 2006). The main results showed that women who live longer seem, on average, to have fewer children, at an apparently older age, particularly for their last children. Nevertheless, only a few of the previous studies have focused on centenarians, and here lies the novelty of our study.

The disposable soma theory on the evolution of ageing states that longevity requires investments in somatic maintenance that reduce the available resources for reproduction (Westendorp and Kirkwood, 1998). As Westendorp and Kirkwood (1998, abstract) demonstrated, "when account was taken only of women who had reached menopause, who were aged 60 years and over, female longevity was negatively correlated with number of progeny and positively correlated with age at first childbirth." The authors emphasize the importance of analyzing the effect of fertility behavior on longevity in post-reproductive ages.

Evolutionary ageing theory predicts that because ageing is a consequence of a trade-off between longevity and reproduction, the age at which organisms begin to reproduce should be positively correlated with maximum longevity, meaning that the driving selective force in the human lifespan is maximizing the period of time during which women can bear children (Hamilton 1966; Charlesworth and Charlesworth 1980; Kirkwood and Rose 1991; Vaupel et al. 1998). In terms of evolutionary fitness, natural selection is expected to favor high fertility, early age at first reproduction, and late age at last births. However, its role is largely influenced by several factors, such as maternal well-being and health status, biological and genetic characteristics, familial wealth and socio-economic level. Recently, Doblhammer (2000), used population data from Austria, England and Wales to find a positive relationship between giving birth after age 40 and longevity, which is consistent with the findings of previous studies (Voland and Engel 1986; Snowdon et al. 1989; Perls et al. 1997; Cooper and Sandler 1998; Müller et al. 2002; McHardle et al. 2006). In addition, her results suggest that the longevity advantage of late mothers depends on a reduction in their mortality risk from circulatory diseases, although at the same time their risk of breast cancer is significantly increased (Doblhammer and Vaupel 1998).

The postponement of reproduction is a widespread characteristic in the recent and past Sardinian population. The geographical pattern of late maternity in Sardinia in the last 20 years of the twentieth century (Astolfi et al. 2009, Tentoni et al 2012) was significantly similar to the geography of longevity, characterized by the presence of a large number of centenarians (Wagner 1950; Contini et al. 1989; Deiana et al. 1999; Poulain et al. 2004; Caselli at al. 2006). The Astolfi et al. study (2009) of Sardinian women in reproductive age showed that late maternity is relatively common and perinatal and infant mortality is relatively unusual. Furthermore, the age of Sardinian mothers at birth does not significantly increase neonatal and infant mortality.

The association between women longevity and infant mortality of their offspring has never been studied.

It is well known that childbearing and neonatal mortality are generally affected by the mother's age at birth or by the birth order of the child (Nault et al., 1990; Dollberg et al., 1996; Astolfi et al., 2002; Joseph et al. 2005; Astolfi et al., 2009 ; Tentoni et al., 2012). Until the first World War, Sardinia had the lowest infant (and especially neonatal) mortality rates recorded in Italy and stillbirth rates lower than the national average (Pozzi, 2000) even though the maternal mean age at birth was particularly high (Caselli et al., 2006).

In a descriptive analysis of data coming from the Sardinian AKeA2^{*} survey, a lower number of deaths in the first year of life was observed among the children of those who survived to become centenarians. For centenarian women, 78 out of 1000 infants died. In contrast, for the controls in the same cohorts as the centenarians, but who died in their 60s or 70s, the death rate of their infant children was 118-172 per thousand (Lipsi et al., 2012). Mothers who became centenarians also suffered a lower death rate among their infant children than did women born in later cohorts, even though infant mortality overall was lower in these later cohorts. In Sardinia as a whole, infant mortality in the period 1925-1930, which roughly coincides with the mean age when centenarians had their children, was 100-105 per thousand (Breschi et al., 2008).

^{*} AKeA2 is the acronym of the survey on Sardinian Centenarians, directed by James Vaupel, Max Planck Institute for Demographic Research, Rostock, Germany (financed by NIA, US, subcontract with Duke University n.03-SC-NIH-1027). The survey follows a previous research project on Sardinian centenarians, named AKeA.

Research Group: Luca Deiana, University of Sassari, Department of Biochemistry; Giovannella Baggio, City Hospital of Padua; Ciriaco Carru, University of Sassari, Department of Biochemistry; Graziella Caselli, Sapienza, University of Rome; Claudio Franceschi, Department of Experimental Pathology, University of Bologna; Gianni Pes, University of Sassari, Department of Biochemistry; Lucia Pozzi, University of Sassari, Department of Business and Economics; James W. Vaupel, Max Plank Institute for Demographic Research, Rostock

The aim of this paper is to analyze the two-way interaction between fertility and longevity, and longevity and infant mortality. In particular, our research questions are: has fertility a protective effect on maternal survival at advanced ages? Have long-lived women been doubly favored, due to their lower fertility being distributed over a greater proportion of their fertility period? And, at the same time, is maternal longevity associated with lower infant mortality in her offspring?

