Perspective

THEORY

Consanguinity and the Developmental Origins of Health and Disease

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Abstract   *Background.* Consanguineous marriage is strongly favored in many regions of the world, despite the prevalent Western belief that the progeny of close kin unions experience developmental disorders and premature mortality. *Objective.* We outline an alternative perspective on the association between consanguinity and disease, in terms of life history theory and the developmental origins of health and disease. *Methods.* Meta-analyses of 64 studies across 14 countries and four continents were performed, comprising some five million births to first-cousin, second-cousin, and nonconsanguineous couples. *Results.* First-cousin marriage was associated with a mean increase of 3.7% in all-causes mortality, which is significantly lower than the large majority of previous reports. First cousins also married younger and showed greater fertility ($P < .0001$), possibly reflecting arranged marriage and the maintenance of family property. *Conclusions.* These findings are consistent with predictions from life history theory. We propose that close kin unions may maximize current reproduction while minimizing reductions in offspring reproductive value under conditions of chronic intergenerational poverty and inequality.

Keywords   consanguinity; inbreeding depression; life history theory; developmental origins of health and disease

1. Introduction

Intrafamilial unions have long been a reproductive strategy for humans [1, 2], especially after the rise of agriculture [3]. Cross-cultural data collated on 763 historical and recent societies showed that 353 (46%) either permitted or favored marriage between first and/or second cousins [4]. Today, in many parts of the world, well over 50% of marriages are consanguineous, predominantly between first cousins with a coefficient of inbreeding (F) of 0.0625, resulting in a minimum of 10.4% of the world's population married to a second cousin or closer ($F \geq 0.0156$) [5, www.consang.net]. An overall decline in consanguinity has been predicted, principally due to urbanization, with smaller family sizes and a consequent reduction in the numbers of marriageable cousins [5]. However, this trend will probably be slow in traditional rural communities [6], and it actually appears to have reversed in regions with a high level of ongoing terrorist violence [7, 8].

2. Does consanguinity cause inbreeding depression?

Notwithstanding its frequency, consanguineous marriage is often variously condemned on moral, religious, and scientific-medical grounds. In the absence of a demonstrably objective basis, moral and religious objections to close kin unions represent ethnocentrism or prejudice with, in some European countries, consanguinity conflated with forced marriage [9, 10]. Furthermore, while scientific-medical objections have been based on both theory and evidence, neither is as convincing as is commonly assumed. The Hardy-Weinberg principle provides the theoretical basis for opposition to cousin marriage: the less common the incidence of a mutant gene causing a recessive disorder, the greater the likelihood that the parents of an affected individual are genetically related. It is not always appreciated, however, that the Hardy-Weinberg principle represents an ideal state, an equilibrium from which changes in gene frequencies can be computed after introducing one or more specific factors that disturb the equilibrium. It does not apply when the equilibrium is disturbed by nonrandom mating, mutation, selection, random genetic drift, gene flow, or meiotic drive. The assumption of random mating is especially unrealistic for humans, the more so in communities where endogamy and consanguinity have been traditionally preferential.

Likewise, the evidential basis for objections to consanguineous marriage on health grounds is not as strong as often supposed. A recent monograph [5] selected studies for a meta-analysis of the association between consanguinity and early deaths that (a) had been published after 1959, (b) had a minimum sample size of 750, and, (c) where

feasible, had at least three consanguinity data points: first cousin, second cousin, and nonconsanguineous. These criteria produced 64 studies across 14 countries and four continents comprising a total of some five million births. Nonparametric sign tests confirmed an association between first-cousin marriage and adverse pregnancy outcomes, with a mean 3.7% increase in all-causes mortality from approximately the seventh month of pregnancy to eight to ten years of age calculated by unweighted regression. This estimate is significantly lower than a large majority of previous reports, which generally suffered from small sample sizes, poor sampling procedures, and failure to control for confounding variables, resulting in highly inconsistent and often exaggerated results [5].

