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**CONSANGUINITY AND LATE FERTILITY: SPATIAL
ANALYSIS REVEALS POSITIVE ASSOCIATION
PATTERNS**

11PV14/0/0

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Consanguinity and late fertility: spatial analysis reveals positive association patterns

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Running head: Consanguinity and late fertility

Keywords: Consanguinity, woman fertility, late reproduction, spatial analysis, kernel smoothing

Summary

The role of consanguinity on human complex traits is an important and controversial issue. In this work we focused on Sardinian population and examined the effect of consanguineous unions on late female fertility. During the last century the island has been characterized by high incidence of marriages between relatives, favoured by socio economic conditions and geographical isolation, and by high fertility despite a widespread tendency to delay reproduction. Through spatial analysis techniques, we explored the geographical heterogeneity of consanguinity and late fertility, and identified in Central-Eastern Sardinia a common excess area where the traits are positively associated. We found that their association did not significantly affect woman's fertility in the area, despite the expected negative role of both traits. Intriguingly, such critical zone includes the genetically homogeneous Ogliastra region, and well matches areas reported by previous studies as peculiar for high frequency of centenarians and for lower risk in pregnancy outcome. The spatial analysis approach we adopted is quite general and can be exploited to single out critical areas where population screenings, carried out at molecular level, could help disentangle determinants of complex biological traits and investigate their association.

INTRODUCTION

The negative effect of inbreeding, due to the increase in homozygosity of autosomal recessive detrimental mutations, has been documented in a wide range of species (Charlesworth & Willis, 2009). In humans the role of consanguinity on fertility and neonatal and post-neonatal deaths remains controversial (Edmond & Braekeleer, 1993; Bittles et al., 2002; Kerkeni et al. 2007; Robert et al. 2009). It has been associated with reduced fertility and increased rates of pre-reproductive mortality and morbidity (Ober et al., 1999; Bittles, 2001), and with recurrent risk of early deaths, infant mortality and birth defects (Stoltenberg et al., 1999a,b). However, such negative effect can be counterbalanced by higher fertility for earlier age at marriage, socioeconomic advantages associated with land and property preserving, and kin help within the extended family (Bittles et al., 2002). During the past century, the widespread propensity to migration determined a general decline in consanguineous marriages, although in many populations they continue to be preferred despite the significant excess of pre-reproductive mortality in the progeny (Bittles & Black, 2010).

For these reasons, evaluating the net effect of consanguinity on complex traits, such as fertility and pre-reproductive mortality, is a hard task for the confounding relevant role of non-biological, namely cultural, demographic and socio-economic determinants. After accounting for such factors, consanguineous unions were reported to lack of any effect on the number of live born children (Bittles et al. , 2002), and even to prolong the reproductive period, by that increasing the chance of a large progeny (Blanco Villegas & Fuster, 2006). Moreover, in a study on the Icelandic population, Helgason et al. (2008) described an n-shaped curve where the maximum reproductive success occurred in couples related at the level of third and fourth cousins.

We focused on Sardinian population since, for the insular environment and its isolation, it is characterized on the one hand by a fairly homogeneous biological and socio-economic context and, on the other hand, by peculiar bio-demographic traits, different from continental Italy as well as from other European countries. Among these traits we can include a long lasting propensity towards consanguineous unions, high fertility, and a diffuse tendency towards late childbearing (Golini, 1967; Livi-Bacci, 1977; Zei et al., 1990; ISTAT, 1990-97, Cavalli-Sforza et al., 2004).

During the past century in the island the incidence of consanguineous marriages steadily remained among the highest values of the Italian regions due to the geographical and historical isolation of the numerous mountain villages, the high endogamy and low immigration rates, the patriarchal family structure, the sheep-rearing economy and a high propensity to preserve flocks and land (Cavalli-Sforza et al., 2004).

As regards female fertility, it can be underlined that all along the past century Sardinian women have been characterized by high fertility despite the propensity to start a family late (Golini, 1967; Livi-Bacci, 1977), which resulted in a higher proportion of aged mothers who experienced reproductive success. In 1961, among 45-49 year old mothers, fertility rate was 4.23 times higher than among the contemporary mainland mothers (Golini, 1967). Such high fertility levels appear in contrast to the well-known association between advanced maternal age and an overall reduction in fertility and in the chance of delivering a healthy child (Stoltenberg et al., 1999a,b; Jolly et al., 2000; Astolfi & Zonta, 2002; Joseph et al., 2005).