The wealth of information gathered in the AKeA2 demographic survey (Caselli et al. 2006; Lipsi et al 2012) focuses particularly on data collection concerning family genealogies of the Sardinian centenarians and control groups.

2. Data and Methods

In the AKeA2 survey, 204 centenarians born between 1890 and 1904 (98 men and 106 women), were picked in 126 municipalities out of the 377 Sardinian municipalities throughout the island. Once the centenarian's consensus was obtained, the local municipal authorities were contacted and a list of individuals (living controls) was requested. From this list, 3 matched individuals for each centenarian born in 1905-1910, 1911-1916 and 1918-1925, and who were aged 80-99 years at the beginning of our study in 2004, were selected. A demographic survey was performed that also involved an additional 2 individuals for each centenarian from the same cohort who died in their late 60s (60-69 years) and late 70s (70-79 years) (dead controls). All the controls were of the same gender as the centenarian, born and still living in the same municipality, and their day and/or month of birth were as close as possible to that of the centenarian (for more information, see Caselli et al. 2006; Lipsi et al. 2012). Individual controls with the same family name were excluded to avoid excessive consanguinity.

To validate the individual's age, the following documents from civil and population registers were examined: birth certificate, marriage certificate(s), the birth certificate of parents as well as their marriage and death certificates, the birth certificates of all children of the sampled individual, and the birth certificates of the individual's siblings. Complete validation was achieved only when the data had been cross-checked and proven consistent.

By applying the validation procedure, genealogies were reconstructed for 1,145 individuals: 204 centenarians, 581 living controls (we were unable to find 31 suitable controls in a few of the smaller municipalities), and 360 dead controls (in some of the smaller

municipalities 48 appropriate persons could not be identified). For each individual we reconstructed his/her life history (Caselli et al. 2006).

Full information (100%) is available for all individuals – centenarians and controls– regarding year and place of birth, date and place of death (if dead), sex of children, and date of death for all dead children. We have 90%-95% of completeness for all other demographic characteristics used in the analysis (Lipsi et al., 2012). Among the 20 demographic information available, for the purpose of this study, we considered, for centenarians and controls women, the following variables: date of birth; date of death; place of birth; number and date of birth of their children; number of siblings and their birth order; date of deaths of their children dead from 0 to 1 years; paternal and maternal age at birth of centenarian and controls.

For each individual in our sample we also collected information on his/her educational level and socio-professional condition in active age. Unfortunately, it was not possible to include the variable of education in our analysis due to the great number of missing data and very low variability in educational characteristics (75.7% of people with available information made no declaration concerning education). For socio-professional condition, all centenarian and live controls women, except one who is a nun, were listed as "housewives". Of course, this information is not available for dead controls.

We implemented a Logistic Regression Model in order to investigate the relationship between fertility and longevity (Harell 2001).

Regarding this aim (i.e. fertility and longevity relationship), for the reference population we included all women with at least one child (N =258) by comparing those who survived after age 80 with those who died between age 60 and 80. We define long-lived as individuals who survive after age 80, based on a previous descriptive analysis of the association between fertility and longevity (Lipsi et al. 2012. See Table 1). In our model, we consider two different dimensions of female fertility: Number of offspring and Timing of reproduction (e.g., age at first child and age at last child). The results were controlled for both parents' longevity and the birth order of centenarian and controls, i.e. factors that can affect the probability of becoming centenarian.

In order to investigate the relationship between longevity and infant mortality we used both a Logistic Regression Model and a Logistic Random-Intercept Model (Harell, 2001; Goldstein, 2003; Twisk, 2006), the latter serving to take into account the fact that children belonging to the same mother could have experienced a similar risk of dying. In fact, the observed deaths between 0-1 years could be influenced by the presence of some mothers with more than one child who died in the first year of life ("cluster" effect). In our sample, considering the distribution of women by number of dead children, a significant proportion (15.5%) of sampled women reported two or more dead children at age 0-1 and they contribute to more than 60% of 263 observed deaths.

In both models the response variable is equal to one if the child died at age 0-1 and zero otherwise. The risk of dying was compared among children (N=2000) of centenarian women and of two other groups of women, namely those belonging to the same cohort as centenarians who died between 60 and 79 years of age, and those belonging to younger cohorts and aged between 80 and 95 years, i.e. contemporaneous to centenarians (Mothers =398).

The results were controlled for birth order and parents' age at the birth of each child, and number of children/siblings; and province and altitude of the mother's place of birth. The latter are characteristics that the literature suggests may influence both longevity and infant mortality (Caselli and Lipsi, 2006; Breschi at al., 2008; Astolfi et al., 2009; Tentoni et al., 2012).

