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The impact of consanguinity on neonatal and infant health.

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The impact of consanguinity on neonatal and infant health

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ABSTRACT

Marriage between biological relatives is widely popular in many parts of the world, with over 1000 million people living in countries where 20–50+% of unions are contracted between couples related as second cousins or closer. Consanguinity is, however, a controversial topic, in part due to public misunderstanding, complicated by often exaggerated past estimates of the adverse health outcomes. While some consanguineous couples are at high risk of conceiving a child with a genetic disorder, they are a small minority. Thus a multi-population meta-analysis has indicated an excess infant death rate of 1.1% in the progeny of first cousins, and even this figure may be compromised by inadequate control for non-genetic variables. The benefits as well as the disadvantages of consanguineous marriage are assessed and discussed, with specific consideration given to the health of migrant communities in Western countries, among whom first cousin marriage remains preferential.

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1. Introduction

For clinical purposes, consanguinity is usually defined as a union between two individuals who are related as second cousins or closer. However, the most common form of consanguineous marriage worldwide is between first cousins, who on average have co-inherited 1/8 of their genes from one or more common ancestors. First cousin offspring will therefore be homozygous at 1/16 of all loci, which is conventionally expressed as a coefficient of inbreeding (F) of 0.0625 [4].

The most recent consanguinity estimate indicated that some 10.4% of the world population are either married to a biological relative or are the progeny of a consanguineous union [6]. In fact, because of a lack of information on consanguinity in many populous South and Southeast Asian countries, and in sub-Saharan Africa, this estimate is deliberately conservative. Furthermore, the data refer only to marriages in the most recent generation, when in many regions of the world consanguineous unions have been a long-standing tradition. For this reason, in a large majority of populations, including communities in which consanguinity previously was considered to have been rare, individuals often exhibit extensive, uninterrupted runs of homozygosity because of close kin marriages in former generations [11].

To a large extent the present-day distribution pattern of consanguineous marriage matches that of adherence to the Islamic faith. But there is no prescription that Muslims should marry within

the family, and first cousin marriage is freely permissible in the Jewish, Christian Protestant, Buddhist and Zoroastrian/Parsi religions [7]. The preferred types of consanguineous marriage vary according to tradition, so that in Arab societies first cousin marriage between a man and his father's brother's daughter is most common, whereas in the Dravidian Hindu populations of southern India the strong preference is for a first cousin marriage between a man and his mother's brother's daughter, or more often marriage between an uncle and niece ($F = 0.125$).

First cousin and other more remote categories of consanguineous marriage are permissible under civil legislation virtually throughout the world. The USA is a notable exception, with varying forms and degrees of restrictive laws on consanguineous unions in 31 of the 50 states. Legislation on the prohibited types of cousin marriage dates back to the mid-19th century in some states, but in the case of Texas the prohibition was only introduced in 2005. Interestingly, equivalent civil law prohibitions on first cousin marriage apply in just two other countries, the People's Republic of China and the People's Democratic Republic of Korea.

In assessing the effects of consanguinity on health it is now accepted that variables such as socioeconomic status, maternal age, maternal education, birth order and birth intervals need to be adequately controlled. An additional factor that to date has not been fully considered is the impact of population subdivision on the expression of genetic disorders, even though intra-community marriage is the norm in regions where consanguineous marriage is favoured. Marriage in these populations is contracted within long-established, usually male lineages, e.g., within caste in India, *intra-biraderi* (literally brotherhood) in Pakistan, and within the *hamula* (clan) and tribe in Arab societies.

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As inter-community gene flow is restricted in most traditional societies, adjacent villages and even co-resident sub-communities may exhibit different and quite distinctive inherited disease profiles, reflecting the influence of small population size and hence limited marriage partner choice, local founder mutations, and genetic drift [4]. Population stratification may therefore be a major influence in the measurement of consanguinity-associated morbidity and mortality, with straightforward comparisons between the progeny of first cousins and unrelated parents genetically invalid unless both sets of parents are known to be members of the same caste, *biraderi*, clan or tribe [3].

