Original Research Article

Effects of Consanguinity on Pre-reproductive Mortality: Does Demographic Transition Matter?

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ABSTRACT   The aim of this study was to investigate whether there is an increase on premature deaths due to genetically determined factors at the beginning of a demographic transition. We also analyzed the effects of parental consanguinity on offspring mortality from an epidemiological viewpoint, using parish records for family reconstitution in a Basque population (1800–1990). Among the offspring of unrelated parents, 13.1% died before their first year of life (infant mortality), and 22.8% died before the age of 16 (pre-reproductive mortality). Significant increases in both infant (23.6%) and pre-reproductive (38.5%) deaths were found among the progeny of first cousins or closer relatives, 1C ($F \geq 0.0625$). The corresponding relative risks of mortality were 1.79 (95% confidence limits: 1.37–2.28) and 1.68 (1.38–2.01), respectively. Estimates of the population attributable risks indicate that 4% of pre-reproductive mortality is ascribable to consanguineous unions, although kinships other than 1C produced only slight increases in offspring mortality. Evidence on the relationship between the demographic transition and the increase in premature deaths due to genetic factors was obtained through a principal component analysis (95.1% of variance accounted for). During the initial stages of the demographic transition, the population experienced substantial elevations in mean family size, natural increase of the population, frequency of close consanguineous matings (1C), and death rate due to congenital anomalies and perinatal diseases. These findings are of interest for the health services of many developing societies in Asia, Africa, and Latin America, which are nowadays immersed in the demographic transition process. Am. J. Hum. Biol. 17:773–786, 2005.   © 2005 Wiley-Liss, Inc.

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4. Result (1): Mortality difference with consanguinity level
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Consanguinity

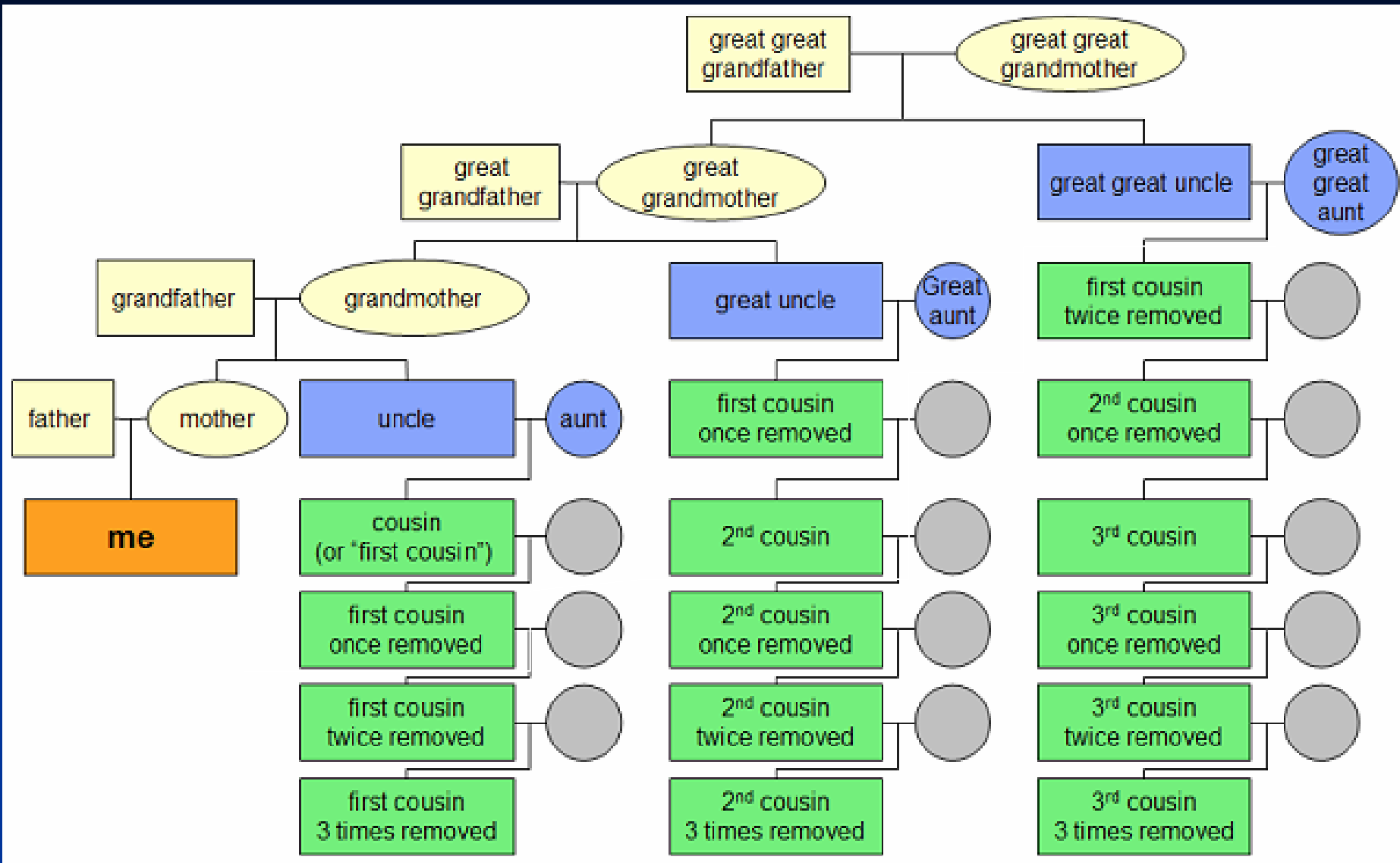First cousin

Second cousin

Coefficient of inbreeding (*F*)