3. Results

3.1 Longevity and Fertility

Table 1 reports the results of the relationship between longevity and fertility, considering the two dimensions of fertility: number of children, and timing of reproduction. First of all, we found no significant effect of the first dimension (number of children) on the probability of survival after age 80. Nor does age at first child have any significance. Nevertheless, having the last child at an advanced age shows a protective effect on the mother's survival (mothers who had their last child at age 45 and over show a probability of becoming long-lived women more than 3 times higher than mothers who had their last child at 32-44 years). Our results seem to be in line with the hypothesis of a positive association between the presence of young children at old ages of the mother (i.e. late timing of the last birth) and increased longevity. The results are also consistent after controlling by maternal and paternal longevity; in particular women having a mother who died at oldest ages are advantaged in terms of life span.

Table 1

3.2 Longevity and Infant Mortality

As regard to the relationships between longevity and infant mortality, the most important result concerns the lower risk of dying at age 0-1 among children of centenarian women compared to children of a mother of the same cohort of centenarians who died between 60-79 years (Table 2).

According to the most relevant literature (Nault et al., 1990; Dollberg et al., 1996; Joseph et al., 2005), the risk of dying in the first year of life increases with the number of children per women, even if the first-order child tends to experience a higher risk than the next orders. By contrast, maternal age at birth has no significant effect, as Astolfi et al. (2009) have pointed out in analyzing more recent Sardinian data. Moreover, as we said, this last study identifies some hill and mountain areas of the island with a higher proportion of centenarians and where a higher proportion of mothers show an aptitude to late childbearing at lower cost in terms of progeny infant survival (lower risk of dying). In accordance with these results, our analysis finds a greater risk of dying at age 0-1 among children of mothers born and living in plain areas where malaria was still endemic (Brown, 1981, 1986). In fact, right up to the 1950s (malaria was eradicated in Sardinia in the years following the Second World War), in highly endemic areas the intense transmission of malaria caused frequent infant mortality although the genetic mutation associated with malaria seems to play a positive role on longevity for more selected people (Zei et al., 199; Kosoy et al., 2011).

Table 2

Looking at the results of the Logistic Random Intercept model, the hypothesis that mothers who experience the death of more than 1 child may affect the infant mortality of our sample seems to be confirmed (Table 3): accounting for 11% of the total variance (see the Intra-class correlation ρ), the group level effect proves to be significant – though low – in explaining the risk of dying between 0-1 year.

Nevertheless, even after controlling for the "cluster" effect, the children of centenarian women continue to have a lower risk of dying at ages 0-1 than children of mothers of the same cohort as the centenarians, but who died between 60-79 years. The direction and magnitude of all other determinants are also confirmed.

Table 3

4. Conclusion and Discussion

The research questions about the relationship between longevity and fertility were: *has fertility a protective effect on maternal survival at advanced ages? Have long-lived women been doubly favored, due to their lower fertility being distributed over a greater proportion of their fertility period?*

As we said, our Sardinian analysis found no relationship between longevity and number of offspring, or for age at first birth. These results are not in accordance with some previous studies (Kirkwood and Rose 1991; Westendropand and Kirkwood 1998; Lycett et al. 2000). Nevertheless, having had the last child at advanced ages shows a protective effect on the mother's survival. Our results are consistent with other previous studies (Voland and Engel 1986, Perls et al. 1997, Doblhammer 2000; Yi and Vaupel 2004) which have supply an extensively discussion on the possible explanation. Some studies emphasize the role of biogenetic factors while other stress socio-economic and cultural determinants. Doblhammer (2000) suggest that certain longevity genes may extend both the childbearing period and the longevity of individual women, and Yi and Vaupel (2004, 19) noted that giving birth at advanced ages could be related to a positive effect of a late menopause. However, for Doblhammer (2000, 175) "an extended period of childbearing and child rising could be associated with healthy behavior. Thus, late mothers may indeed experience menopause at a later age than that of young mothers but this could be due to healthy behavior rather than to a lower rate of ageing". Doblhammer's study contains a long discussion of the impact of socioeconomic factors.

On the same topic, Müller et al (2002) proposed another interesting explanation: "it is plausible that extended longevity confers a selective evolutionary advantage to women who have had children later in life". In particular, they suggested that the "presence of a young child at oldest ages has a life-prolonging effect on the mother because of their role of care-givers. [...]. According to the latter, as long as mothers are required as care-givers, post-reproductive ageing needs to be held at bay. This role of care-giver tends, in other terms, to positively select mothers in terms of longevity. In this framework, late childbirth can be considered as a longevity-assurance factor". In the Sardinian context, the care-giver hypothesis can be extended by assuming the last child as care-giver. A late fertility mother has the possibility, not only of taking care of her last child at advanced ages but also of receiving care from her last adult young child when she becomes an oldest-old. In this way a care-giving child can guarantee the mother both a better quality of life and a prolonged life.