2. The influence of consanguinity on reproductive behaviour

Across populations, mean maternal age at marriage and at first birth is generally lower in consanguineous unions. There also is evidence that women in consanguineous unions continue to bear children at later ages, which in part may be due to lower contraceptive usage. It could be argued that maternal–fetal genetic compatibility is enhanced in consanguineous pregnancies, to the benefit of the developing fetus. Alternatively, it has been proposed that a degree of maternal–fetal incompatibility is essential for fetal growth and development. An early report indicated lower rates of Rhesus (Rh) incompatibility in consanguineous pregnancies. It also was reported that pre-eclamptic toxemia was less common in consanguineous pregnancies, but more recent studies on pre-eclampsia have been equivocal, with some failing to confirm this result or even indicating a higher rate of the condition among mothers with first cousin partners.

Given their enhanced reproductive span, most studies have reported larger numbers of successful pregnancies and surviving children among consanguineous couples. In a meta-analysis of the mean number of live births to first cousin and non-consanguineous couples based on 40 individual studies, first cousin couples had a larger mean number of live births in 33 studies, which translated into an average of 0.08 additional births per family ($r^2 = 0.67$, $p < 10^{-9}$) [7]. Although the difference in the number of live births to first cousin and non-consanguineous couples is small, at population level the greater fertility of first cousins means that if both partners carry the same recessive mutation, there is a greater probability that they will bear one or more children with the encoded genetic disorder.

Matched genealogical data confirmed that in Iceland reproductive success was greatest at a level of parental relatedness approximating to third to fourth cousins ($F = 0.0039$ – 0.00098), suggesting a significant underlying biological contribution to the enhanced fertility of at least some consanguineous couples [10]. However, there is evidence that the greater mean number of births to first cousins may also reflect reproductive compensation, with early deaths rapidly replaced either by parental choice or because of the cessation of lactational amenorrhoea following the death of a breast-fed infant. Besides increasing mean fertility, where reproductive compensation does occur it can partially counteract the elimination of detrimental recessive alleles from the gene pool due to the death of an affected child.

3. Consanguinity, prenatal losses and stillbirths

Consanguinity does not appear to be associated with elevated rates of pathological sterility. Similarly, a large majority of studies failed to detect any significant increase in fetal loss rates among consanguineous couples. Care is needed in the interpretation of these latter data as the focus was largely on events in the last trimester, although most losses are believed to occur during the early stages of pregnancy, both pre- and post-implantation. The majority of abortions occurring during early pregnancy due to genetic disorders or other causes are therefore effectively discounted, resulting in significant under-estimation of prenatal losses. However, indirect indicators of fetal

survival, such as multiple birth rates and the secondary sex ratio, also have failed to indicate any adverse effect of consanguinity.

To determine the influence of consanguinity on early deaths, results were derived from a series of meta-analyses using a dataset assembled from 79 studies conducted in 15 countries across four continents, with information on some five million pregnancies and births ([6]: Supplementary Information S1). For inclusion, each study had to include a minimum of 750 subjects and three consanguinity categories. The dataset optimally contained information on six categories of consanguineous relationship: uncle–niece/double first cousin ($F = 0.125$), first cousin ($F = 0.0625$), first cousin once removed ($F = 0.0313$), second cousin ($F = 0.0156$), beyond second cousin ($F < 0.0156$), and non-consanguineous ($F = 0$). The number of categories of relationship for which data were available varied between individual studies, but first cousin unions were by far the most numerous form of consanguineous marriage. Data derived from the meta-analyses are presented in Figs. 1–3 as unweighted linear regressions comparing stillbirths ($n = 46$ studies), neonatal deaths ($n = 30$ studies), and infant deaths ($n = 48$ studies) in the progeny of first cousin versus non-consanguineous couples.

