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Consanguinity and Prereproductive Mortality in the Utah Mormon Population

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Key Words
Consanguinity · Inbreeding · Prereproductive mortality · Utah Mormons

Abstract
To test the effects of parental consanguinity on mortality among offspring, inbreeding coefficients were estimated for 303,675 members of the Utah Mormon population who were born between 1847 and 1945. Although consanguinity has been relatively rare in this population, the large sample size permitted the identification of more than 3,500 inbred offspring. Among the offspring of unrelated parents, 13.2% died before the age of 16. Significant elevations in prereproductive mortality were seen among the offspring of first-cousin marriages (22%) and among the offspring of closer unions (32%). The corresponding relative risks are 1.70 (95% confidence limits = 1.52, 1.91) and 2.41 (95% confidence limits = 1.59, 3.41), respectively. Other categories of relationship did not produce significant elevations in offspring mortality. Similar results were obtained when a case-control approach was used to remove the effects of socioeconomic variation. Consistent with many other studies of populations with low consanguinity rates, this population experienced a relatively high absolute increase in mortality among the offspring of first-cousin marriages (9%). Preliminary evidence is offered for the hypothesis that mortality differentials are larger in populations with low inbreeding and low mortality because nongenetic causes of death do not obscure the effects of consanguinity.

The effects of consanguinity on human morbidity and mortality have long been the subject of inquiry and controversy [1–5]. The great majority of studies show that the offspring of consanguineous unions experience significant elevations both in morbidity and mortality, although the magnitude of these effects varies substantially among studies. This variation results from a variety of factors, including measurement error, small sample size, and the inability to control for confounding factors such as socioeconomic status. Despite these difficulties, the results are reassuringly consistent with population genetic theory in showing a general increase in morbidity and mortality among the offspring of consanguineous parents.

The Utah Latter-Day Saints (LDS, or Mormon) population offers several advantages for the study of the health effects of consanguinity. This population has been relatively homogeneous genetically [6, 7], and an extensive collection of family history records is available through the Utah Genealogical Society. These records have been assembled into a computerized genealogical database (Utah Population Database, or UPDB) containing more than 1.6 million individuals, affording an exceptionally

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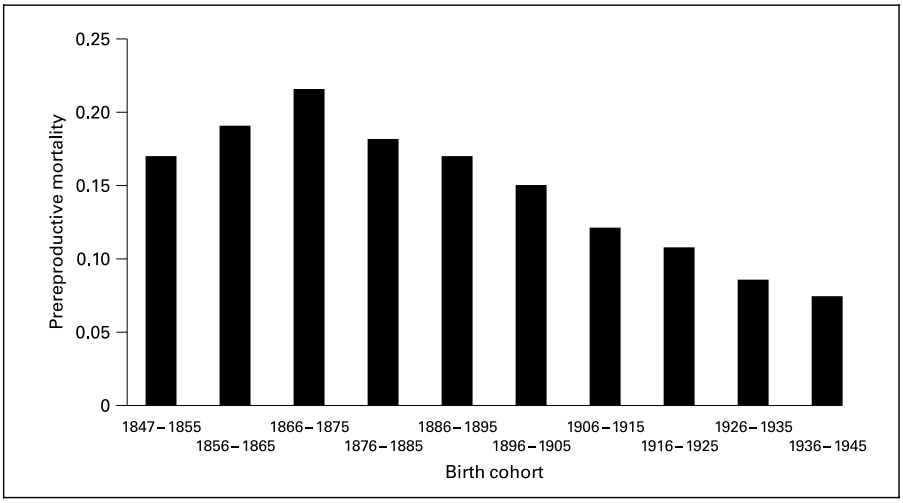

Fig. 1. Prereproductive mortality (death before age 16), expressed as a proportion, in each birth cohort.

Table 1. Sample sizes for each birth cohort

Year of birth	Number of births
1846–1855	1,022
1856–1865	4,237
1866–1875	10,122
1876–1885	21,729
1886–1895	34,372
1896–1905	43,491
1906–1915	51,225
1916–1925	53,432
1926–1935	45,297
1936–1945	31,951

large sample size. The Utah LDS population has been the subject of numerous genetic and demographic studies, facilitating detailed and accurate interpretation of results. Here, we report the results of a study of the effects of parental consanguinity on prereproductive mortality in a sample of more than 300,000 Utah-born subjects.