The coexistence of high fertility and late reproduction in a population living in a fairly homogeneous socio-economical and cultural context drove us to assume Sardinian population of the past century suitable for investigations on the possible relation between consanguineous unions and late childbearing. We used methods of spatial analysis i) to provide effective

geographic representations of a few indicators of the traits of interest, ii) to assess whether their spatial course is significantly heterogeneous, and iii) to identify critical areas where an association between the traits can be hypothesized.

On the population of such areas future research efforts can be focused to investigate the role of consanguinity and the determinants of late fertility more closely, through ad hoc population screenings carried out individually and directly at molecular level.

MATERIALS AND METHODS

Data sources

In order to explore whether consanguinity may have contributed to shape late fertility patterns we used two distinct data sets: the first one concerns consanguineous marriages and the second one female fertility.

Data on marriages derive from religious archives, since in Italy until the end of the last century almost all marriages were religious; if the partners of the couple were relatives, the consanguinity degree and the necessary dispensation by ecclesiastic authority were registered.

The consanguinity degree was very carefully defined in the Canonical Law (Corpus Iuris Canonici) of 1917 that reported which marriages were completely forbidden, which ones were permitted under dispensation from religious authority, and which ones did not require any dispensation. However, the need for dispensation changed through time: before 1917 ecclesiastical dispensation was required for degree of relationship ranging from uncle-niece/aunt-nephew to third cousins. In 1917 the consanguinity impediment was reduced from third cousins to second cousins, and in 1983 was further reduced to first cousins.

The largest archive of data on Italian consanguineous marriages was collected by a priest, Antonio Moroni, who obtained from the highest Catholic Authority the permission to extract

information on consanguinity dispensations from ecclesiastic registers of parishes, dioceses, or Vatican archives (Moroni et al., 1972, Cavalli-Sforza et al. 2004). In particular, in Sardinia, data on consanguineous dispensations were extracted from the archives present in the different dioceses which provided information on the marriages occurring in each municipality of the island between 1768 and 1969. However, since complete and reliable information was available only for the period 1930-1969, we considered only the marriages occurring in these years: 331,513 marriages of which 11,314 were consanguineous. Unions between relatives regarded uncle-niece or aunt-nephew (12), first cousins (22), first cousins once removed (23) and second cousins (33) for which the dispensations was requested at that time.

In order to investigate Sardinian female fertility and, in particular, late fertility we used data from a special investigation carried out by the Italian Central Institute of Statistics (ISTAT) as a part of the 1961 Italian Census. The original data set accounts for 306,421 records of all women who lived in Sardinia at Census time. Each record reports the following pieces of information about each woman: birth place and year, educational level, marital status and marriage year, number of live-born children, birth date of the first and last child. From the data set we selected all the women who married between 1930 and 1961, so as to obtain a data subset temporally consistent with that of consanguineous marriages. We further selected all the mothers who were older than fifty in 1961 and had by then ended their reproductive period, having born at least two children. The final sample size accounted for 29,096 records.

During the period covered by both data sets Sardinian municipalities underwent subdivisions/aggregations and, consequently, we adjusted the corresponding information.

Methods

The approach we adopted exploits ideas and methods from spatial statistical analysis (Cressie, 1993; Lawson, 2001; Silverman, 1986; Kelsall & Diggle, 1995; Astolfi et al., 2009).

The geography of consanguinity was studied through the consanguinity coefficient α , estimated by averaging the inbreeding coefficients of the marriages which occurred in each

municipality: $\alpha = \sum_{i \in \{12,22,23,33\}} p_i F_i$, where p_i is the relative frequency of the consanguineous

marriages with inbreeding coefficient F_i .

The study of late fertility grounds on the distribution of maternal age at last childbirth in each municipality. We first explored the spatial course of the means of such local distributions to highlight their spatial heterogeneities. Late fertility was then more precisely investigated by means of an indicator, I_L , of advanced age at last childbirth, defined as the mean age at last child plus one standard deviation.