The overall picture for stillbirths is summarized in Fig. 1, and shows an excess 1.5% deaths at first cousin level ($r^2 = 0.27$, $p < 0.0002$). The rather low r^2 value for stillbirths is largely caused by two outlier results (numbers 20 and 21) representing two different caste communities in a single rural South Indian study. If these two studies are omitted, r^2 increases to 0.55 indicating a more cohesive dataset, and the excess mean stillbirth rate at first cousin level is reduced from 1.5% to 0.7%.

4. Consanguinity, birth outcomes and measurements

Surprisingly, few studies appear to have been conducted into possible associations between consanguinity and neonatal distress as measured by Apgar scores. As with the data on prenatal losses and stillbirths, the results of investigations into the relationship between consanguinity and birth measurements have been mixed. While some authors have reported that babies born to consanguineous parents are smaller, lighter, and therefore less likely to meet developmental milestones or survive, an approximately equal number failed to detect any significant consanguinity-associated difference. Possible reasons for these contradictory findings include variability of the investigative protocols employed, the use of simplistic 'consanguineous' versus non-consanguineous comparisons, and limited or no control for

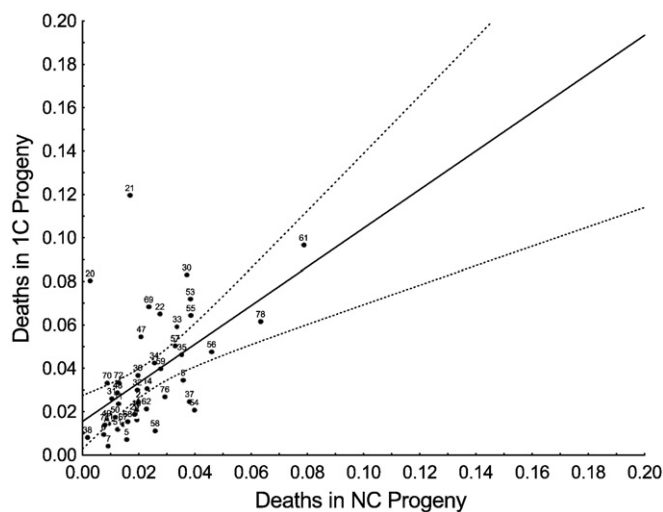


Fig. 1. Comparative stillbirths (%) in first cousin (1C; $F = 0.0625$; y axis) versus non-consanguineous progeny (NC; $F = 0$; x axis) in 46 study populations. Dashed lines indicate 95% confidence limits.

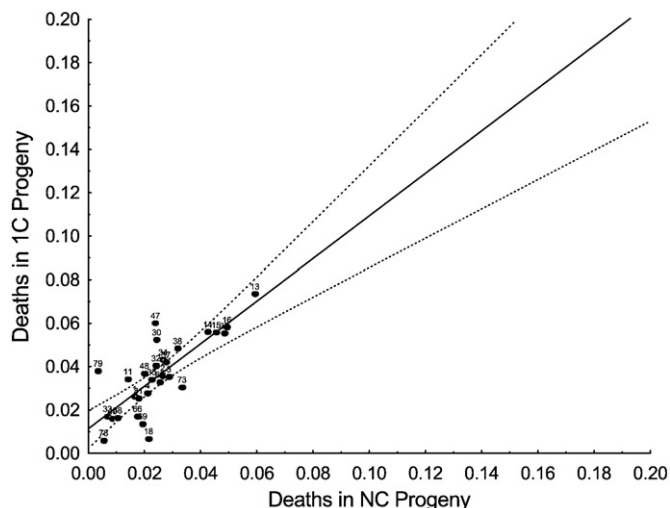


Fig. 2. Comparative neonatal deaths (%) in first cousin (1C; $F=0.0625$; y axis) versus non-consanguineous progeny (NC; $F=0$; x axis) in 30 study populations. Dashed lines indicate 95% confidence limits.

potential confounding factors, including socioeconomic status, and maternal age, nutrition, health status and disease. The importance of these latter factors was illustrated in a study in Jordan. Although univariate analysis indicated a highly significant positive association between consanguinity and low birth weight, when multivariate analysis was used to control for age, body mass index, occupation, education, smoking, gravidity, parity, medical problems during pregnancy, and a family history of premature deliveries, the statistical significance of the association with consanguinity disappeared [12].