Demographic transition

Pre-reproductive mortality

Principle component analysis

The term "<u>consanguinity</u>" is used to describe the unions between individuals who are known to share genes inherited from one or more common ancestors.

http://en.wikipedia.org/wiki/Image:Cousin_tree.png

<u>Coefficient of Inbreeding</u> : A measure of how close two people are genetically to each another. The coefficient of inbreeding, symbolized by the letter F, is the probability that a person with two identical genes received both genes from one ancestor.

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Coefficient of inbreeding (F)

> In general terms, the most common type of consanguineous mating is between first cousins, who are predicted to have 12.5% of their gene pools in common, and so on average their progeny will be homozygous at 6.25% of gene loci, equivalent to a coefficient of inbreeding (F) of 0.0625 (Bittles, 2001).
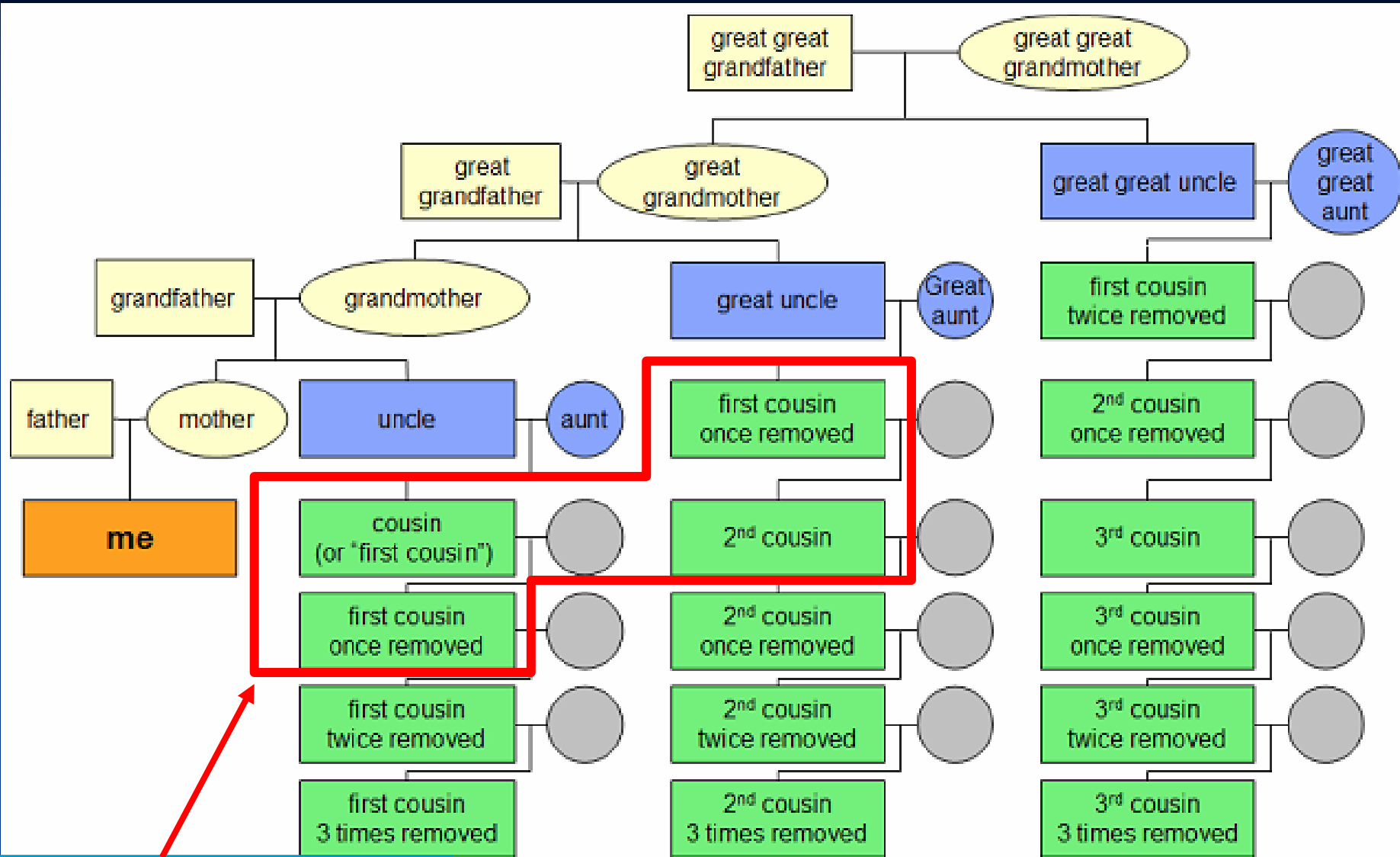
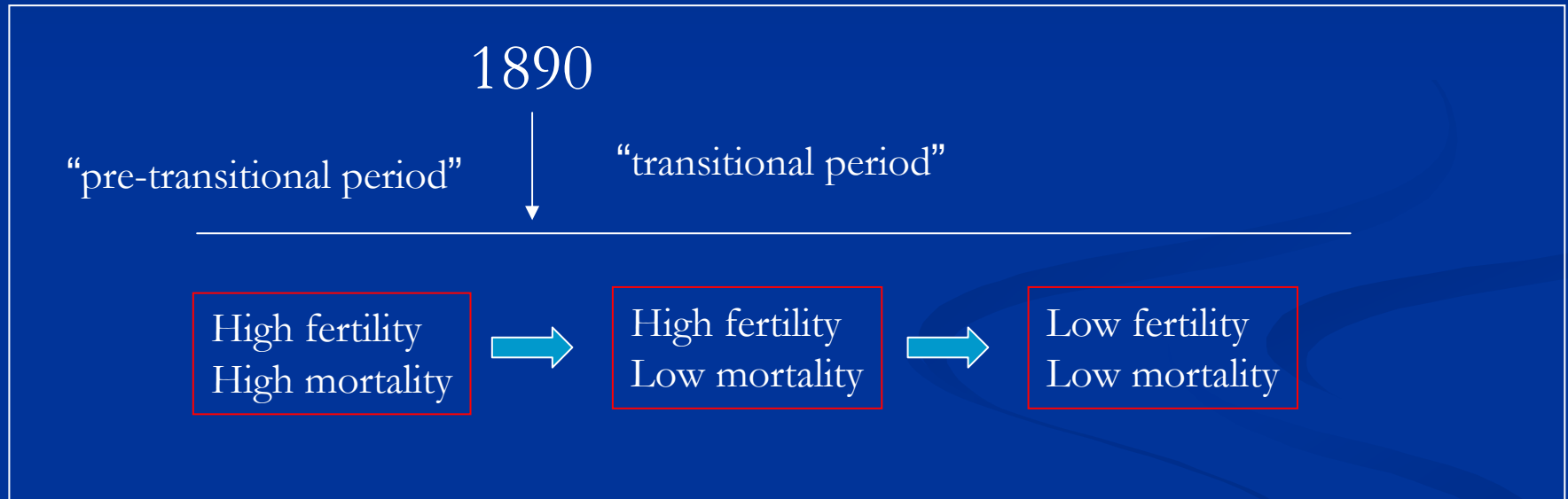First cousins: F=0.0625
Second cousins: F=0.0156 } "Consanguineous"