A particular failing of most early studies was inadequate control for sociodemographic variables such as parental socioeconomic status, parity, interbirth intervals, and maternal age and literacy, each of which is known to have an independent effect on infant and child survival [5, 11, 12, 13, 14, 15]. From a genetic perspective, they also failed to adequately control for possible founder effects, effective population size, genetic drift, and population stratification, which have been shown to strongly influence the levels of genomic homozygosity at population level [16]. Since consanguinity mainly influences the expression and incidence of rare recessive disorders, in numerically small communities with a strict history of endogamous marriage some disorders may be widespread and the causative alleles may thus be too common for their expression to be significantly influenced by consanguineous marriage [5, 15]. In such a community, a recent study showed just a 1.8% increased postnatal risk of autosomal recessive lethal disorders at first-cousin level, raising the additional possibility that recurrent kin marriage in successive generations may have led to the effective purging of deleterious recessives from the gene pool [17].

3. Life history theory

In assessing the biological outcomes of consanguinity, environmental risk or uncertainty are also factors which, to date, generally have been overlooked (Figure 1). The optimality assumption in evolutionary biology [18] holds that selection will favor the capacity of organisms to preferentially allocate their limited resources, whether energy, nutrients, time, and so on, to solving their most pressing local adaptive problem in terms of fitness (i.e., staying alive, growing and developing, and producing and rearing offspring). Life history theory, formal modeling, and cross-taxa evidence show that when environmental conditions are risky or uncertain, resulting in high or unpredictable extrinsic mortality rates, the optimal reproductive strategy is to allocate resources preferentially to reproducing as early and/or as often as possible (the so-called "current" reproductive strategy). When resources are limited, those allocated to maximizing
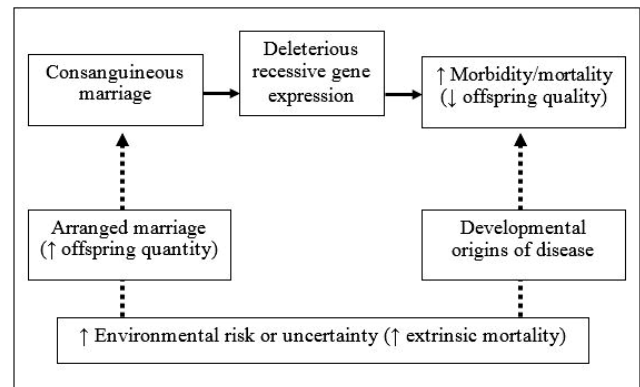
Figure 1: Schematic of the proposed relationship between consanguineous marriage and child health and survival. The standard model (solid lines) holds that consanguineous marriage results in the increased expression of deleterious recessive genes causing increased offspring morbidity and mortality. By comparison, our life history theory/DOHaD model (dotted lines) holds that environmental risk or uncertainty, manifested as chronic poverty or inequality, increases both the risk for the developmental origins of disease, with reduced offspring quality, and the probability of consanguineous marriage.

offspring quantity are unavailable for investment in offspring quality or reproductive value. In risky and uncertain environments, the quantity-quality tradeoff can be the optimal choice because parents often lack the resources necessary to improve offspring survival or reproductive success. Furthermore, maximizing the number of offspring increases the chance that at least one of their progeny will survive and reproduce, thereby minimizing the chance of lineage extinction in the short term. Hence, under unfavorable conditions, where lifespans are relatively short or unpredictable, it can be evolutionarily rational to sacrifice offspring health and survival to facilitate lineage continuation [19, 20, 21, 22].

