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Inbreeding Effects on Fertility in Humans: Evidence for Reproductive Compensation

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Summary

The effects of inbreeding on prereproductive mortality have been demonstrated in many natural populations, including humans. However, little is known about the effects in inbred individuals who survive to adulthood. We have investigated the effects of inbreeding on fertility among inbred adult Hutterites and demonstrate significantly reduced fecundity among the most inbred Hutterite women, as evidenced by longer interbirth intervals ($P = .024$) and longer intervals to a recognized pregnancy ($P = .010$) but not by increased rates of fetal loss ($P > .50$). These data suggest the presence of recessive alleles that adversely affect fecundity among the population. In contrast, completed family sizes do not differ among the more and the less-inbred Hutterite women who were born after 1920, suggesting that reproductive compensation is occurring among the more-inbred and less-fecund women. This recent reproductive strategy would facilitate the maintenance of recessive alleles and contribute to an overall decline in fertility in the population.

Introduction

The deleterious effects of inbreeding on fitness are well documented in natural populations (reviewed in Thornhill 1993). In humans, small but significant increases in prereproductive mortality in the offspring of consanguineous matings have been demonstrated (Morton et al. 1956; Morton 1958; Schull 1958; Schull and Neel 1972; Khoury et al. 1987*a*, 1987*b*). The deleterious effects of inbreeding are presumably due to homozygosity for recessive alleles that adversely affect survival to adulthood, and they reflect the degree of relatedness between the parents of inbred offspring. Indeed, prereproductive mortality due to rare autosomal recessive disorders has been noted in human reproductive isolates and founder populations (reviewed in Vogel and Motulsky 1997). Thus, in human populations, consanguinity carries a theoretical risk for fetal abnormalities or death in early life (Harper 1988).

Because most studies of inbreeding in humans have focused on prereproductive stages of the life cycle, little is known about the effects of inbreeding in adults. However, inbred offspring who survive to adulthood may themselves show decreased fertility due to recessive alleles that could influence pathways involved in gametogenesis, hormonal cycling, sperm transport, ovulation, fertilization, or implantation. Recent studies in rodents have reported inbreeding effects in adult animals that result in reduced numbers of surviving offspring born to inbred mothers mated to unrelated males (Margulis 1996). The decreased fertility is attributable to the effects of recessive alleles in the inbred mother per se and not in her offspring, who were themselves outbred.

We initiated this study among Hutterites to evaluate the effects of inbreeding on fertility. Earlier studies in this population did not detect an association between the degree of relatedness between spouses (ϕ_{SP}) and the completed family size, but sample sizes were too small to evaluate the effects of inbreeding (F) of each spouse (Mange 1964). Consistent with these earlier findings, ϕ_{SP} was not associated with fetal loss rates or the length of intervals to conception in more recent studies in the Hutterites (Ober et al. 1992, 1998). Herein, using data derived from a 15-year study among Hutterites, we evaluate the effects of inbreeding on fertility among the inbred adult population.

Subjects and Methods

The Population

The Hutterites are an Anabaptist sect that originated in the Tyrolean Alps in the 1500s. The basic religious tenets of the population are the belief in adult baptism and the practice of a communal lifestyle. For the first

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200 years of their existence, religious persecution necessitated migrations throughout Europe, but in the 1770s, the Hutterites were granted religious freedom in Russia, where they lived for ~100 years. During their tenure in Russia, the population flourished and grew in size from ~120 to >1,000 members (Hostetler 1974). In the 1870s, they were denied religious freedom in Russia, and ~900 migrated to what is now South Dakota in the northern United States; roughly half of the Hutterite immigrants settled on three communal farms, and the rest settled as single-family farmers. Because of a high natural fertility rate and the proscription of contraception among communal Hutterites (Sheps 1965), the population expanded dramatically since migrating to the United States. Today there are >35,000 Hutterites living on >350 communal farms (called colonies) in the northern United States and western Canada. Genealogic records, collected by Steinberg and his students in the 1950s and 1960s (Bleibtreu 1964; Mange 1964; Steinberg et al. 1967), trace all extant Hutterites to <90 ancestors who lived during the early 1700s to the early 1800s (Martin 1970). The relationships between these ancestors are unknown, but some of them may have been related. As a result, our estimates of inbreeding based on the known genealogy may be underestimates of the true inbreeding coefficient. The three original South Dakota colonies have given rise to the three major subdivisions of Hutterite population structure, called the Schmiedeleut (S-leut), Dariusleut, and Leherleut, and members of each leut have remained reproductively isolated from each other since 1910 (Bleibtreu 1964).