Kinship beyond second cousins $\doteqdot$ general couples

Consanguineous

http://en.wikipedia.org/wiki/Image:Cousin_tree.png

Demographic transition is defined as a radical shift in human reproduction, which started in the late 19th century (in Europe).

1890

"pre-transitional period"   "transitional period"

| High fertility
High mortality | → | High fertility
Low mortality | → | Low fertility
Low mortality |

Industrialization
New socioeconomic scenario

Epidemiological transition

Infectious diseases
→ Non-communicable diseases

"Pre-reproductive mortality"

Infant Mortality <1 year ↑
Pre-reproductive mortality <16 years ↑

Genetically determined deaths

↑

Actions of deleterious genes
Expression of recessive genes

↑

Consanguineous marriages

↑

Population increase

↑

Demographic Transition

?

Previous evidences :

In population where consanguineous unions are encouraged, increased levels of morbidity and mortality at early ages were found.
(Bittles et al., 1991; Bundey and Alam, 1993, UK born Pakistani; Jorde, 2001, Utah Mormon; Stoltenberg et al., 1999, Norway)

Consanguinity increased in Europe between 19th and 20th century, because demographic pressure increased the number of biological relatives who were potential mates.
(Pena et al., 2002, and theoretically hypothesized by Cavallis-Sforza et al, 1966 and others)

Aim

1800   **1890**   Consanguinity ↑
Pre-reproductive mortality ↑   1990

Demographic Transition
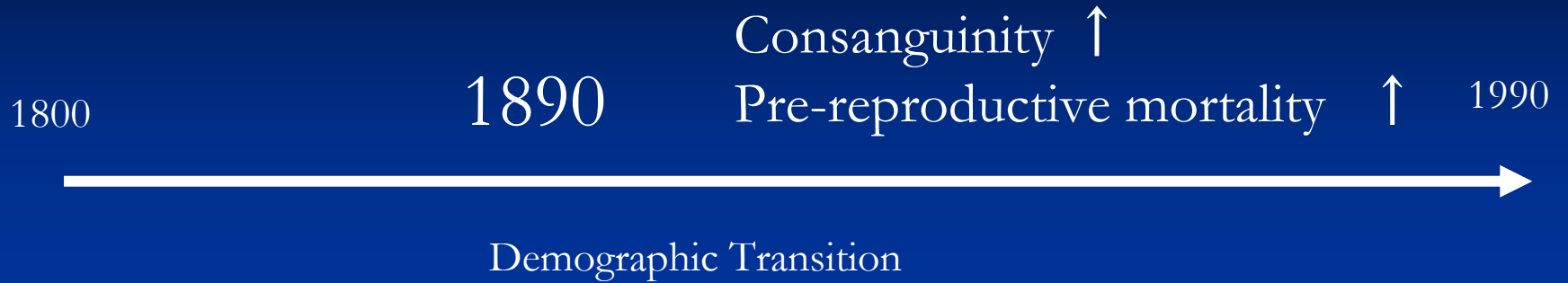
Spain

Basque County
Lanciego community, Northern Spain

Rural agricultural areas
<2000 inhabitants

Change in population structure with modernization
      e.g., endogamous marriages ↓

Consanguinity of a target population has been changed over time

   \ ?