In fact, interviewing the oldest old in the AKeA2 survey, we observed that the majority of centenarians lived in the last child's family, usually with their last daughter. In Sardinia, the elderly generally lived at home (only 1% of the total population of the elderly aged 65 and over live in institutions - Istat, database 2004).

Other contextual and genetic Sardinian traits, which differ from continental Italy as well as from other European countries, may explain the founding association between longevity and fertility. Regarding the socio-economic and demographic context, Sardinia is characterized by the patriarchal structure of the family and a sheep-rearing economy, by the historical characteristics of high and late fertility, the persisting tendency to postpone marriage and childbearing (Livi Bacci 1977; Zei et al. 1990; Astolfi et al. 2002) and, last but not least, the high rate of exceptional longevity in internal/mountain areas (Poulain 2004; Caselli and Lipsi 2006; Caselli et al. 2006). Genetic peculiarities of internal areas of Sardinia, such as the high frequency of ancient genetic markers of mitochondrial and Y chromosomes, might derive from the action of micro-evolutionary forces on isolated populations (Cavalli-Sforza et al., 1994; Zei et al., 2003; Carru et al., 2003; Scola et al., 2004; Astolfi et al., 2009). The consequent genetic makeup is also partially determined by endemic malaria in the past (Modiano et al., 1986; Caglia et al, 1997). The AkeA researchers found that the gene pool in the Sardinians of this particular remote mountainous region is relatively small. For example, the local people have small red blood cells which is thought to protect them against malaria and help prevent blood clots (Kosoy et al., 2011). Among these distinctive traits, we can include low immigration rates (Golini 1967). Historically, Sardinians have ensured the continuation of their way of life as a means of protecting themselves from the constant invaders coming in from the sea and wanting a slice of this wild and beautiful island.

Looking at the main features of the Sardinian population, the association between longevity and late fertility can be explained by a combination of both genetic factors and socio-economic and cultural determinants (Caselli et al, 2012).

The third research question was: *is maternal longevity associated with lower infant mortality in her offspring*?

Controlling by fertility characteristics and other contextual variables our analysis confirms the results of previous descriptive studies (Lipsi et al, 2012), showing, as we said, significantly lower infant mortality among the children of the Sardinians who survived to become centenarians. In particular, the children born to those women belonging to the same cohorts as the centenarians, but who died before 80 years old, experienced a higher risk of infant mortality than our centenarian women. The fact that significant differences in infant

mortality are found only for these ancient cohorts is very important for two reasons. First of all, because, by comparing the same cohorts, we can conjecture that the differences observed do not depend on a different infant deaths data quality and in particular on a different attitude to registering a birth following an immediate decease. The criterion of "legal vitality" had been in force in Italy from the end of the XIX century down to 1970. Newborn babies were regarded as living if they gave signs of viability up to the moment of being registered (to be done within 5 days of birth). Those who died before being registered were to be regarded as still born babies from a legal point of view and, consequently, were often not even registered. While the oldest cohorts (the centenarians) may well have been less sensitive to the question of registering the birth and death of their children than the younger cohorts (living controls), leading to a possible underestimate of the infant mortality of their children, it is unlikely that these underestimates discriminated between individuals who became centenarians and those of the same cohort who died before reaching 80 years.

Secondly, our result is important because it raises many questions about the potential determinants affecting the lower mortality of the children born to our centenarian women .

Is it possible that the genes favoring an individual's longevity may transmit also robustness to their progeny? And again, can territorial characteristics that favor the longevity of individuals also have a positive impact on the infant survival of their children?

In order to evaluate possible protective genetic factors available at territorial level, Astolfi et al. (2009) estimated in Sardinia, for the period 1850-1969, the consanguinity level by the percentage of consanguineous marriages and the average inbreeding coefficients (Moroni et al., 1972 ; Cavalli-Sforza et al., 2004). Both estimates presented higher values in internal/mountain areas, where the presence of centenarians was higher (Poulain et al. 2004). They suggested an association between the propensity to marry within the same familial group and the aptitude to late and successful maternity. Moreover, the other contextual and genetic Sardinian traits, previously discussed, may explain the underlying association.

The present study finds that a higher age for the mother's at final birth is not a discriminating factor for infant mortality (Table 2 and 3) and, in addition, that infant mortality in Sardinia is higher in plain areas (Table 2) than in the mountain areas where our centenarians mainly come from.

For a more accurate interpretation of the observed differences in infant mortality, it would be important to measure the evolution of the risk of death in specific stages during the first year of life, distinguishing in particular the early neonatal mortality rates which are more influenced by genetic factors as well as by maternal health. This future analysis would give more support to the hypothesis of the existence of biological and genetic factors that could favor both women's longevity and the lowest infant mortality rates of their children.