The subjects of our studies, the S-leut Hutterites of South Dakota, are descendants of 64 Hutterite ancestors. In addition to being among the more-inbred human populations (Bittles and Neel 1994), the Hutterites are also among the most fertile (Sheps 1965), with average completed sibship sizes among S-leut families ranging from >10 in 1964 (Mange 1964) to ~8 in 1992 (Ober et al. 1992). The decrease in family size is due, at least in part, to the increased use of measures to limit family size, such as contraception and surgical sterilization.

Since 1982, we have visited 31 Hutterite colonies in South Dakota as part of our studies of human leukocyte antigen (HLA) and fertility in this population (Ober 1995, 1998). During our visits, a detailed reproductive history questionnaire was administered to all married adults who were present in the colony ($n = 396$). In addition, vital statistics (dates of birth, death, and marriage) were recorded from the colony records. In 1986, we initiated a prospective study of pregnancy outcomes in the Hutterites. Details of our protocol have been described (Ober et al. 1992, 1998). In brief, all married women who were still in their reproductive years ($n = 251$) were recruited into this study. Participants were provided with a calendar diary and e.p.t.® pregnancy test kits (Warner-Lambert) and were instructed to test for pregnancy 1 mo after their last menstrual period if menses had not begun. Dates of menses and results of all pregnancy tests were recorded in the diaries, which were collected yearly along with a short questionnaire eliciting additional information on use of birth control and nursing practices during the preceding year. Approval for this study was obtained from the Institutional Review Board of the University of Chicago.

Measures of Fertility

Three measures of fertility were used to assess the effects of inbreeding in three overlapping data sets. First, we examined interbirth intervals in the sample of 396 married women who were interviewed. We assumed that longer interbirth intervals would reflect either lower conception or implantation rates or higher fetal loss rates. This sample included subjects in the prospective study. Second, we examined both the length of the interval from the resumption of menses (after a previous pregnancy) to a positive pregnancy test (time to pregnancy) and fetal loss rates in the 251 women in the prospective study. Women who were practicing birth control or who were still nursing at the time of their first period were excluded from the study of interval lengths to pregnancy. We assumed that longer intervals would reflect lower conception or implantation rates. Last, we evaluated the completed family size in all S-leut women born after 1900 who are in our database ($n = 947$). The latter includes both US and Canadian S-leut women and all subjects with completed families in the first and second data set described above.

Statistical Methods

We calculated inbreeding coefficients (F) for each husband and each wife in our sample, using all known relationships in the genealogy, by the algorithm of Boyce (1983). The two variables, time to pregnancy and interbirth interval, were considered as "survival" times because they were censored time-to-event measures. Because our objective was to determine the effect of inbreeding on these two measures, the Cox proportional hazards model was used (Cox and Oakes 1984). Both univariate and multivariate analyses were used to assess the effects of those factors that were considered to be heterogeneous in the population and were thought to be associated with the time-to-event measures; these included mother's age and parity. Because our data include multiple observations for most couples, we used the method of Wei et al. (1989), with each couple's pregnancies as the cluster, to correctly estimate the standard errors (SEs), P values, and confidence intervals. All analyses were stratified by the mother's birth cohort (described below). The study of interbirth intervals included

2,286 intervals in 396 couples; the analysis of the intervals to a positive pregnancy test included 308 intervals in a subset of 155 couples who participated in our prospective studies (Ober et al. 1992, 1998).

Initial examination of the data indicated that the demographic and genetic structure of the population had changed over time. In particular, family sizes have decreased and inbreeding has increased (fig. 1). The Cox model assumes that hazards of covariates are proportional and that the proportionality remains constant over time. To take this time dependency into account, we stratified the model on age cohort, assuming that the hazards of each covariate remain proportional within each strata but that baseline hazards differ between the strata. Thus, we stratified our sample into three age cohorts. The first included women born prior to 1920. These subjects are roughly the same sample of Hutterites with completed families that was studied by Mange (1964). The second cohort included women born between 1921 and 1940. Nearly all of these women would have completed their families by 1980, the date of our last complete census of the S-leut population. The third cohort included women born after 1940 who had completed their families at the time of our last visit or interview. The mean (SD) pedigree depth for each of the three age cohorts was 7.7 (0.817) generations, 8.6 (0.062) generations, and 9.4 (0.62) generations, respectively.

