the British Medical Journal. These selected respondents reported a very high incidence of first-cousin marriages in their families. A smaller proportion of marriages were with more distant cousins, but Pearson remarked that second and third cousins in these families were also often related in more than one line. He lumped them all together and concluded that ‘consanguineous marriages in the professional classes probably occur in less than 8% and more than 5% of cases’. Yet, only 1.3% of patients in the Great Ormond Street Hospital for Children were the children of cousins. Pearson concluded that ‘the diseases of children are not largely due to any consanguinity between their parents’.21

Endorsed by the Darwinian establishment, George Darwin’s conclusions reassured many people whose family trees featured marriages between cousins. Englishmen could also rest more easy when they considered that Queen Victoria was married to a first cousin, and that several of her descendants had also married cousins. And Darwin’s conclusions seemed only common sense to landowners in the House of Lords, who knew that the inbreeding of good stock was sound policy.

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parents who are related as first cousins or closer, whereas it is not clear that similar effects are seen among children of parents who are second cousins or more distant relatives. Recent studies on the frequency of consanguinity have shown that it is not rare and declining in human populations, but prevalent and perhaps increasing globally. To date, studies on the effects of consanguinity at a population level have not been successful in establishing consensus about the kinds and sizes of these effects. However, as other causes of disease and death are declining in many regions of the world where consanguinity is prevalent, the relative importance of consanguinity as a risk factor for disease and death increases.2–4

A project to determine the global burden of disease due to consanguinity has been established under the leadership of Alan H Bittles, and the results of this project will be important for evaluating the public health impact of consanguinity worldwide (Alan H Bittles, personal communication).

The global prevalence of consanguineous marriage

Historically, there has been a diversity of rules concerning marriage between close relatives, changing over time, and varying between different societies and social classes. There are indications that the ancient Egyptians in certain periods encouraged mating between brothers and sisters. Cleopatra VII was the child of a brother and a sister. She married her two younger brothers, but had no children with them. Later, she gave birth to children in her relations with Marcus Antonius and Julius Caesar.5

It is now clear that consanguineous marriage is common in many parts of the world. The most thorough overview of the global prevalence of consanguineous marriage has been compiled by the British–Australian geneticist and professor Alan H Bittles. He has conducted extensive research on the prevalence and medical consequences of consanguineous marriage during the last three decades, and is the leading international authority within the field. The overview is accessible at Bittles’ web site http://www.consang.net 6 and in several of his publications.1,7–9

According to current studies, consanguineous marriage is most common in North Africa, the Middle East, Western Asia and South India. In these areas, 20–50% of all marriages are between consanguineous partners. In South America, North India and Central Asia, the proportion is 1–10%. In other words, more than half of the world’s population live in areas where consanguineous marriage is widespread.

In Japan, consanguineous marriage used to be common, but the tradition declined as the country was industrialized and became prosperous after World War II.1 In poor countries, the family is often the main—sometimes the only—provider of welfare and security. The choice of spouse is not only a matter of personal preference, but also a matter of securing the welfare and property of the family. In most countries where consanguineous marriage is common, it is most prevalent among those with low income and little education, and among people living in rural areas.1 This pattern is not without exceptions, because consanguineous marriage is also practiced by rich families to preserve properties and estates. Consanguinity was common among European royalty and aristocracy up until the middle of the 1900s, and the two first Norwegian kings after independence from Sweden in 1905, Haakon VII and Olav V, were both married to first cousins, the British Queen Maud and the Swedish Crown Princess Märtha, respectively. As described by Adam Kuper12 in a commentary in this issue of the IJE, George Howard Darwin (1845–1912) published a study in 1875 on ‘Marriages between first cousins in
England and their effects,13 where he made an immense effort to make up for the evidence lost when a proposal to insert the words ‘Were your father and mother first cousins or not?’ in an upcoming census was defeated in the House of Commons. George Darwin describes in a personal tone, with great detail and honesty, how he suffers the ordeals of complex data collection, only to achieve data that are at best indicative of what he could have had if the information had been collected routinely from the total population.

Rediscovering consanguinity

Studies on consanguinity have to a large extent aimed at identifying patterns of inheritance and single mutations in families where rare diseases occur, whereas there has been limited interest in the gross effects of consanguinity on a population level. Although some countries, such as Pakistan, have included questions about consanguinity in demographic surveys and censuses, there is, to the author’s best knowledge, no country in the world other than Norway that performs routine registration of close biological relations between parents.

A small group of people has been important for the rediscovery of the high prevalence and effects of consanguinity, and for introducing epidemiological perspectives into the field. In 1987, Khoury and collaborators published a review of studies on the effects of consanguinity on mortality before the age of 20 years, using relative and attributable risks to assess the role of consanguinity.10 Khoury then concluded, in line with textbooks and common perceptions at the time, that consanguinity was rare and had little effect both on an individual level and on public health. The belief that frequencies of consanguinity were low and declining was challenged a few years later when Allen Bittles and his collaborators published a groundbreaking article in ‘Science’, where they estimated that between 20 and 50% of all marriages in many regions of Africa and Asia are consanguineous.7 In the same year, Khlat and Khoury reviewed reports that the proportions of consanguineous marriages in Arab countries ranged between 22 and 54%.14 After 1991, several reports on high frequencies of consanguinity have been published. For example, data from the 1990/91 Pakistan Demographic and Health Survey showed that at a national level 49.4% of all marriages were between first cousins, 10.8% were between second cousins and 1.4% were categorized as between other cousins.15 One reason why the high global prevalence of consanguinity was discovered in the 1990s may be that it is common in some immigrant populations of Western Europe, as shown in British and Norwegian studies.16–18 Sarah Bundey and collaborators estimated the coefficients of inbreeding for babies in Birmingham using ancestral information for four generations, showing that 69% of the Pakistani children had parents who were closely related, and 40% had parents who were more closely related than first cousins.16 Data from the Medical Birth Registry and Statistics Norway show that among parents with Pakistani origin, ~44% were related as first cousins or closer and the total prevalence of parental consanguinity was 55% up until 2001, after which the proportion of couples who are first cousins has declined to about 29% and the total prevalence to 40%, thus showing a decline in the frequency of consanguineous marriage over time and generations since the 1980s.3,18