Other explanations could be proposed. Might the socio-economic and cultural factors that are behind the longevity of centenarians be partly the same as those protecting their offspring? Most certainly. Theoretically, a woman who protects her own health and survival by her behavior will also protect the health of her offspring, both directly (as she is in a better state of health at the time of childbearing) and indirectly (as she is more careful of her children's health). Practically, Sardinian centenarian women and their controls are an exceptionally homogenous group in terms of occupational and educational status: they were housewives whose education was either non-existent or went no further than primary school. The sociooccupational status of their husbands is unknown, but the men in ancient cohorts were usually either peasants or shepherds, following an age-old tradition handed down from parent to child. In view of the role the socio-occupational and educational factors plays in infant mortality studies, these are not discriminatory factors in our study of Sardinian centenarians.

Probably, the women feeding habits and the familial conditions are represented by other factors not identified in our survey, e.g. just as being or not being the owner of a flock could be a discriminant condition between rich and poor individuals.

In conclusion, as longevity, reproductive behavior and infant mortality, broadly speaking, are the outcome of various factors of a genetic or external nature, we suggest, like Astolfi et al. (2009), that Sardinia might be a candidate for in-depth studies on the association of longevity with reproductive longevity, including the positive infant survival of the offspring of longevous women.

References

- Abbott, M.H., Murphy, E.A., Bolling, D.R., Abbey, H. 1974. The familial component in longevity. A study of offspring of nonagenarians. II. Preliminary analysis of the completed study. *Hopkins Med. J.*, 134: 1-16.
- Abbott, M.H., Abbey, H., Bolting, D.R., Murphy, E.A., 1978. The familial component in longevity: A study of offspring of nonagenarians III. Intrafamilial studies. *American Journal of Medical Genetics*, 2, 105-120
- Astolfi, P., Caselli, G., Fiorani, O., Lipsi, R.M., Lisa, A., Tentoni, S., 2009. Late reproduction behaviour in Sardinia: spatial analysis suggests local aptitude towards reproductive longevity. *Evolution and Human Behavior*, 30: 93–102.

- Astolfi, P., Ulizzi, L., Zonta, L., 2002. Trends in childbearing and stillbirth risk: heterogeneity among Italian regions. *Human Biology*, 74 (2): 185-196.
- Behr, M.A., Small, P.M., 1997. Middle-age mothers live longer. Nature, 389: 133-134.
- Breschi M., Mazzoni S., Melis P.M, Pozzi L., 2007. Nuove indagini per l'analisi della mortalità nei primi anni di vita in Sardegna, in M. Breschi and L. Pozzi L. (eds), Salute, malattia e sopravvivenza in Italia fra '800 e '900, FORUM, Udine, 195-220.
- Brown P.J., 1981. New considerations on the distribution of malaria, thalassaemia amd glucose-6-phosphate dehydrogenase deficiency in Sardinia, *Human Biology*, 53, 367-382
- Brown P.J., 1986. Cultural and Genetic Adaptations to Malaria; Problems of Comparison, *Human Ecology*, 14(1) 311-332.
- Caglia A., Novelletto A., Dobosz M., Malaspina P., Ciminelli B.M., Pascali, V.L. 1997. Ychromosome STR loci in Sardinia and continental Italy reveal islander-specifi c haplotypes. *Eur. J. Hum. Genet*, 5:288–292.
- Caselli G., Lipsi, R.M., Lapucci E., Vaupel, J.W., 2012. Exploring Sardinia Longevity: Fertility and Parental Longevity. Presented at the International Conference on Determinants of Unusual and Differential Longevity. Wien, 21-23 November 2012.
- Caselli, G., Lipsi, R.M., 2006. Survival differences among the oldest old in Sardinia: who, what, where, and why? *Demographic Research*, 14: 267-294.
- Caselli, G., Pozzi, L., Vaupel, J.W., Deiana, L., Pes, G., Carru, C., Franceschi, C., Baggio, G., 2006. Family clustering in Sardinian longevity: A genealogical approach. *Experimental Gerontology*, 41(8):727-736.
- Cavalli-Sforza, L.L., Menozzi, P., Piazza, A., 1994. The history and geography of human genes. Princeton University, Princeton NJ, USA.
- Cavalli-Sforza, L. L., Moroni, A., Zei, G., 2004. Consanguinity, inbreeding, and genetic drift in Italy. In S. A. Levin, & H. S. Horn (Eds.), *Monographs in Population Biology*. Princeton University Press: Princeton and Oxford.
- Carru, C., Pes, G.M., Deiana, L., Baggio, G., Franceschi, C., Lio, D., Balistreri, C.R., Candore, G., Colonna-Romano, G., Caruso, C., 2003. Association between the HFE mutations and longevity: a study in Sardinian population. *Mechanisms of Ageing and Development*, 4(4): 529-32.
- Charlesworth, D., Charlesworth, B., 1980. Sex differences in fitness and selection for centric fusions between sex-chromosomes and autosomes. *Genetical Research*, 35:205-214.
- Contini, M., Cappello, N., Griffo, R., Rendine, S., & Piazza, A., 1989. Géolinguistique et géogénétique, une démarche interdisciplinaire. *Géolinguistique*, 4, 129–197.
- Cooper, G.S., Sandler, D.P., 1998. Age at Natural Menopause and Mortality. *Annals of Epidemiology*, 8(4):229-235.