To find out whether in some areas unexpectedly high values of the consanguinity coefficient α were associated with an advanced maternal age at last childbearing we then explored and compared the spatial distributions of α and I_L . In the following, we first outline the method we used to estimate the indicators on a grid built over the study region, reduce noise, and by that obtain smooth isopleth maps of their spatial course. We then outline how, for indicators α and I_L , “critical contours” were obtained that single out the respective significant excess areas, $S^+(\alpha)$ and $S^+(I_L)$.

Let m denote the number of municipalities of the study region R , over which we built a uniform, sufficiently fine grid; to this aim a grid spacing of 2.8 km was used. To obtain a smooth map of consanguinity, α was estimated at each grid point (x,y) in R as a weighted average of the values available at each municipality (X_i, Y_i) , $i=1, \dots, m$:

$$\hat{\alpha}(x, y) = \frac{\sum_{i=1}^m \alpha_i w_i(x, y)}{\sum_{j=1}^m w_j(x, y)}, \quad w_i(x, y) = n_i G\left(\frac{x - X_i}{h_i}, \frac{y - Y_i}{h_i}\right)$$

where the weights w_i measure the proximity of (X_i, Y_i) to (x, y) , according to the standard Gaussian $G(u, v)$, while taking into account the local sample size n_i . Thus the weight given to each observation is a function of the distance between that observation's location and the grid point at which an estimate is desired. The amount of smoothing is modulated by h_i , which defines the smoothing window size. In our computations, to take into account the inhomogeneous spatial distribution of municipalities and ensure the appropriate level of smoothing everywhere, we let h_i vary between 5 and 12 km, according to the local density of municipalities, with higher values being used in more sparsely populated areas. The idea is borrowed from the role of bandwidth in variable kernel density estimators of spatial intensity functions (Silverman, 1986; Astolfi et al., 2009).

Estimates of the other indicators were similarly obtained.

In order to better read and evaluate their spatial course, each indicator was standardized by taking its ratio to the corresponding Sardinian average, so that values higher than 1 corresponded to values exceeding the reference Sardinian value. Then isopleths, i.e. contours connecting points of equal values, were generated, and a shaded contour map filled with gray levels was drawn for each indicator.

With the aim of highlighting the area of significant excess of a generic indicator g with respect to the reference value, we tested the null hypothesis that factors affecting it were uniform throughout the region, $H_0 : g = 1$, against the alternative hypothesis of increased local values $H_A : g > 1$, and used Monte Carlo sampling to construct a pointwise p -value surface and assess significance (Kelsall & Diggle, 1995). More precisely, if $g^{(o)}(x)$ denotes the original estimate of the indicator at x , a sufficiently high number M of samples consistent with

H_0 were obtained at each municipality, $g^{(k)}(x)$, $k=1, \dots, M$ were estimated, and the probability $P[g(x) < g^{(o)}(x) | H_0]$ accordingly evaluated. Then, the “95%-tolerance contour” was singled out as the 0.95-valued isopleth of the p -value surface, and superimposed on the map of the original estimate $g^{(o)}$ to outline its significant excess area, denoted by $S^+(g)$.

To visually highlight areas where two indicators g_1, g_2 both take critical values, for example both significantly higher than the regional reference, we singled out the overlap profile by geometrical intersection of the two critical areas, that is $S^* = S^+(g_1) \cap S^+(g_2)$, and complemented such qualitative visual information with a quantitative measure of the degree of overlap, obtained as the ratio of the intersection area over the mean extension of the two areas.

Software procedures for gridding/smoothing, isopleth mapping and identification of critical areas were ad hoc developed in MATLAB 2010b 7.11. Choropleth maps were obtained by ARCVIEW GIS version 3.2. Other statistical analyses were performed by means of SPSS v. 8.2 procedures and MATLAB Statistical Tool Box.