Methods

The study sample consisted of 303,675 individuals, extracted from the UPDB, who were born in Utah from 1847 through 1945 and for whom information was available regarding mortality and parental consanguinity. Prereproductive mortality was defined as death occurring before age 16. Individuals were designated as 'survivors' if their age of death exceeded 15 or if they were married (the latter criterion permitted the identification of individuals who survived but whose date of death was not recorded). Stillbirths were excluded from the analysis because of potential inaccuracy and reporting bias in family records. To assess temporal variation, the study sample was divided into 10-year birth cohorts.

Prereproductive mortality was first compared in the offspring of consanguineous and nonconsanguineous marriages. The database does not contain sufficient information on socioeconomic status to allow direct measurement of this variable. Previous studies have used nonconsanguineous siblings of consanguineous maters as controls [8], arguing that brothers are likely to have similar socioeconomic status. Using this scheme, we identified 676 brothers of consanguineous males who had married an unrelated female and produced offspring. A second comparison of mortality was then carried out for the 3,545 offspring of 676 consanguineous unions and the 3,723 offspring of 676 nonconsanguineous control marriages.

The inbreeding coefficient, F, was estimated for each individual using standard methods [9]. These coefficients were averaged for the total sample and for all members of each birth cohort.

Prereproductive mortality was estimated for the offspring of first-cousin, first-cousin-once-removed, second-cousin, and third-cousin matings and for a small sample of matings between relatives closer than first cousin (uncle-niece and double first cousins). The magnitude of the consanguinity effect in each category (relative to no consanguinity) was assessed statistically using odds ratios, relative risks, and population attributable risks.

Results

The sample size for each birth cohort is given in table 1. As the table indicates, most birth cohorts contained 10,000–50,000 or more individuals, and all cohorts contained at least 1,000 individuals. For the total sample, 13.2% of offspring died before age 16. As shown in figure 1, prereproductive mortality was substantially higher in earlier birth cohorts, exceeding 20% in the 19th

century. It then decreased substantially during the 20th century, reaching a low of 7% in the 1936–1945 birth cohort.

Among the 303,675 study subjects, 3,551 were the products of consanguineous unions. Of these, 1,048 were the products of first-cousin matings, 517 were produced by first cousins once removed, and 1,129 were produced by second-cousin matings. A small number of individuals (63) were the products of closer consanguinity (double first-cousin and uncle-niece matings), and the remainder resulted from more distantly related unions.

As seen in figure 2, mortality among the offspring of second- and third-cousin matings differed little from that of the offspring of unrelated parents. However, mortality increases substantially among the offspring of closer relatives. In particular, 22.4% of the offspring of first-cousin matings died before age 16, compared to 13.2% of the offspring of unrelated individuals. This represents a 9% absolute increase and approximately a 70% relative increase in prereproductive mortality for the offspring of first cousins. As expected, prereproductive mortality for the offspring of closer unions is even higher: approximately 31.7%.

To test for temporal effects, the sample was divided into pre-1900 and post-1899 birth cohorts. As expected, the mortality rates were higher for the earlier cohort: the proportions of offspring of unrelated couples dying before age 16 were 17.5 and 11.4% in the earlier and later cohorts, respectively. Among the offspring of first cousins, the proportions dying were 23.9% in the earlier cohort and 20.4% in the later cohort. For the offspring of first cousins once removed and second cousins combined, the percentages dying were 15.3 and 12.9% in the two cohorts, respectively. It is noteworthy that the mortality differential between the offspring of related and unrelated parents is substantially larger in the later birth cohort than in the earlier one.

Figure 2 also shows the mortality rates for the case-control study consisting of consanguineous males and their nonconsanguineous brothers. For most categories, the mortality rates do not differ appreciably from those of the total sample, indicating that this case-control matching procedure has little effect on the results. To the extent that this matching procedure controls for socioeconomic status, it can be concluded that socioeconomic status is not a significant confounding factor in this population.