- Deiana, L., Ferrucci, L., Pes, G.M., Carru, C., Delitala, C., Ganau, A., Mariotti, S., Nieddu, A., Pettinato, S., Putzu, P., Franceschi, C., Baggio, G., 1999. AKEntAnnos. The Sardinia Study of extreme longevity. *Aging, Clinical and Experimental Research*, 11:142-149.
- Doblhammer, G., 2000. Reproductive history and mortality later in life: A comparative study of England and Wales and Austria. *Population Studies*, 54:169-176.
- Doblhammer, G., Vaupel, J.W. 1998. Reproductive history and mortality later in life. WP 1999-012, Max Planck Institute for Demographic Research
- Doblhammer, G., Oeppen, J., 2003. Reproduction and longevity among the British Peerage: the effect of frailty and health selection. *Proceedings the Royal Society, Series B Biological Sciences* 270, (1524): 1541-1547.
- Dollberg, S, Seidman, D.S, Armon, Y, Stevenson, D..K., Gale, R, 1996. Adverse perinatal outcome in the older primiparae. *J Perinatal*, 16, 93–97.
- Golini, A., 1967. Aspetti demografici della Sardegna. Quaderni del seminario di Scienze Politiche dell'Università degli Studi di Cagliari. Giuffrè Editore, Milano, Italia.
- Hamilton, W. D., 1966. The moulding of senescence by natural selection. *Journal of Theoretical Biology*, 12: 12-45.
- Harrell, E E., 2001. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer-Verlag.
- Istat, 2004. 14° Censimento generale della popolazione e delle abitazioni 21 ottobre 2001. www.istat.it.
- Kirkwood, T.B.L., Rose, M.R., 1991. Evolution of senescence: late survival sacrificed for reproduction, *Phil.Trans. R. Soc. Lond. B*, 332: 15–24.
- Kosoy, R., Ransom, M, Chen, H., Marconi, M., Macciardi, F., Glorioso, N., Gregersen, P K., Cusi D., Seldin, M.F., 2011, Evidence for malaria selection of a CR1 haplotype in Sardinia, *Genes and immunity*, 12(7):582-588.
- Joseph, K.S., Allen, A.C., Dodds, L. Turner, L.A., Scott, H., Liston ,R., 2005. The perinatal effects of delayed childbearing. *Obstet Gynecol*, 105:1410-18.
- Larke, A, Crews, D.E., 2006. Parental investment, late reproduction, and increased reserve capacity are associated with longevity in humans. *Journal of Physiological Anthropology*, 25(1):119-131.
- Lipsi R.M., Caselli G., Pozzi L., Baggio G., Carru C., Franceschi C., Vaupel J.W., Deiana L. 2012. Demographic Characteristics of Sardinian Centenarian Genealogies: Methodology and Preliminary Results of the AKeA2 Study. Submitted to *Demographic Research*.
- Livi Bacci, M., 1977. A history of Italian fertility during the last two centuries. Princeton University Press, Princeton, NJ, USA.
- Lycett, J.E., Dunbar, R.I.M., Voland, E. 2000. Longevity and the costs of reproduction in a historical human population. *Proceedings the Royal Society, Series B Biological Sciences*, 267: 31-35.