5. Consanguinity and deaths in the neonatal, postneonatal and infant periods

There is a general consensus that postnatal morbidity and mortality are both elevated in the progeny of consanguineous unions. Estimates of the overall adverse effects of consanguinity have been very variable and in many cases they appear to be improbably high, in large part due to inadequate control for important non-genetic variables that are known to influence childhood health, including maternal age and education, birth order, and birth intervals. It also is unclear whether gynaecological immaturity is a significant factor,

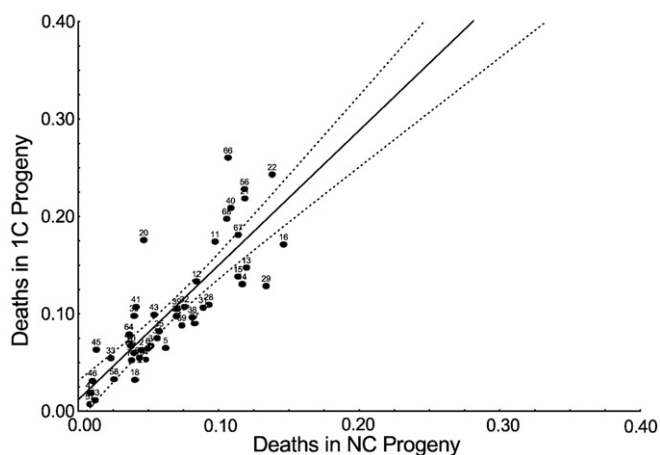


Fig. 3. Comparative infant deaths (%) in first cousin (1C; $F=0.0625$; y axis) versus non-consanguineous progeny (NC; $F=0$; x axis) in 48 study populations. Dashed lines indicate 95% confidence limits.

given the younger mean ages at first pregnancy of women in consanguineous relationships.

As illustrated in Fig. 2, among first cousin progeny there was a mean excess of 1.1% deaths ($r^2=0.61$, $p<10^{-5}$) during the neonatal period, and for infant deaths (Fig. 3) the equivalent figure also was 1.1% excess deaths ($r^2=0.70$, $p<10^{-5}$). As with the data on stillbirths, both the neonatal and infant mortality plots identified small numbers of outliers. However, at both age intervals no consistent association with particular studies was apparent and the effects appeared to be random.

6. Consanguinity and birth defects

A significant positive association has been consistently demonstrated between consanguinity and morbidity, and congenital defects with a complex aetiology appear to be both more prevalent in consanguineous families and have a greater likelihood of recurrence. Childhood deafness has been commonly associated with consanguinity and, for example, in the United Arab Emirates 92% and 57% respectively of cases of non-syndromic and syndromic deafness were attributed to autosomal recessive inheritance [1]. Although consanguinity-associated blindness is less frequent, autosomal recessive retinitis pigmentosa is a more common finding in populations where intra-familial marriage is favoured, and increased rates of congenital cataracts also have been reported in several populations.