In the total sample, the average inbreeding coefficient of the offspring who died before age 16 was 0.00056, which is significantly higher than the average inbreeding coefficient of those who survived (0.00035, $p < 0.0001$ by t test). A similar difference is seen when comparing the offspring who survived ($F = 0.016$) with those who died before age 16 ($F = 0.020$) in the case-control cohort ($p < 0.0001$ by t test).

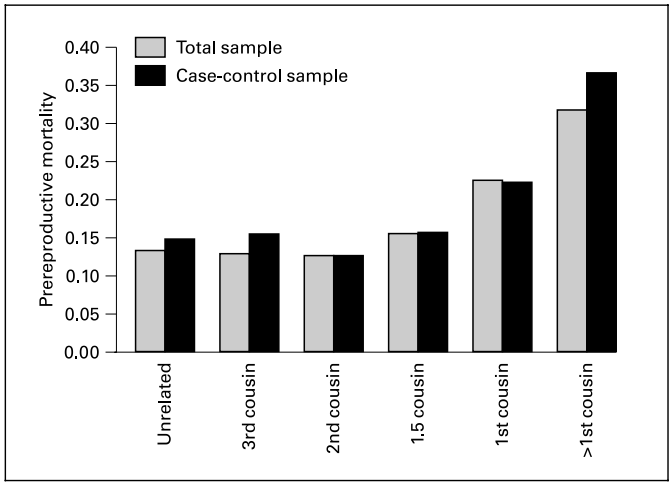

Fig. 2. Prereproductive mortality, expressed as a proportion, for the offspring of unrelated and related unions. Results are shown for the total sample of 303,675 individuals, as well as for the case-case control sample of the offspring of consanguineous matings and the offspring of nonconsanguineous brothers.

Table 2 shows the relative odds, relative risks, and population attributable risks obtained in comparing prereproductive mortality among the offspring of related and unrelated parents. The odds ratios are significantly elevated ($p < 0.0001$) for first cousins and closer relatives but not for other relationship classes. The relative risk for the offspring of matings closer than first cousin is 2.4, while it is 1.7 for the offspring of first cousins. Highly similar results were obtained when only the case-control sample was analyzed. The population attributable risks are very low, however, reflecting the fact that consanguineous unions are relatively rare in this population. Thus, although consanguinity at the first cousin level or greater exerts a significant effect on prereproductive mortality, it accounts for only a very small proportion of the total prereproductive mortality in this population (e.g., only 1 in 357 prereproductive deaths can be ascribed to first-cousin mating).

In table 3 relative risks for prereproductive mortality among the offspring of related and unrelated parents are compared for the two birth cohorts (pre-1900 and post-1899). Consistent with the mortality differentials noted above, the later birth cohort has higher relative risks for each consanguinity category than does the earlier one.

Table 2. Odds ratios, relative risks, and attributable risks (95% confidence limits in parentheses) comparing prereproductive mortality in the offspring of unrelated and related parents.

Relationship	Odds ratio	Relative risk	Attributable risk
>1st cousin	3.07* (1.75, 5.36)	2.41* (1.59, 3.41)	0.0003 (0.0001, 0.0006)
1st cousin	1.91* (1.65, 2.21)	1.70* (1.52, 1.91)	0.0028 (0.0020, 0.0035)
1.5 cousin	1.19 (0.93, 1.52)	1.16 (0.94, 1.43)	0.0003 (–0.0001, 0.0008)
2nd cousin	0.92 (0.77, 1.10)	0.93 (0.79, 1.09)	0.0
3rd cousin	0.96 (0.73, 1.26)	0.96 (0.76, 1.22)	0.0

* $p < 0.0001$, using χ^2 test with Yates correction.

Table 3. Relative risks (95% confidence limits in parentheses) comparing prereproductive mortality in the offspring of unrelated and related parents for births in pre-1900 and post-1899 cohorts

Relationship	Relative risk pre-1900	Relative risk post-1899
>1st cousin	1.75* (1.12, 2.52)	4.68 (0.86, 8.51)
1st cousin	1.37* (1.18, 1.58)	1.83* (1.49, 2.23)
1.5 cousin	1.13 (0.69, 1.74)	1.27 (0.98, 1.63)
2nd cousin	0.70 (0.42, 1.13)	1.10 (0.91, 1.33)
3rd cousin	–[1]	1.01 (0.73, 1.38)

* $p < 0.0001$, using χ^2 test with Yates correction.