- Modiano, G., Terrenato, L., Scozzari, R., Santachiara-Benerecetti, S.A., Ulizzi, L., Santolamazza, C., Petrucci, R., Santolamazza, P., 1986. Population genetics in Sardinia (with a historical account of the birth of the Haldane "malaria hypothesis"). Atti Accademia Nazionale dei. Lincei, 18:257–330.
- Moroni, A., Anelli, A., Anghinetti, W., Lucchetti, E., Rossi, O., Siri, E., 1972. La consanguineità umana nell'isola di Sardegna dal secolo XVIII al secolo XX. L'Ateneo parmense. Acta Naturalia, 8 (1), 69–92.
- Müller, H.G., Chiou, J.-M., Carey, J.R., Wang, J.L., 2002. Fertility and Life Span: Late Children Enhance Female Longevity. *Journal of Gerontology: Biological Science*, 57A (5): B202-B206.
- McArdle, P.F., Pollin, T.I., O'Connell, J.R., Sorkin, J.D., Agarwala, R., Schäffer, A.A, Streeten, E.A., King, T.M., Shuldiner, A,R., Mitchell, B.D., 2006. Does having children extend life span? A genealogical study of parity and longevity in the Amish. *Journal of Gerontology: Medical Sciences*, 61A(2):190-195.
- Nault, F., Desjardins, B., Legare, J., 1990. Effects of reproductive behaviour on infant mortality of French-Canadians during the seventeenth and eighteenth centuries, *Population Studies*, 44, 273-285.
- Perls, T., Albert, L., Fretts, R.C., 1997. Middle-aged mothers live longer. Nature, 389:133.
- Poulain, M., Pes, G.M., Grasland, C., Carru, C., Ferrucci, L., Baggio, G., Franceschi, C., Deiana, L., 2004. Identification of a geographic area characterized by extreme longevity in the Sardinia island: the AKeA study. *Experimental Gerontology*, 39:1423-1429.
- Pozzi, L. 2000. La lotta per la vita. Evoluzione e geografia della sopravvivenza in Italia fra[']800 e[']900. FORUM, Udine.
- Scola, L., Crivello, A., Candore, G., Colonna-Romano, G., Caruso, C., 2004. Association between longevity and cytokine gene polymorphisms. A study in Sardinian centenarians. *Aging Clinical* and Experimental Research, 16(3):244-8.
- Snowdon, D. A., Kane, R.L., Beeson, W.L., Burke G.L., Sprafka J.M., Potter, J., Iso H., Jacobs D.R., Phillips, R.L. 1989.Is early natural menopause a biological marker of health and aging? *American Journal of Public Health*, 79(6): 709–14.
- Tentoni, S., Lisa, A., Fiorani, O., Lipsi, R.M., Caselli, G., Astolfi, P. 2012. Spatial Analysis of the aptitude to late maternity on the Island of Sardinia, *Journal of Biosocial Sciences*, December 2010. J ci. 2011 Oct 26:1-16, vol. 44., Issue 03, May 2012, p. 257-272.
- Twisk, J.W.R., 2006. Applied Multilevel Analysis. A Practical Guide. Cambridge University Press.
- 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., Zeng, Y., Manton, K.G., Curtsinger, J.W. 1998. Biodemographic trajectories of longevity. *Science*, 280: 855–860.
- Vinogradov, A.E. 1998. Male reproductive strategy and decreased longevity. *ActaBiotheoretica*, 46:157-160.

- Voland, E., Engel, C., 1986. Ist das postmenopausale Sterbealter Variable einer fitness-maximierenden Reproduktionsstrategie?. *Anthropologischer Anzeige*, 44(1):19–34.
- Wagner, M. L., 1950. La lingua Sarda. Storia spirito e forma. Berna, Francke
- Westendorp, R.G.J., Kirkwood, T.B.L. 1998. Human longevity at the cost of reproductive success. *Nature*, 396 (24): 743-746.
- Voland, E., Engel, C., 1986. Ist das postmenopausale Sterbealter Variable einer fitness-maximierenden Reproduktionsstrategie?. *Anthropologischer Anzeige*, 44(1):19–34.
- Yi, Z., Vaupel, J.W., 2004. Association of Late Childbearing With Healthy Longevity among The Oldest-Old in China. *Population Studies*, 58(1): 37-53
- Zei, G., Lisa, A., Fiorani, O., Magri, C., Quintana-Murci, L., Semino, O., Santachiara-Benerecetti, A. S., 2003. From surnames to the history of Y chromosomes: The Sardinian population as a paradigm. *European Journal Human Genetics*, 11:802–807.
- Zei, G., Lisa, A., Astolfi, P., 1990. Fertility and malaria in Sardinia. Ann. Hum. Biol., 17:315-330.
- Zei, G., Piazza, A., Moroni, A., Cavalli-Sforza, L.L., 1986. Surnames in Sardinia. III. The spatial distribution of surnames for testing neutrality of genes. *Ann. Hum. Genet*,50 (Pt. 2), 169–180.

	N (=258 women)						
Characteristics	Not Died	Died	0.0		10050/		
	(n=133)	(n=125)	UK	UK		1095%	
N• child							
1-4	43	56	1.00				
5-8	70	46	1.49		0.65;	3.38	
9+	20	23	0.63		0.22;	1.83	
Age at first child							
<=20	14	13	1.34		0.53;	3.40	
21-32	83	91	1.00				
>=33	14	21	0.66		0.23;	1.86	
Missing	22	0	-				
Age at last child							
<=31	14	20	0.76		0.27;	2.14	
32-44	80	97	1.00				
>=45	17	8	3.76	**	1.39;	10.13	
Missing	22	0	-				
Mother age at deat	th						
<=69 years old	38	52	0.47	**	0.24;	0.90	
70-79 years old	27	34	1.00				
>=80 years old	51	36	0.61		0.29;	1.28	
Missing	17	3	3.18		0.74;	13.74	
Father age at death	h						
<=69 years old	55	49	0.96		0.49;	1.89	
70-79 years old	24	38	1.00				
>=80 years old	42	30	0.56		0.26;	1.21	
Missing	12	8	0.51		0.13;	2.00	
Birth Order							
1st	32	29	1.00				
2nd - 3th	45	40	0.99		0.47;	2.08	
4th-7th	47	47	0.80		0.39;	1.67	
8th+	9	9	1.08		0.33;	3.51	