4. The developmental origins of health and disease

Poverty and inequality cause substantial morbidity and premature mortality worldwide and are leading sources of environmental risk and uncertainty for humans [23, 24, 25, 26]. The most insidious pathways from poverty and inequality to morbidity and premature mortality begin at conception. These pathways have been collectively studied under the rubric of DOHaD, the "developmental origins of health and disease" [27]. According to the DOHaD model, chronic maternal malnutrition and psychosocial stress (hypothalamic-pituitary-adrenal activation) can adversely affect both fetal development (especially birthweight) and infant development, with a subsequent increased risk for many diseases and shortened lives [27, 28, 29, 30, 31, 32]. From the perspective of life history theory, these effects

are not, strictly speaking, pathological, but rather they represent the natural cost of reproduction under suboptimal circumstances. The assumption of optimality leads to the prediction that, under such conditions, organisms will have been selected to mature as early as possible, thus maximizing current reproduction. At the same time, this strategy entails sacrificing growth and development in the short term, even at the cost of future ill-health and increased mortality.

Mounting evidence is consistent with this prediction. First, in many parts of the developing world women with chronically inadequate nutrition typically begin childbearing in their teens and go on to have large families [33, 34, 35]. This superficial paradox—malnutrition accompanied by early reproduction—makes evolutionary sense. Reproductive suppression may be an adaptive response to acute stress, but chronically stressful environments are not likely to improve, making accelerated reproduction the evolutionarily optimal strategy [22, 35]. Second, women who experience chronic psychosocial stress in childhood due to risky, uncertain environments often have earlier menarche [36, 37, 38], which tends to maximize current reproduction. Consanguineous marriage itself also helps to maximize current reproduction through ease of marital arrangements, in turn permitting younger age at marriage and first live birth [5, 12, 39].

5. The ecology of consanguinity

In contemporary societies, consanguineous marriages are typically concentrated in countries and social groups or strata with low per capita income, and among first- and second-generation immigrants from these countries [5]. In such communities, low per capita income is coupled with inadequate maternal nutrition, poor public health, and low literacy, leading to an increased incidence of transplacental infection; low birth weight; high perinatal, infant, and child mortality; and stunting and wasting among surviving children. High rates of infant and child mortality result in early cessation of lactational amenorrhea, facilitating reproductive compensation and a decreased waiting time to the next pregnancy [39], thereby increasing the risk of uterine depletion.

On the other hand, consanguineous marriages are almost always arranged and often are associated with a significantly reduced or no dowry or bridewealth [40, 41, 42, 43]. Especially in unfavorable environments, with high and unpredictable mortality rates, consanguinity is widely regarded as a means of maintaining family property, including landholdings, strengthening intrafamilial relationships [5, 11, 44], and ensuring female status within the household [45, 46, 47, 48]. Individually and collectively, these social arrangements would tend to maximize current reproduction. This may be why first-cousin couples were found to be younger than noncousins at marriage and/or first birth in 17

of 18 studies conducted across 14 countries [5]. Further, a meta-analysis of 41 studies into the relationship between degree of consanguinity and fertility, measured as total live births, showed a positive association across all levels of consanguineous marriage, attaining statistical significance for first-cousin ($F = 0.0625$, $P < .0001$) and first-cousin once removed ($F = 0.0313$, $P < .02$) unions. In addition, a recent study of 12,439 marriages in 46 small-scale societies found a negative correlation between fertility and consanguineous marriage in foraging societies but a positive correlation in agricultural societies [3], possibly reflecting the increased risk and uncertainty associated with rising inequality after the origin of agriculture [49]. These findings are consistent with predictions from life history theory.

6. Conclusion

We propose that close kin unions have served as a form of downside risk protection against lineage extinction—that is, an evolutionarily adaptive cultural response to chronic intergenerational environmental risk and uncertainty. Consanguineous marriage tends to maximize current reproduction while minimizing reduction in offspring reproductive value. It may thus optimize the breeding distance between partners [3, 50], balancing the cost of deleterious homozygous recessive genes against the benefits of maintaining coadapted gene complexes [51], and concentrating limited resources in biological relatives. Future research could profitably approach consanguineous marriage as a form of cooperative breeding [52] in which kin "pool" their energy and material budgets and social capital [53, 54] in order to invest in offspring reproduction in the face of chronic poverty and inequality.

Conflict of interest The authors declare that they have no conflict of interest.

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