Prior to examining the effects of inbreeding on the outcome variables (interbirth intervals and time to pregnancy), we determined the effect of each covariate (maternal age and parity) on the outcome variables by categorizing each continuous variable and fitting cohort-stratified Cox models. The results of the analysis evaluating the effects of maternal age on interbirth interval are shown in table 1. The parameter estimates indicate that the relationship between maternal age at childbirth and interbirth interval is monotonic but not linear (in the hazard ratio scale). If the relationship were linear, the parameter estimate would have exhibited a

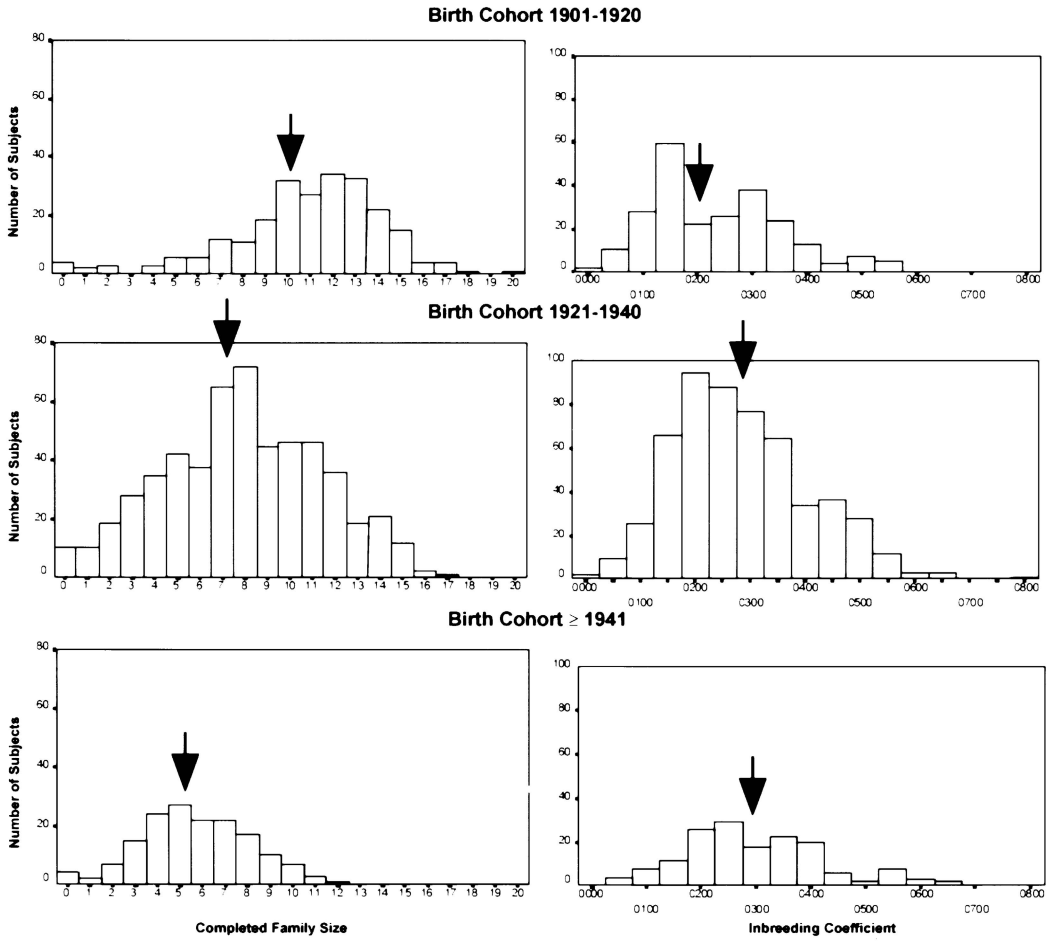

Figure 1 Distributions of inbreeding coefficients and completed family sizes among wives in three birth cohorts. Arrows show the mean value for each distribution. See text for details.

constant rate of change from one category to the next. Because the Cox model assumes that hazard ratios for continuous variables are log linear in the value of the variable, maternal age was included in the final model as one of four age categories (≤30, 31–35, 36–40, ≥41 years). In a similar manner, parity was included as one of two categories (0–1, ≥2 offspring).