A higher prevalence of birth defects has been reported among first cousin couples in all populations, but the excess rates among first cousin progeny have varied from 0.7% to 7.5%, with differing study protocols, variable sample sizes, and limited control for sociodemographic variables making a detailed summary problematic. Elevated rates of consanguinity have been consistently reported for congenital heart defects, in particular atrial septal defect and ventricular septal defect, suggesting the involvement across populations of recessive gene variants with similar phenotypic outcomes. For other abnormalities, such as transposition of the great vessels, coarctation of the aorta, pulmonary atresia and tetralogy of Fallot the results varied between study centres, indicating that population-specific mutations may have been responsible. Studies on neural tube defects also have shown positive associations with consanguinity, possibly in conjunction with the generally poorer socioeconomic status of consanguineous couples, but to date published information on oral and facial clefts has been variable, with both positive and negative associations reported.

A recessive gene coding for non-disjunction of chromosome 21 was proposed to explain the apparent excess of Down syndrome babies born to younger consanguineous parents in Kuwait, but the existence of such a predisposing gene for trisomy 21 has been disputed in other populations. Definitive resolution of this issue will require large-scale epidemiological studies incorporating control for all appropriate non-genetic variables, in particular maternal age. In the interim, a genetic explanation for an association between Down syndrome and consanguinity in some specific Middle Eastern kindreds and sub-populations remains possible. The observation that congenital heart defects appear to be more severe, and some specific types of defect are more common in individuals with Down syndrome born to consanguineous parents also merits further study, especially given the rapidly increasing life expectancy of people with Down syndrome.

As with birth defects, single gene disorders with an autosomal recessive mode of inheritance are present at higher frequency in consanguineous progeny, and the rarer the disorder the greater the proportional influence of consanguinity on its expression [2]. To avoid community misunderstanding, it is important to clearly differentiate between risk estimates cited at the population versus the family level. Thus although excess incidence rates of 2–4% are widely quoted for autosomal recessive disorders in the children of first cousins, at

individual family level the observed risk can vary from zero to 25% or higher [15].

In countries and communities in which endogamous marriage has resulted in distinct genetic subdivisions, and dependent on the age of the mutation, specific single gene defects have been shown to be unique to particular sub-groups or individual families. Multiple recessive mutations may segregate in individual consanguineous families within highly endogamous communities, which can significantly complicate genetic education and genetic counselling programmes [8]. In some consanguineous families the situation is made even more complicated by the co-existence of different mutations encoding the same recessive disease phenotype.

7. Migrant communities and consanguineous marriage in Western societies

Until the mid-19th century, first cousin marriage was quite common in Great Britain and other Western European countries, especially among wealthier, landed families. Thereafter the prevalence of consanguineous marriage declined, partially in response to the major population relocations that accompanied industrialization, and less than 1% of marriages in most autochthonous populations in Europe are currently consanguineous (www.consang.net). But since the middle of the 20th century there has been substantial immigration from countries where consanguineous marriage is preferential, and informal estimates for Western Europe suggest at least 10 million such resident migrants, mainly drawn from North and sub-Saharan Africa, the Middle East, Turkey and Central Asia, and South Asia.

8. Consanguineous marriage in UK migrant communities

Population ethnicity data for the UK are somewhat dated, but according to the 2001 Census there were approximately 1.05 million people of Indian ancestry, 750,000 Pakistanis, 283,000 Bangladeshis and some 250,000 persons from other Asian countries. In addition, there were an estimated 485,000 Black African residents in the UK, many of whom, together with the sizeable Somali community, are of probable consanguineous parentage. Currently, little reliable or representative information is available on these sub-populations.

Nationally representative data for Pakistan collected in the early 1990s indicated that 61.2% of marriages were consanguineous, equivalent to a mean coefficient of inbreeding (α) = 0.0332; i.e., the consanguinity level of the population as a whole approximated to a first cousin once removed relationship (F = 0.0313). Comparable data for the UK Pakistani community, which mainly originates from the district of Mirpur in Azad Kashmir and from northern Punjab, have indicated similar and even higher levels of cousin marriage, and with no obvious recent decline in the prevalence of first cousin unions as recently reported for the Pakistani community in Norway. However, a report from Nottingham suggested a much lower level of consanguineous marriage (33–37%) in the local Pakistani community, which may indicate some degree of heterogeneity in the marriage preferences of individual UK Pakistani sub-communities.