Health status, Morbidity, Mortality

Materials and Methods

Parish records between 1800 and 1990
* 3060 marriages
* 13298 birth (baptism)
* 8152 death (burial)

RECONS : linked the vital events
* 1527 marriages
* 6336 birth

30-year cohorts:
1800-1829, 1830-1859, 1860-1889,
1890-1919, 1920-1949, 1950-1990

Analytical Framework

Comparison of mortality between:

    A. The offspring of non-consanguinity union (NC)

    B. The offspring of consanguinity union (CM)

1C: First cousin or closer (F=<0.0625)
2C: Second cousin or first cousin once removed (0.0156<F<0.0625)
3C: Other kinships (F<0.0156)

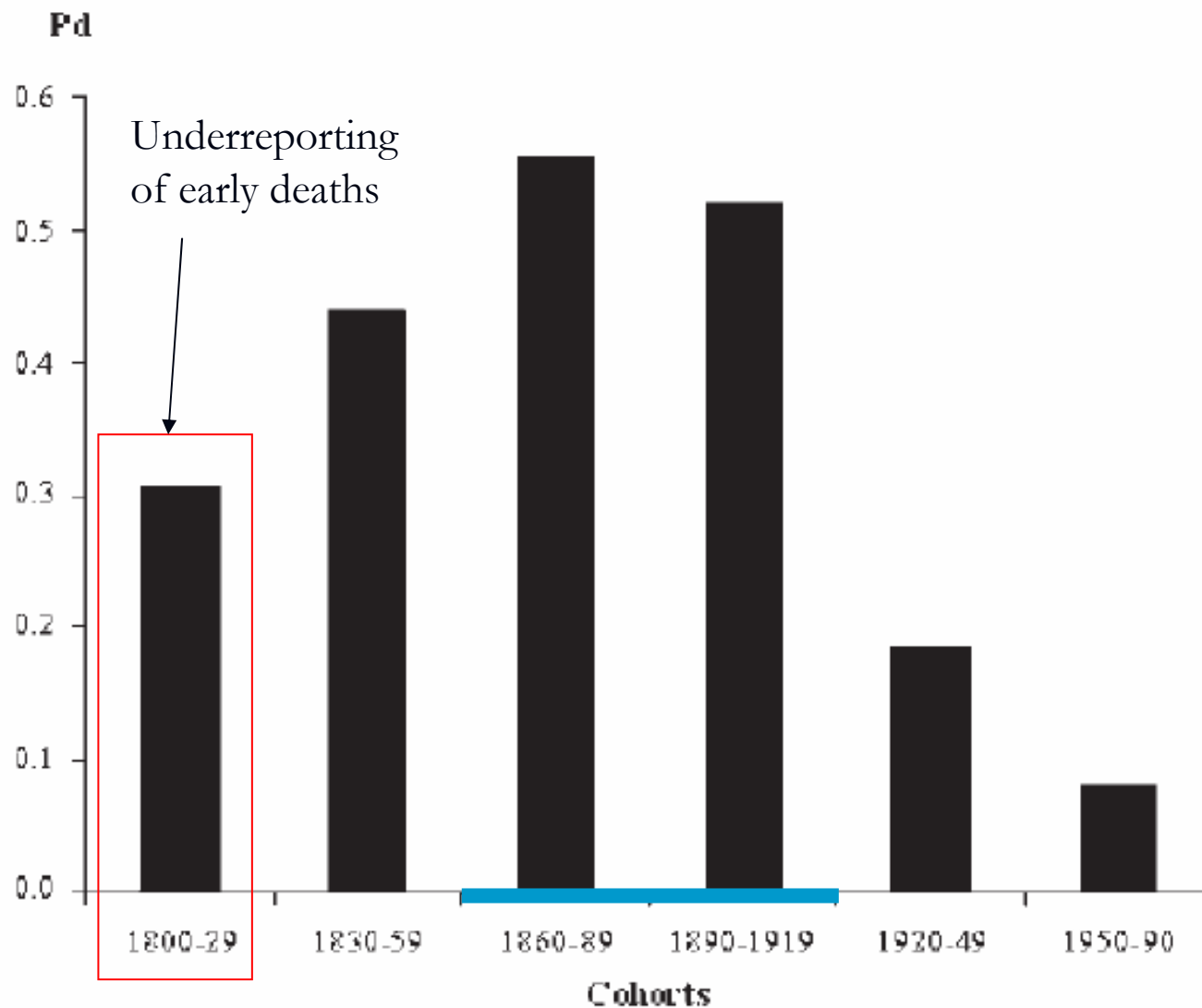No socioeconomic variation was expected among the unions of varied consanguinity.