This same strategy was used to consider each wife's F (F_w), each husband's F (F_h), and each couple's ϕ_{SP}. Initial category assignments for F_w, F_h, and ϕ_{SP} were based on the quartiles of the distribution of each variable. The Cox model parameters for these measures are shown in table 1. The only measure of inbreeding that approached statistical significance was F_w ($P = .07$ for $F_w > 0.037$). In addition, the magnitude of the effect as reflected by the parameter estimate was minimal for all categories of $F_w \leq 0.037$. On the basis of these results, the remaining models include two categories of F_w ($F_w \leq 0.037$ and $F_w > 0.037$). F_h and ϕ_{SP} were not included in any subsequent models. The final model evaluating the effects of F_w on interbirth intervals and time to pregnancy included the wife's birth cohort, maternal age at childbirth category, parity category, and F_w category.

The effects of inbreeding on fetal loss rates were evaluated by logistic regression analysis; the generalized estimating-equation approach of Liang and Zeger (Liang and Zeger 1986) was used to obtain SEs for the logistic regression analyses of the effects of inbreeding, HLA matching, and maternal age, as in our previous study (Ober et al. 1998). (In our previous study, we demonstrated that HLA matching and maternal age were significantly associated with fetal loss rates [Ober et al. 1998].) This method is preferable to standard logistic regression SEs because it allows for repeated observations (multiple pregnancies) per couple (Hauck and Ober 1991). The analysis of fetal loss included 251 pregnancies in 111 couples.

Among the 947 women with completed families, completed family sizes were compared among age cohorts by analysis of variance (ANOVA) and inbreeding by the general linear model (GLM), including pedigree depth as a covariate (SPSS statistical software package, version 7.5; SPSS Inc.).

Table 1

Estimation of the Effects of Categorized Variables on Interbirth Interval Lengths with the Cox Model

Variable	Parameter Estimate	SE	*P* Value	Rate of Change[a]
Maternal age (years)[b]:				
≤30	Baseline	…		…
31–35	−.6902	.0701	<.001	−.690
36–40	−.7802	.0818	<.001	−.090
≥41	−1.7196	.1947	<.001	−.939
Parity:				
1	Baseline	…		…
2–5	−1.2294	.0624	<.001	−1.229
≥6	−1.5564	.0715	<.001	−.327
Inbreeding coefficient:				
F_w:				
<.021	Baseline	…		…
.021–.028	−.0508	.0643	.43	−.051
.029–.037	−.0559	.0647	.39	−.005
>.037	−.1173	.0656	.07	−.061
F_h:				
<.021	Baseline	…		…
.021–.028	.0153	.0662	.82	.015
.029–.037	−.0279	.0636	.66	−.043
>.037	.0256	.0628	.68	.054
ϕ_{SP}:				
<.026	Baseline	…		…
.026–.035	−.0688	.0653	.29	−.069
.036–.046	−.0871	.0645	.18	−.0183
>.046	−.0772	.0665	.25	.0099

[a] Difference in parameter estimate from one level to the next.
[b] Mother's age at delivery.

Results

The distributions of F_w and completed family sizes for each birth cohort are shown in figure 1 for the 947 S-

Table 2

Cox Proportional Hazards Model of the Effects of Wife's Inbreeding, Maternal Age, and Parity on Interbirth Intervals in 396 Hutterite Women Stratified by Birth Cohort

Variable	Parameter Estimate	Robust SE	χ^2	Lower 95% CL	Upper 95% CL	Adjusted *P* Value
$F_w \geq .037$	.159	.071	5.05	.743	.980	.025
Maternal age (years):						
31–35	.630	.077	66.69	.457	.619	<.001
36–40	.759	.109	48.47	.378	.580	<.001
≥41	1.691	.190	78.93	.127	.268	<.001
Parity:						
2–5	1.210	.117	106.95	.237	.375	<.001
≥6	1.076	.133	65.96	.262	.442	<.001

NOTE.—Reference groups were $F < .037$, age ≤ 30 years, parity ≤ 1. CL = confidence limit.

leut women who had completed their families. Mean completed family size has decreased from 10.8 (SD = 3.88) in the 1901–1920 cohort to 7.9 (SD = 3.56) in the 1921–1940 cohort to 5.7 (SD = 2.44) in the post-1940 cohort (ANOVA, $P < .001$). However, the mean F has increased from 0.023 (SD = 0.012) to 0.028 (SD = 0.012) to 0.029 (SD = 0.013) in the three cohorts, respectively (GLM adjusted for generation depth, $P = .002$). Among the 396 women in our pregnancy study, which includes 132 women who have not yet completed their families, mean $F = 0.032$ (SD = 0.014).