As the UK Indian community largely originates from North India where there is a strict proscription on consanguineous marriage for Hindus, their overall level of consanguineous marriage is low. Conversely, consanguineous marriage would be expected to be widely preferential among migrants from the southern states of India, and in Muslim communities from all regions of India. There is only fragmentary information on the prevalence of consanguineous marriage in Bangladesh, but consanguinity does appear to be quite common in the UK Bangladeshi community, albeit with no firm confirmatory data. With respect to persons from other Asian countries, in most South, Central and West Asian countries some 20–30% of marriages are consanguineous (www.consang.net), and it

would be expected that this pattern would be continued in first and probably second generation migrant families.

Many studies have drawn attention to the below average health status of the UK Pakistani community, with their high prevalence of consanguineous marriage often identified as a causal factor for the elevated rates of single gene disorders and other syndromic conditions. Indeed, a five-year prospective study on births in Birmingham during the 1980s concluded that if the tradition of consanguineous marriage was abandoned by the Pakistani community, a 60% reduction in deaths and severe morbidity would be achieved [5]. An associated study further reported that the overall prevalence of inborn errors of metabolism in UK Pakistani children was ten-fold higher than in children of European heritage, among whom parental consanguinity was estimated to be 0.2%.

A puzzling feature of these studies is that the prevalence of rare recessive disorders was reported to be high in the UK Pakistani community; yet only consanguineous couples gave birth to children with a recessive disorder, which implies that the overall incidence of the causative disease genes in the community must be low. This is a serious contradiction which, as yet, has not been satisfactorily addressed or explained, and is best considered in terms of the marriage preferences and practices of the Pakistani and other communities which favour consanguineous marriage, and the effects that these practices have on the transmission of genes.

From a genetic perspective the major and ongoing oversight is failure to adequately consider and allow for the effects and influence of population subdivision, which in the UK Pakistani community is mainly determined by *biraderi* membership, where the *biraderi* are hereditary social/occupational lineages intimately involved in many aspects of family and community life. As previously discussed, where population substructure exists, whether due to ethnic, geographical, religious or social divisions, the sizes of the breeding pools of each sub-community are reduced, thereby simultaneously decreasing marriage partner choice and increasing the influence of genetic drift. The net result is random inbreeding, with rapid divergence of sub-community marker allele frequencies, and with specific mutations restricted to individual sub-communities or even to specific families [3,6,13]. For this reason, in genetically subdivided communities, calculation of the frequency of recessive disease genes from combined disease prevalence data and overall consanguinity estimates is inappropriate and predictably results in erroneously elevated estimates.

It could be argued that the practice of seeking brides and grooms from Pakistan for UK-born members of the Pakistani community widens the potential choice of marriage partners. In reality this does not occur, as most such trans-national marriages are contracted between couples who are consanguineous, or are at least members of the same *biraderi* [14], and hence they are genetically related to a significant degree. Given the absence of detailed data or discussion on this central aspect of the genetic structure of the Pakistani community, it is currently impossible to determine the extent of the resultant exaggeration of the adverse consanguinity effect on health. However, it seems beyond doubt that significant exaggeration has occurred, and the nexus between population substructure, gene expression and the frequency of genetic disorders needs to be urgently addressed.

9. Discussion

Consanguineous marriage remains a subject that arouses fierce debate in many parts of the world, with partisan opinions expressed on all sides. Unfortunately, and all too frequently, these opinions are based more on prejudice than fact. Confidentiality concerns can restrict or even preclude access to health records, which seriously limits the quality of the data available for analysis. The highly publicized interventions of possibly well-meaning, but certainly

under-informed politicians, also have been notably unhelpful in fostering informed discourse.