Fig. 1.   Secular evolution of pre-reproductive mortality in a Basque population (Lanciego, Spain). Pd is the proportion of deaths before the age of 16 among the offspring.

Descriptive results

Reconstructed families = 1527
Children assigned = 6336

Offspring of consanguineous matings =1245 (19.6%)
Offspring of non-consanguineous matings = 5091 (80.4%)

Offspring died before the age of 16 = 1522 (24.0% of births)

Result (1): pre-reproductive mortalities were higher among the offspring of consanguineous unions

TABLE 1. Effect of the parental genetic relatedness on infant (<1 year) and pre-reproductive (<16 years) deaths in a Basque rural population (period 1800–1990)

	Marital type[a]					Total
Variables	1C	2C	3C	CM	NC	
Families	48	76	169	293	1,234	1,527
Offspring[b]	195	353	697	1,245	5,091	6,336
Consanguinity rates (%)	3.14	4.98	11.07	19.20	—	—
Mortality rates (%)						
Before 1 year	23.6	14.4	15.6	16.6	13.1	873
Between 1 and 15 years	14.9	10.2	12.9	12.5	9.7	649
Before 16 years	38.5	24.6	28.5	29.1	22.8	1,522

[a]Abbreviations: 1C, close consanguinity (first cousin or closer relatives, $F \geq 0.0625$); 2C, intermediate consanguinity (first cousin-once removed and second cousin, $0.0156 < F < 0.0625$); 3C, remote consanguinity (kinship beyond second cousin, $F < 0.0156$); CM, consanguineous marriages; NC, non-consanguineous marriages.
[b]Number of offspring in reconstructed families.

TABLE 2. *Relative risks (95% confidence limits in parentheses) and population attributable risks of infant (<1 year) and pre-reproductive (<16 years) deaths in the offspring of related and unrelated parents*

Marital type[a]	Relative risk	Attributable risk
Infant mortality		
1C/NC	1.79 (1.37–2.28)	1.18
2C/NC	1.10 (0.86–1.35)	0.45
3C/NC	1.19 (1.03–1.38)	1.77
CM/NC	1.23 (1.11–1.37)	3.50
Mortality between 1 and 15 years		
1C/NC	1.52 (1.06–2.09)	0.92
2C/NC	1.05 (0.77–1.39)	0.24
3C/NC	1.33 (1.13–1.54)	2.75
CM/NC	1.27 (1.12–1.43)	3.98
Pre-reproductive mortality		
1C/NC	1.68 (1.38–2.01)	1.08
2C/NC	1.08 (0.90–1.28)	0.37
3C/NC	1.26 (1.09–1.42)	2.29
CM/NC	1.25 (1.14–1.37)	3.75

[a]Abbreviations: 1C, close consanguinity (first cousin or closer relatives, $F \geq 0.0625$); 2C, intermediate consanguinity (first cousin-once removed and second cousin, $0.0156 < F < 0.0625$); 3C, remote consanguinity (kinship beyond second cousin, $F < 0.0156$); CM, consanguineous marriages; NC, non-consanguineous marriages.

The relative risk (RR), which is the ratio of mortality in the consanguineous group to that in the non-consanguineous group, was calculated using

$$RR = RC/RNC;$$

where RC and RNC are the risks among offspring of consanguineous and non-consanguineous parents, respectively (Khlat and Khoury, 1991; Khoury et al., 1987).

The attributable risk (AR) relates RR to the frequency of consanguineous marriages in the population and gives the <u>fraction of precocious mortality that can be ascribable to consanguineous unions</u>. It works out as

$$AR = p(RR - 1)/[1 + p(RR - 1)],$$

where p is the frequency of consanguineous unions in the population (Khoury et al., 1987; Levin and Bertell, 1978).

AR=p × RR+(1-p) × 1 (AR=1 when RR=1, AR is higher when p and RR were high).

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$(AR-1) \times 100$

= % of pre-reproductive mortality explained by the consanguinity effect

Principle component analysis

In order to assess interactions between demographic variables (as indicators of the stage of the demographic transition) and the effects of consanguinity on early mortality over time (by cohorts), a principal component analysis (PCA) was performed (Hair et al., 1999).

Principle component analysis

<CONSANGUINITY variables>
(i) coefficient of inbreeding (FINB),
(ii) frequency of first cousin or closer relative marriages (1C),
(iii) frequency of first cousin-once removed and second cousin marriages (2C),

<DEATH AT EARLY AGE variables>
(iv) pre-reproductive mortality (MPRE), expressed as a percentage from total live births,
(v) deaths due to congenital anomalies and disease of the perinatal period (CONG) per 1,000 live births, classed according to the International Classification of Disease, 9th ed. (ICD-9), (vi) overall mortality rate (MORT, per 1,000 inhabitants),
(vii) infant mortality rate (MINF, per 1,000 live births),

<POPULATION PRESSURE variables>
(viii) birth rate (BIRT, per 1,000 inhabitants),
(ix) average number of live births per marriage or mean family size (FAMS),
(x) natural increase of the population (NINC).

…. marriage cohorts except for that of 1800-29.