RESULTS

We first considered the consanguinity data and evaluated the consanguinity coefficient both globally at regional level and locally at municipality level. At regional level, on a total number of 331,513 marriages, the proportions of consanguineous unions were $p_{12} = 2.2 \text{ e-}4$, $p_{22}=0.0129$, $p_{23}=0.0045$, $p_{33}=0.0168$, and the estimated consanguinity coefficient was $\alpha_R=0.0012$. The distribution of the coefficients α_i , $i=1, \dots, m$, each one estimated at municipality level, has quartiles 0.00055, 0.0013, 0.0026, and its spatial pattern is depicted by the choropleth map in panel A of Figure 1. In panel B of Figure 1 we show the smoothed

isopleth map, that discloses the prominent geography of the indicator, characterized by higher values in the northern half of the island, particularly in its eastern part.

Thereafter we examined the age distribution at last childbirth at regional level, and found that it is slightly negative skewed with mean of 39 ± 0.026 years and quartiles corresponding to 36, 40, 42 years (Figure 2). Across the municipalities the distribution of the mean age at last child has quartiles 38.66, 39.44, 40.01, and its spatial pattern is depicted by the choropleth map in panel A of Figure 3. The corresponding smoothed isopleth map highlights how higher values occur in the north-eastern part of the region (Figure 3, panel B).

In order to examine the relation between advanced age at last child and consanguinity, we estimated the I_L indicator and compared its isopleth map with that of α . In Figure 4 we report such maps, and single out the 95% tolerance contours that bound the respective areas of significant excess, $S^+(\alpha)$ in panel A and $S^+(I_L)$ in panel B. By map comparison, it appears that an advanced age at last child is observed in mostly the same north-eastern region, where a high level of consanguinity is reported. The region, where significant higher values of both indicators occur, was singled out by intersection of the areas $S^+(\alpha)$ and $S^+(I_L)$. Figure 5 shows the intersection area $S^* = S^+(\alpha) \cap S^+(I_L)$ and the 80 municipalities lying within it. The overlap degree of the two S^+ areas amounts to 0.64.

In Table 1 we report the numerical values of consanguinity parameters computed for the whole Sardinia, the critical common excess area S^* , and the remaining part of the island, outside S^* . The consanguinity coefficient α is about three times higher inside S^* than outside; the proportion of first cousins once removed, p_{23} , is 3.7 times higher, and the proportion of the other types of consanguineous marriages is always over 2.5 times higher inside S^* than outside.

In order to explore whether the spatial distribution of consanguinity correlates with other reproductive behaviors besides age at last childbirth, we considered three further indicators: the

age at first child, the length of the period intervening between first and last child (age at last- age at first childbirth), and the total number of children. In Table 2 we report some descriptive statistics regarding these fertility indicators inside and outside S*, and in the whole region.

We found that the mean ages at first and at last childbirth, and the average number of children per woman were significantly higher inside than outside S*; otherwise, the time period intervening between age at first and at last childbirth was not significantly different between the areas. These findings reveal that in S* women reproduce later, without any negative effect on fertility, neither in the total number of children nor in the length of the whole period between first and last child.

In order to get some insight into clustering of aged mothers we estimated the incidence of mothers over 42 years at last child, that is the 75th centile of the regional age distribution, and found it significantly higher inside S*: 28.2% inside vs 20.3% outside S* ($\chi^2=153.71$, $P<0.0001$). Similarly the proportion of mothers over 32 years at first child, that is the 75th centile of the regional age distribution, resulted significantly higher inside than outside S*: 27.6% vs 20.0% ($\chi^2=141.69$, $P<0.0001$), respectively. Finally we found that the incidence of mothers who had the first child over 32 and the last over 42 years was significantly higher inside S* than outside: 10.5% vs 6.0% ($\chi^2=133.45$, $P<0.0001$).

DISCUSSION

The present study focuses on consanguinity of Sardinian population and its relation with woman's fertility. In particular we explored, within a spatial analysis framework, the population's consanguinity and late reproduction, looking for evidence of possible associations.

We described the geography of both traits, and searched for areas where endogamy combined with childbirth at advanced age, thus suggesting the role of underlying common determinants.

Consanguinity of Italian population has been widely studied (Cavalli-Sforza et al., 2004), but its pattern in Sardinia has not yet been described at micro-geographical level. Our study, based on Sardinian historical data, explores its geography and reveals spatial heterogeneity, with higher values in the Northern half part of the island (Figure 4, panel A); within such area, a smaller Eastern zone is identified, characterized by extremely high values with respect to the rest of the island (Table 1).