Over-emphasis on the contributory role of consanguinity alone to ill-health has led to numerous misconceptions among health care practitioners and in the public mind. It also has caused unease and upset in communities which traditionally have favoured consanguineous marriage. In assessing the overall impact of consanguinity on health outcomes a number of points merit emphasis:

1. Consanguineous marriage is not restricted to specific religions or to population isolates. Rather it is a long-standing practice in many regions of the world and it continues to be preferred by many populations, with more than 1000 million people living in countries where 20–50+% of marriages are consanguineous. It often is forgotten that judgements on the outcomes of consanguineous marriage are largely dependent on the current socioeconomic (and political) circumstances of a population. As these circumstances alter, the balance between the benefits and disadvantages of consanguinity also varies.
2. Close kin marriage facilitates the expression of rare recessive disease genes, but consanguinity does not *cause* genetic disease. It is noteworthy that since the mid-20th century estimates of consanguinity-associated pre-reproductive mortality have declined from 11.0% to 3.5%, reflecting improved sampling protocols and control for non-genetic variables. Consanguinity studies based on small numbers occasionally produce data that are outliers (e.g., Fig. 1). While of interest, it is inappropriate and unwise to extrapolate and generalize from such results.
3. In assessing health problems that may be associated with consanguinity, risk rates should be expressed in absolute and not in proportional terms. Expressions such as a 'doubling of risk' are essentially meaningless unless accompanied by a denominator, and they frequently provoke misunderstanding and unnecessary alarm.
4. In families which are known to carry a recessive mutation, it is unwise to assume that the affected progeny of a consanguineous union will necessarily be homozygous for the disease allele. While the inheritance of identical disease alleles from each parent would usually be expected, increasing numbers of examples have been reported in which affected offspring were compound heterozygotes.
5. The critical role of intra-community marriage in determining the spectrum and incidence of mutations has been consistently underestimated and/or ignored. Reliance on composite estimates for the incidence of inherited disorders in populations comprising multiple, endogamous sub-communities can produce spurious results and lead to inappropriate genetic counselling guidance. While the avoidance of consanguineous marriage in subdivided populations should reduce the incidence of recessive disorders, the effect will be less pronounced than has been supposed.
6. Consanguinity can have favourable as well as unfavourable biological effects, via the homozygous expression of beneficial recessive genes. In populations which favour consanguineous marriage, the circle of family members who can act as successful tissue donors also is significantly extended thus reducing reliance on sibling donors.

10. Conclusions

Most countries where consanguineous marriage is favoured are currently undergoing rapid urbanization which, together with enhanced educational and employment opportunities for males and females, offers access to larger potential marriage pools. At the same

time family sizes are declining, to the extent that in future generations there may not be a biological relative of appropriate age and the socially preferred type of cousin relationship for a close kin marriage to be considered. It therefore seems inevitable that in these populations the prevalence of consanguineous marriage will decline in future generations, as was the case in Western Europe from the mid-19th century onwards. What remains unclear is the extent of the beneficial effect this change will exert on genomic heterozygosity and overall population health [9], especially if marriages continue to be preferentially contacted within sub-communities.

The perceived social and economic benefits of consanguinity are often under-estimated, yet in the case of chronic incapacitating diseases the role of family support is of great importance. A decline in the prevalence of consanguineous marriage could result in the effective loss of extended family support networks, with the burden of disease increasingly focused on parents. Against this background, and in the light of the statistically significant but quite limited levels of consanguinity-associated mortality and morbidity, calls in the UK for legislation to prohibit first cousin marriage, while superficially credible, are in reality quite facile. To facilitate the prevention of genetic disorders and ensure that families with an affected child receive the necessary medical and social assistance, premarital, preconceptional and prenatal genetic education and genetic counselling programmes focused on, and delivered at, family and community levels offer a preferable and more efficacious option.

Supplementary materials related to this article can be found online at doi:10.1016/j.earlhumdev.2010.08.003.

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