Variables that are correlated with a Factor share the tendency of temporal change

<Factor 1>
Overall mortality (0.990)
IMR (0.986)
Birth rate (0.973)
Mean family size (0.812)
Coefficient of inbreeding (0.730)

<Factor 2>
Frequency of 2C (0.951)
Frequency of 2C (0.934)
Natural increase rate (0.932)
Death resulting from congenital anomalies (0.923)

Coefficient of inbreeding (0.682)
Mean family size (0.562)

Impact of the modernization of the population on the progressive decrease of inbreeding levels, family size, and birth and mortality rates, including epidemic mortality.

Influence of the demographic transition on the expected frequency of consanguineous marriages, and the effects of interaction between demography and consanguinity on the frequency of premature deaths due to genetic factors.

Factor 2: Influence of the demographic transition on the expected frequency of consanguineous marriages, and the effects of interaction between demography and consanguinity on the frequency of premature deaths due to genetic factors.
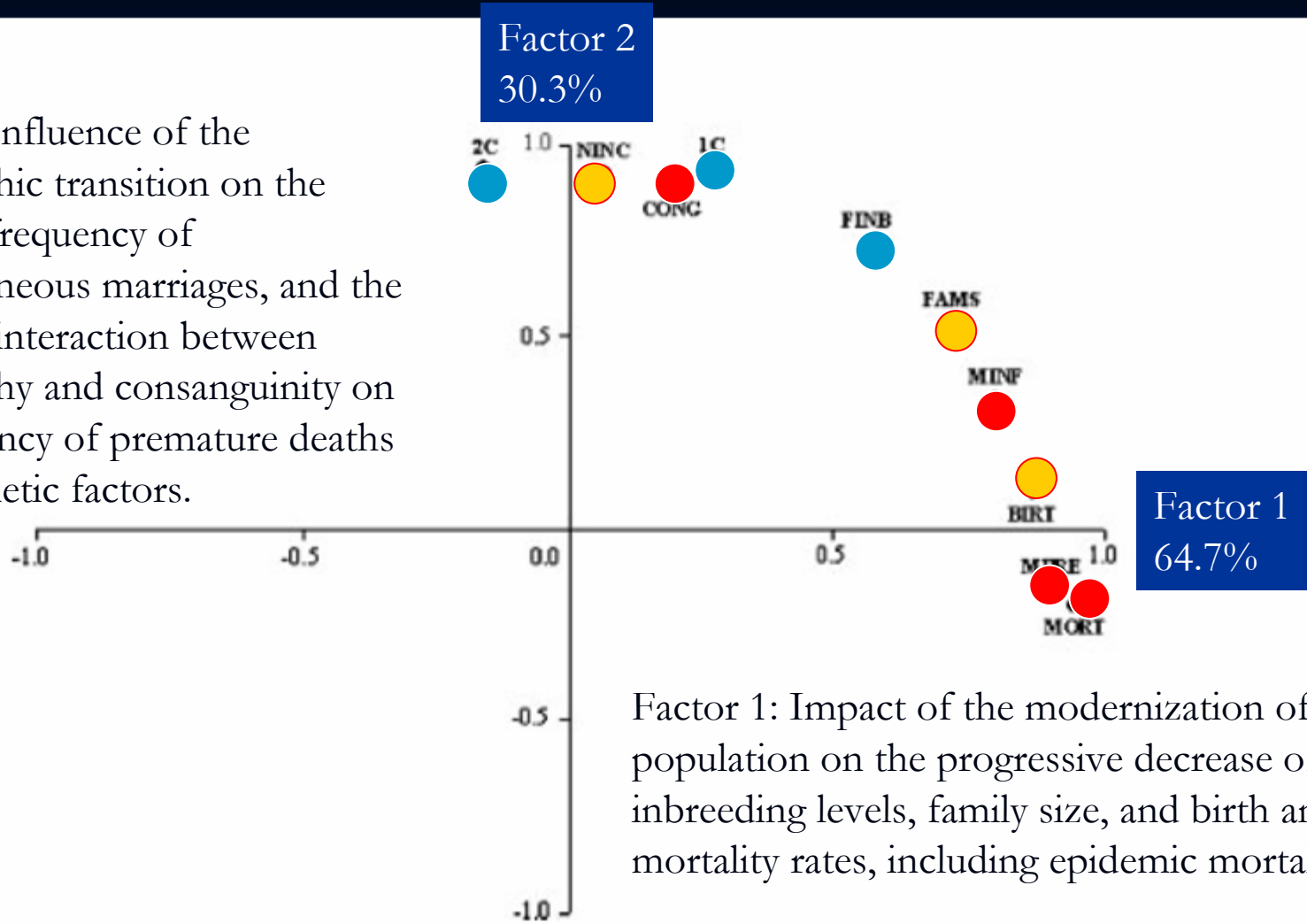
Factor 1: Impact of the modernization of the population on the progressive decrease of inbreeding levels, family size, and birth and mortality rates, including epidemic mortality.