F_w was a significant predictor of the interbirth interval length ($P = .025$) (table 2). Mother's age, mother's cohort, and parity were also significant predictors of the length of the interbirth intervals (table 2). Table 3 shows examples of interbirth interval lengths for mothers in the 36–40-year age cohort at parity 2–5. There were no statistically significant effects of father's F or couples' ϕ on the interval lengths ($P > .5$; data not shown).

To determine whether longer interval lengths in the more-inbred women were due to increased fetal loss rates or increased time to a recognized pregnancy, we evaluated these two outcomes in members of the prospective study. As reported elsewhere (Ober et al. 1998), F_w was not a significant predictor of fetal loss (parameter estimate, 0.0284; robust SE, 0.108; $P = .792$, adjusted for HLA sharing and maternal age), but it was a significant predictor of the length of the interval to a positive pregnancy test ($P = .010$). The median time to pregnancy was ~6 mo in women with $F \geq 0.04$, compared with <5 months in women with $F < 0.04$ (fig. 2). Thus, the longer interbirth intervals among the more-inbred women are due to longer intervals to a recognized pregnancy, not increased fetal loss rates.

Consistent with our finding of reduced fecundity among the more-inbred women, completed family sizes were smaller among women with $F \geq 0.04$ in the 1901–1920 cohort ($P = .019$), during which time completed family sizes were among the highest ever recorded in the Hutterites (table 4). However, family sizes in both groups of women have become smaller in more recent cohorts, and differences in size between the less-inbred and more-inbred women were neither larger nor significantly different in the 1921–1940 ($P = .589$) or the 1940–1960 ($P = .378$) cohorts.

Table 3

Interbirth Interval Lengths for Mothers Age 36–40 Years at Parity 2–5, as Predicted by the Cox Regression Model

Birth Cohort	Mother's Inbreeding	Median Interbirth Interval (mo)
Born:		
Before 1920	<.037	23.7
	≥.037	25.4
1920–1940	<.037	22.3
	≥.037	23.7
After 1940	>.037	25.0
	≥.037	28.2

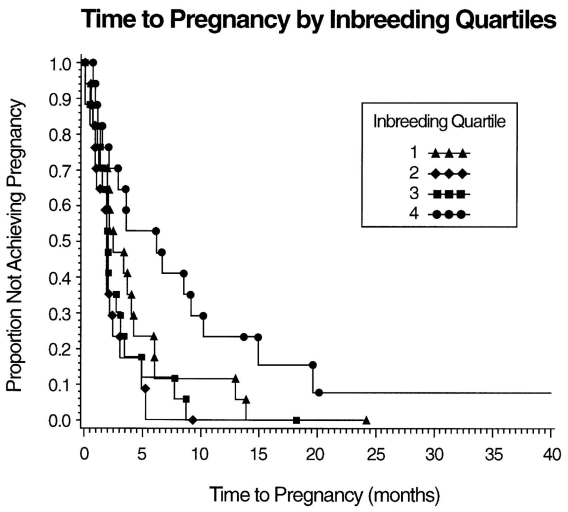

Figure 2 Survival analysis of time to pregnancy in prospective study. Each point on the "curve" represents the proportion of women who achieved pregnancy (y-axis) within a certain number of months (x-axis). Women were grouped by inbreeding coefficient into four quartiles. The fourth inbreeding quartile corresponds to $F \geq 0.04$.