Table 1 – Longevity and Fertility:Results of the Logistic Regression Model

*** p-value<0.001; ** p-value<0.05; *p-value<0.1

N (2000 1911)							
Chans stanists -	N (=2000 children)		-				
Characteristics	Not Died $(N-1727)$	Died	OD		IC95%		
Dinth and an	(N=1/37)	(1N=203)	UK				
Just	200	65	1.00				
18t 2m d 24h	509	03	1.00	***	0.26.	0 70	
	570	07	0.55	**	0.30;	0.78	
4th to /th	663	97	0.57	<u> </u>	0.35;	0.92	
8th +	155	32	0.58		0.28;	1.17	
Mother age at birth							
until 29 years old	713	120	0.98		0.67;	1.43	
30-39	817	112	1.00				
40+	207	31	1.16		0.72;	1.87	
Father age at birth							
until 29 years old	229	39	0.92		0.60;	1.42	
30-39	796	124	1.00				
40+	712	100	0.83		0.59;	1.18	
Cohorts							
Centenarians	270	33	1.00				
Same Cohorts	523	112	1.58	**	1.03;	2.43	
Younger Cohorts	944	118	0.93		0.61;	1.42	
N• child							
until 4 child	389	40	1.00				
4-8 child	884	118	1.48	*	0.97;	2.28	
9+ child	464	105	2.43	***	1.50;	3.96	
Altidute of place of	f birth						
HillCoast	345	51	1.00				
HillInside	631	99	1.17		0.79;	1.72	
MountainInside	385	57	0.87		0.57;	1.34	
Plane	376	56	1.58	*	0.96;	2.60	
Province of birth			-		,		
Nuoro	658	76	1.00				
Sassari	688	132	0.52	***	0.36:	0.75	
Cagliari	120	23	0.92	**	0.54:	1.57	
Oristano	271	32	0.44		0.26:	0.75	

Table 2 – Longevity and Infant Mortality:Results of the Logistic Regression Model

*** p-value<0.001; ** p-value<0.05; *p-value<0.1

	N (=2000 children)						
Characteristcs	Not Died (N=1737)	Died (N=263)	OR		IC95%		
Birth order							
1st	309	65	1.00				
2nd-3th	570	67	0.52	***	0.35;	0.77	
4th to 7th	663	97	0.56	**	0.34;	0.92	
8th +	155	32	0.55		0.26;	1.15	
Mother age at birth							
until 29 years old	713	120	0.98		0.66;	1.45	
30-39	817	112	1.00				
40+	207	31	1.21		0.74;	1.97	
Father age at birth							
until 29 years old	229	39	0.94		0.60;	1.46	
30-39	796	124	1.00				
40+	712	100	0.82		0.57;	1.18	
Cohorts							
Centenarians	270	33	1.00				
Same Cohorts	523	112	1.60	**	1.00;	2.55	
Younger Cohorts	944	118	0.95		0.60;	1.50	
N• child							
until 4 child	389	40	1.00				
4-8 child	884	118	1.51	*	0.97;	2.37	
9+ child	464	105	2.49	***	1.49;	4.16	
Altidute of place of birth							
HillCoast	345	51	1.00				
HillInside	631	99	1.15		0.76:	1.75	
MountainInside	385	57	0.87		0.54:	1.38	
Plane	376	56	1.53		0.88:	2.63	
Province of birth					,		
Nuoro	658	76	1.00				
Sassari	688	132	0.52	***	0.35;	0.77	
Cagliari	120	23	0.94		0.53;	1.67	
Oristano	271	32	0.45	***	0.25;	0.79	
Null Model	Value	Std. Err.			/		
σ_{μ} 2nd-level	0.42	0.15					
ρ	0.11						
Full Model							
σ_{μ} 2nd-level	0.19	0.13					
-	0.05						

Table 3 – Longevity and Infant Mortality:Results of the Logistic Random Intercept Model

 $\begin{array}{c} \rho & 0.05 \\ \hline & \ast \ast \ast p \text{-value} < 0.001; \ \ast \ast p \text{-value} < 0.05; \ \ast p \text{-value} < 0.1 \\ \rho = \sigma_{\mu} / (\sigma_{\epsilon} + \sigma_{\mu}) \ \text{where} \ \sigma_{\epsilon} = \pi_2 / \ 3 \\ \text{Notes: LR test for variance component =0: } \chi^2_1 = 14.42 \ (p \text{-value} < 0.001) \end{array}$