Fig. 2.   Two-dimensional representation of a principal component analysis on 10 demographic and consanguinity variables. Variables are overall mortality rate (MORT), infant mortality rate (MINF), pre-reproductive mortality (MPRE), birth rate (BIRT), death rate due to congenital anomalies and disease of the perinatal period (CONG), mean family size (FAMS), natural increase of the population (NINC), coefficient of inbreeding (FINB), frequency of first cousin or closer kin unions (1C), and frequency of first cousin-once removed and second cousin unions (2C). The total variance accounted for is 95.1%.
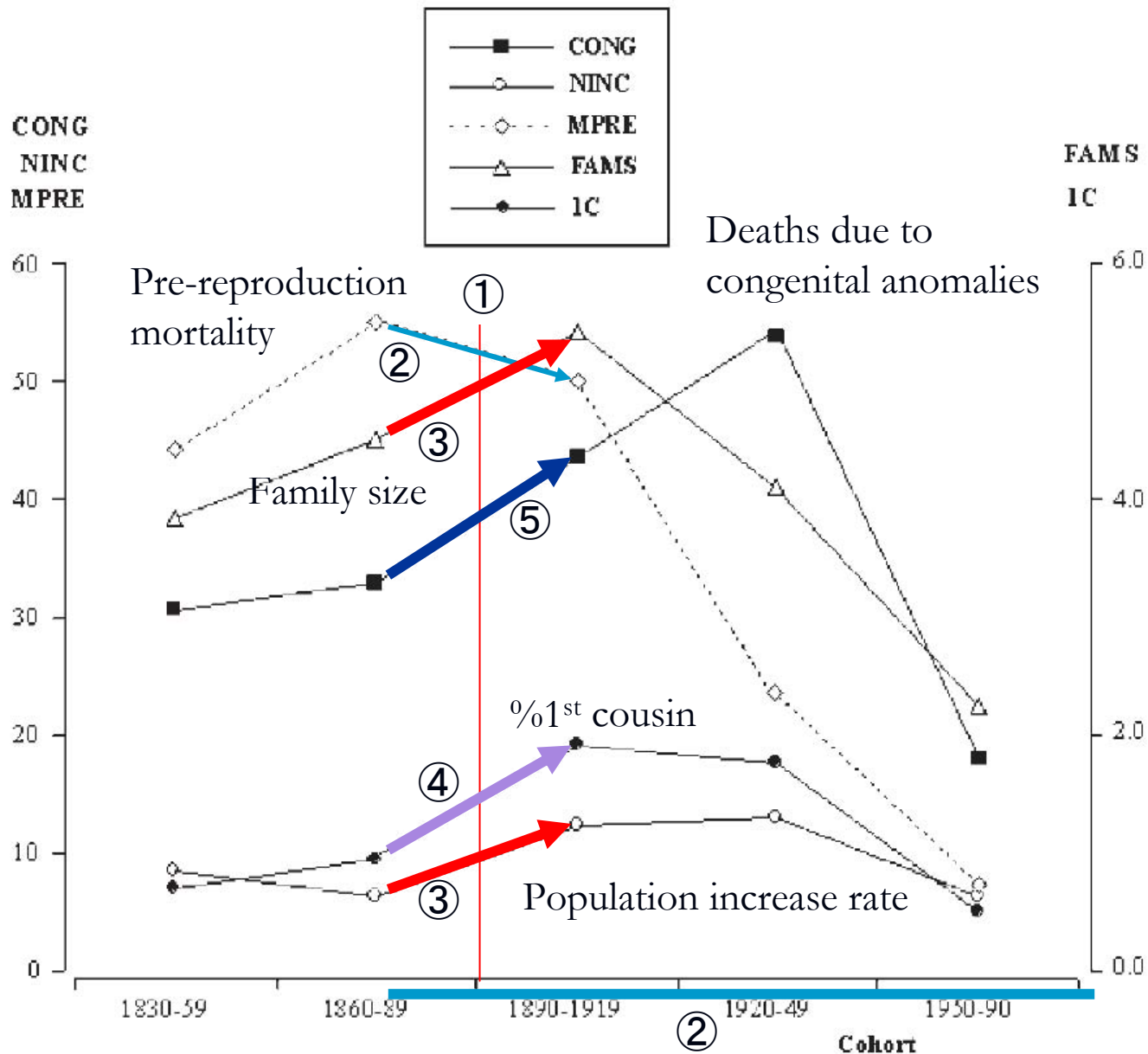
Fig. 3. Secular trend (1830–1990) in death rates due to congenital anomalies and disease of the perinatal period (CONG, per 1,000 live births), natural increase of the population (NINC, in %), pre-reproductive mortality (MPRE, in %), mean family size (FAMS, average number of live births per family), and frequency of first cousin or closer relative unions (1C, in %) in a Basque population (Lanciego, Spain).
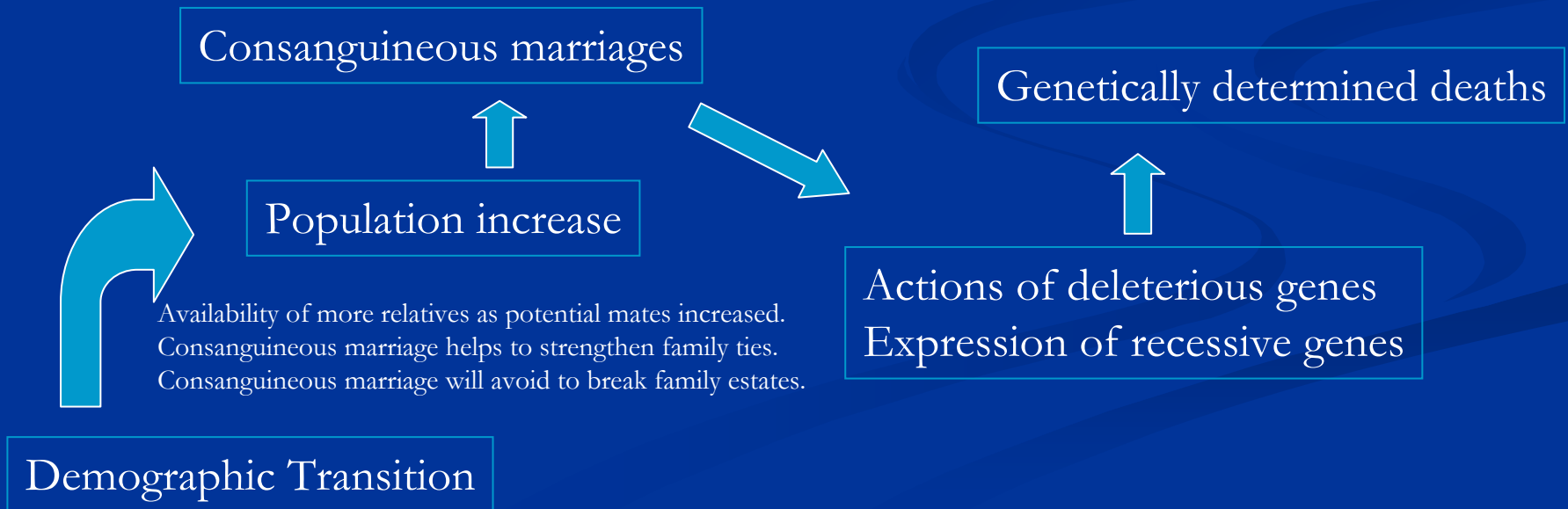
TABLE 3. Relative risks (95% confidence limits in parentheses) comparing prereproductive mortality in the offspring of related and unrelated parents in pre-1890 and post-1889 periods