Discussion

The effects of inbreeding during prereproductive stages of the life cycle have been well documented in animal and human populations, but few studies have focused on the effects in inbred individuals who survive to adulthood. The Hutterite communal lifestyle provides the opportunity to evaluate the effects of inbreeding without the confounding effects of socioeconomic factors, which are relatively uniform within the Hutterite population. To our knowledge, this study demonstrates for the first time a negative relationship between inbreeding and fitness in inbred adult women, suggesting that recessive alleles with adverse effects on fecundity are segregating in the population. Hutterite women with $F \geq 0.04$ show significantly longer interbirth intervals, which are due to longer intervals to a recognized pregnancy, not to increased fetal loss rates. Longer intervals to pregnancy could be due to either lower conception rates or higher peri-implantation loss rates in inbred women. Although it is impossible to distinguish between these alternatives at present, these data nonetheless indicate the presence of recessive alleles that affect female fecundity in the Hutterites.

Of interest, completed family sizes are not smaller among the more-inbred Hutterite women born after 1920, even though the adverse effects of inbreeding on fecundity are evident in these cohorts. These observa-

Table 4

Mean Completed Family Sizes in Birth Cohorts by Inbreeding Level

Birth Cohort	*n*	Mean (SD) Family Size		*P*[a]
		$F < .04$	$F \geq .04$	
Born:				
1901–1920	239	10.97 (3.38)	9.05 (3.67)	.019
1921–1940	547	7.92 (3.58)	7.71 (3.44)	.589
1941–1960	161	5.79 (2.40)	5.34 (2.62)	.378

Note.—Includes all S-leut women in our database with completed families (i.e., all women who survived to age 40 years and who were either ⩾40 years old or had undergone surgical sterilization at time of the last census). Not all women in the 1941–1960 birth cohort had completed their families at the time of our last census.

[a] By Student's *t* test.

tions suggest that reproductive compensation may be occurring in the more-inbred, less-fecund women in the latter two birth cohorts. In the classical sense, reproductive compensation after fetal loss or death of homozygous offspring among parents who are carriers of recessive alleles would slow the rate of loss of deleterious recessive alleles and maintain a balanced polymorphism in the population (Reed 1971; Schull and Neel 1972). Presumably, reproductive compensation occurs by reducing the interval to the next pregnancy after a miscarriage or the death of a child. However, in this case, the deleterious effects of homozygosity for recessive alleles are not apparent until the inbred children reach adulthood. Thus, the carrier parents would not have had the opportunity to compensate and would ultimately have passed relatively fewer of their genes to subsequent generations, because of the reduced fitness of their inbred daughters. In this scenario, the recessive alleles should eventually be eliminated from the population. The fact that there is no evidence of reduced fitness among the carrier parents of inbred offspring (i.e., couples with $\phi_{SP} \geq 0.04$) in the Hutterites suggests that this indeed should be the case. However, the distributions of family sizes shown in table 4 suggest that reproductive compensation may be occurring among the homozygous women in recent birth cohorts. This could occur if the culturally defined "optimal" family size was less than the reproductive potential of the population.

It is likely that the family sizes of the women with $F < 0.04$ who were born between 1901 and 1920 represent the maximum reproductive potential of the Hutterites and that women in this cohort reproduced to the end of their reproductive years. Thus, it would be very difficult (or impossible) for the more-inbred and less-fecund women in this birth cohort to "compensate" for their reduced fecundity. As a result, the women who were homozygous for deleterious recessive alleles affecting fecundity would have contributed relatively fewer genes to subsequent generations. However, an overall decline in fertility (as measured by completed family size) is evident in both the less-inbred and more-inbred women in both birth cohorts born after 1920; this is presumably due, at least in part, to the increased use of deliberate measures to limit family sizes. The decline in fertility among the less-inbred women has provided the more-inbred women with the opportunity to compensate for their lower fecundity, so the difference between the groups is reduced to nonsignificant levels. Thus, the more-inbred women have been contributing relatively more of their genes to the population in recent years as a result of the decline in fertility in the less-inbred women born after 1920. Such reproductive compensation among the more recent cohorts should facilitate the maintenance of these deleterious recessive alleles in the population.

In summary, reduced fecundity in the more-inbred Hutterite women indicates the presence of recessive alleles that adversely affect either conception or peri-implantation loss rates in the population. In contrast, completed family sizes among women born after 1920 are not different among the less-inbred and more-inbred women, which suggests that there is reproductive compensation among the more-inbred women, presumably to achieve a culturally defined optimal family size. This reproductive pattern should result in the maintenance of recessive alleles in the population that influence fecundity.

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