[1] No deaths were seen in the small number of offspring of 3rd cousins in this cohort.

Discussion

Previous studies of the Utah Mormon population have demonstrated low rates of inbreeding, as measured by isonymy, migration matrices, and genealogical data [6, 10, 11]. Each of these studies demonstrated a gradual decline in consanguinity through time. Genealogical analysis shows little evidence of founder effect in this population [12]. Analyses of blood groups and protein polymorphisms demonstrated that this population is genetically very similar to northern European populations, indicating little genetic drift [13]. Furthermore, studies using restriction fragment length polymorphisms from eight subdivisions within Utah demonstrated a high level of genetic homogeneity in the population [7, 14]. These findings are consistent with the demographic history of the Utah Mormon population, which was founded by more than 100,000 individuals and has continued to receive large numbers of new immigrants. These studies are important in showing that the Utah Mormon population is genetically similar to other North American European-derived populations.

As in a previous study [6], the present analysis shows that the average inbreeding coefficient for this population is very low (F = 0.0004). Indeed, this F value is considerably lower than that of most other religious minorities in the United States. For example, an F value of 0.032 has been reported for a Hutterite population [15], a value of 0.011 has been reported for an Old Order Amish population [16], and values of 0.0062 and 0.0027 have been reported for Mennonite populations in 1800 and 1980, respectively [17]. Each of these populations was established by a much smaller number of founders than the Utah population, and, unlike the Utah population, they have remained relatively closed to outside immigration.

Although consanguineous unions are relatively rare in the Utah Mormon population, they do exert substantial effects on prereproductive mortality. A compilation of worldwide population data by Bittles and Neel [2] showed that the difference in prereproductive mortality between the offspring of first cousins and those of unrelated couples varied from nearly zero to approximately 29%. The 9% difference observed in this study thus lies well within this range, although it exceeds the reported median difference of 4.4%. This relatively large difference is consistent, however, with a pattern observed by Khlat and Khoury [4] in another large compilation: populations with lower rates of inbreeding (as in the case of Utah) tend to display larger prereproductive mortality differentials among the offspring of related versus unrelated couples. They attribute this to the successive elimination of deleterious recessive genes in populations that have experienced consanguinity for many generations. However, the evidence for this effect is necessarily rather sketchy, and the hypothesis has been questioned [1].

Another possible explanation, and one that has not yet been adequately explored, derives from the fact that most of the populations with higher inbreeding rates are located

in areas in which proportionately more deaths are caused by relatively 'nongenetic' factors, such as infectious disease. High mortality as a result of nongenetic factors may tend to obscure the effects of genetic factors, particularly if deaths due to nongenetic causes tend to occur earlier in life than deaths due to genetic causes. Some support for this hypothesis is offered by the data compiled by Bittles and Neel [2]. They list the mortality differential for the offspring of first-cousin and unrelated matings in 38 populations, along with the upper age at which mortality was monitored. Although the association is far from perfect, a positive and significant correlation ($r = 0.36$, $p < 0.03$) is observed between the mortality differential and upper age. This implies that genetic factors tend to play an increasingly important role in the mortality differential as inbred individuals and non-inbred controls become older.

Further support for this hypothesis is offered by the comparison of mortality differentials and relative risks in the pre-1900 and post-1899 birth cohorts. As noted above, the mortality differentials and relative risks are substantially smaller in the earlier birth cohort, when infectious disease played a larger role in mortality [18]. A similar pattern was observed by Khoury et al. [19], who observed higher relative risks due to consanguinity in their post-1930 Amish cohort than in their pre-1930 cohort. They postulate that inbreeding effects may be more readily observed under the 'favorable environmental conditions' experienced by the later cohort. To test this hypothesis more rigorously, analyses of specific causes of death in inbred and non-inbred subjects (stratified by age of death) should be carried out.

The relative risks and odds ratios show that consanguinity significantly elevates prereproductive mortality. However, consanguinity has always been relatively rare in the Utah population. Thus, it accounts for only a small proportion of early deaths, as revealed by the population attributable risk estimates. This analysis underscores the importance of considering the total public health burden of consanguinity in human populations.

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