Marital type[a]	Relative risk	
	Pre-1890	Post-1889
1C	1.43 (1.05–1.87)	1.99 (1.58–2.47)
2C	0.97 (0.71–1.26)	1.11 (0.82–1.43)
CM	1.14 (0.98–1.33)	1.47 (1.30–1.69)

↑ 40%

<

[a]Abbreviations: 1C, close consanguinity (first cousin or closer relatives, $F \geq 0.0625$); 2C, intermediate consanguinity (first cousin-once removed and second cousin, $0.0156 < F < 0.0625$); CM, consanguineous marriages.

Summary and Discussion

1. Pre-reproductive mortality was higher among the offspring of first cousins than those of unrelated union by 15.7%. (Homogenous SES setting)
   cf. Worldwide population data: 0～29% (Bittles and Neel, 1994)

2. During the early stage of demographic transition, the population experienced elevation in mean family size, natural increase rate, frequency of 1C union, and death rate due to congenital anomalies. The increase of RR during the early stage of transition was high among the offspring of 1C unions. Epidemiological transition usually obscure such patterns.

Consanguineous marriages

Genetically determined deaths

Population increase

Actions of deleterious genes
Expression of recessive genes

Availability of more relatives as potential mates increased.
Consanguineous marriage helps to strengthen family ties.
Consanguineous marriage will avoid to break family estates.

Demographic Transition

Implication to Human Ecology study

Language: Inter-marriage among those who speak the same language

e.g., average population of one language group = 7000, Papua New Guinea
e.g., endogamous rate within a same ethnic group is usually high

⬇

Coefficient of inbreeding is high

Population structure: Close → Open
    e.g., In the Kombio in Papua New Guinea,
endogamous rate within a language group: 91% → 82%;
endogamous rate within a dialect group: 74% → 39%
            (Umezaki and Ohtsuka, 1996)

Ethnic identity
Pre-reproductive mortality
or overall demographic structure

Biological pathways that link
modernization and health

Papers published by the authors:

Alfonso-Sa´nchez MA, Pen˜a JA, Caldero´n R. 1997. Consanguinidad y endogamia en una comunidad rural del Paı´s Vasco (Lanciego, provincia de Alava). Rev Espan˜ola Antropol Biol 18:73–91.

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Alfonso-Sa´nchez MA, Pen˜a JA, Caldero´n R. 2003. Time trends and determinants of completed family size in a rural community from the Basque area of Spain (1800–1969). J Biosoc Sci 35:481–497.

Alfonso-Sa´nchez MA, Caldero´n R, Pen˜a JA. 2004. Opportunity for natural selection in a Basque population and its secular trend: evolutionary implications of epidemic mortality. Hum Biol 76:361–381.

Caldero´n R. 1989. Consanguinity in the Archbishopric of Toledo, Spain, 1900–79: types of consanguineous matings in relation to premarital migration and its effects on inbreeding levels. J Biosoc Sci 21:253–266.

Pen˜a JA, Alfonso-Sa´nchez MA, Caldero´n R. 2002. Inbreeding and demographic transition in the Orozco Valley (Basque Country, Spain). Am J Hum Biol 14: 713–720.