Although it has been largely reported that mating between relatives negatively affects progeny's health and survival (Stoltenberg et al., 1999 a,b; Charlesworth and Willis, 2009; Robert et al., 2009; Postma et al., 2010), our study highlights an area S^* , where excess of both consanguinity and late reproduction is reported (Figure 5): consanguineous marriages are about 3 times more frequent, and mean ages at first and at last child are significantly higher than in the rest of Sardinia (Table 1 and 2). Though both late reproduction and consanguinity are expected to negatively affect the pregnancy outcome (Stoltenberg et al., 1999a, Ober et al., 1999; Jolly et al., 2000; Joseph et al., 2005), our results do not reveal any negative effect on the mothers living in S^* , neither on the total number of liveborn children nor on the time interval between first and last child.

In conclusion, we highlighted a Central Eastern area, S^* , that includes 80 mountain villages where unions between relatives were deep-rooted in traditions and mothers reproduced later; nevertheless such mothers did not suffer any reduction in the length of the time interval between first and last child or in the overall number of children. In such zone, common socio-economical determinants may have concurred to the positive association of consanguinity and late fertility, so reducing their negative impact. In villages characterized by rural and sheep

farming economy, the economic advantages and kin help, associated with marriages within an extended familial group, have likely improved health and survival of mothers, particularly of frailly aged mothers, and their neonates (Bittles et al., 2002; Sear and Mace, 2008; Helgason et al., 2008). In addition, it cannot be excluded the role of marriages between relatives in increasing homozygosity in multiple genetic determinants possibly associated with a favourable pregnancy outcome, even occurring in aged mothers. Through generations, such inheritable factors may have been positively selected and/or submitted to the effect of the genetic drift, mainly relevant in small inland isolated villages (Montesanto et al., 2008).

The present study highlights an area that well matches a zone previously reported to show high frequency of late maternities combined with a reduced risk of unfavourable pregnancy outcomes; such results were underpinned by the further finding that the aptitude towards late reproduction persisted in time (Astolfi et al., 2009; Tentoni et al., 2012).

Further reasons make this area noticeable from various points of view. It includes the Ogliastra region that, for its genetic homogeneity, has been considered a proper candidate for studies on genetic isolates (Caramelli et al., 2007; Pistis et al., 2009); it was characterized as refuge land of Sardinian people from past invasions by genetic, archaeological and linguistic studies (Contini et al., 1989; Zei et al., 2003); it mostly overlaps zones already known for high frequency of centenarians (Poulain, 2004) and reproductive/ post-reproductive longevity (Tentoni et al., 2012).

Finally, we would like to remark that the spatial analysis approach we adopted can be generally applied to identify local heterogeneities in the geographical pattern of single traits and their association. The opportunity it offers to single out critical areas, where *ad hoc* population screenings can be carried out at molecular level, can help disentangle determinants of complex biological traits. In the Central Eastern area we identified, where significant excess of

consanguinity and late fertility occurs, environmental factors, such as the population's life style and socio-economic and demographic structure, likely interacted with genetic factors that, in homozygous combination, can have contributed to enhance healthy, even if late, reproduction.

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FIGURE CAPTIONS

Figure 1. Spatial distribution of the consanguinity coefficient α , illustrated by quartile choropleth map (panel A), and kernel smoothed isopleth map (panel B).

Figure 2. Sardinian distribution of maternal age at last childbirth.

Figure 3. Spatial distribution of the mean age at last childbirth illustrated by quartile choropleth (panel A) and kernel smoothed isopleth maps (panel B).

Figure 4. Isopleth maps of consanguinity (α) and late childbirth (I_L) indicators, and 95% tolerance contours that bound the areas of respective significant excess, $S^+(\alpha)$ in panel A and $S^+(I_L)$ in panel B.

Figure 5. The area $S^* = S^+(\alpha) \cap S^+(I_L)$, filled in gray color, where significant higher values of consanguinity and late childbearing both occur. Panel A : the intersection area S^* ; panel B: the corresponding municipalities, in gray color.