Genetic effects of consanguinity

Careful examination of inbred families is a widely used method for identifying recessive diseases, but studies on consanguinity can be used to evaluate the effect of increased homozygosity in any disease. The probability of homozygosity for any allele increases, including alleles that are deleterious and may cause disease and death. Consequently, offspring of consanguineous parents are at an increased risk both for monogenic autosomal recessive disorders and for conditions with multifactorial inheritance. Theoretically, the increase in risk is proportional to the degree of inbreeding (expressed as the coefficient of inbreeding, F). For conditions with recessive inheritance the relative increase may be considerable, whereas for multifactorial inheritance, the risk to offspring of consanguineous parents is moderately increased ‘relative’ to the risk to offspring of unrelated parents.

The theoretical model for conditions with an underlying continuous liability and a threshold for disease is outlined by Falconer.19 The model assumes that genetic action is additive, and that the phenotype reflects the summed effect of a number of genetic and environmental risks, each with small or moderate influence. Under these circumstances, the liability is assumed to be normally distributed in the general population. Consanguinity increases the population variance of traits that are determined by several genes and continuously distributed in the population, whereas there may be no, or only slight, depression of the mean. The depression of the mean is due to dominance deviations, which are interactions between alleles at a locus or epistasis, resulting in non-additivity.19 Increased variance and depression of the mean due to consanguinity have been demonstrated for birth weight.31 When the model is extended to offspring of consanguineously related parents, the distribution of the liability for disease will still be normal and the threshold for disease will be the same. However, a larger proportion of the population develops the disease due to the greater variance in the population.20 This phenomenon is illustrated in Figure 1.
The ‘relative risk’ of recessive and multifactorial conditions for inbred children ‘decreases’ as the risk for these conditions increases in the general population (Figure 2). However, the ‘absolute’ difference in risk between the inbred and the non-inbred groups may be constant, despite changes in the risk for the non-inbred population. A constant risk difference between offspring of first-cousin parents and unrelated parents has been demonstrated for death before the age of 10 years in a meta-analysis of data from populations with different mortality rates in the reference group.21

Conditions that have a monogenic ‘autosomal dominant inheritance’ may also be more prevalent among offspring of consanguineous parents.22 Homozygosity of dominant genes may be associated with an earlier age at onset, higher penetrance and more serious development of the disease compared with the heterozygous state.

There are few studies on the potential positive biological effects of consanguinity among humans. Plant and animal breeding is a well-known method for producing traits that are advantageous for specific purposes or under specific environmental conditions. Theoretically, there will be similar effects in inbred human populations that should be possible to demonstrate with appropriate data. Some studies, including a recent intriguing study from Iceland,23 have demonstrated positive associations between consanguinity and fertility. However, most of these studies have serious problems accounting for possible residual confounding due to socio-economic and cultural factors.

**Effects of consanguinity on disease and death**

The biological basis for the influence of parental consanguinity on birth defects and early death is well established through case reports, experimental studies on animals and plants and studies of familial aggregation of specific recessive diseases. In spite of the extraordinarily strong evidence, it has been challenging to establish the effects of consanguinity on mortality and morbidity in human populations.9,10,14,15 In addition to the general dearth of data, both on consanguinity and relevant outcomes, these difficulties are primarily due to insufficient information on socio-economic factors, rarity of the condition under study, small samples, problems with definitions and ascertainment of the outcomes, aggregation of different types of consanguineous marriages diluting the effect of inbreeding and refined categorization of consanguineous types leading to loss of statistical power.

Generally, the effects of consanguinity on infant death seem to be the most consistent result in studies of human inbreeding, whereas the results for stillbirth and birth defects tend to vary from no effect to small effects when measured as relative risks. In a registry-based Norwegian study, the number of first-cousin marriages was sufficiently large and the analyses adjusted for the effects of socio-economic factors, maternal age, parity and other possible confounders in multivariate analyses.2,3 The Norwegian data show, for the first time, a significant effect of consanguinity on stillbirth, and also indicates an effect of consanguinity on mortality throughout childhood and young adulthood, in addition to the expected effects on infant death and birth defects.3

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**Figure 1** Distribution of genetic liability with random mating and with first-cousin mating (coefficient of inbreeding $F = 1/16$). The areas at the right of the threshold indicate the increase in frequency of a threshold character. Adapted from Vogel and Motulsky 1997, chapter 6 ‘Formal Genetics of Humans: Multifactorial Inheritance and Common Diseases’, page 214, figure 6.20. Springer-Verlag Berlin Heidelberg with kind permission of Springer Science plus Business Media20

**Figure 2** Increased risk of autosomal recessive and multifactorial characters among children from first-cousin matings compared with the population risk. Adapted from Vogel and Motulsky 1997 chapter 6 ‘Formal Genetics of Humans: Multifactorial Inheritance and Common Diseases’, page 214, figure 6.21. Springer-Verlag Berlin Heidelberg
Almost all studies of the effects of consanguinity on populations focus on early death and congenital disorders. So far, very few have addressed adult diseases although there is clearly a large potential for such studies in populations where consanguinity is prevalent, provided that it is possible to obtain reliable data in an ethically and culturally sustainable way.

**How should we measure effects of consanguinity?**

Does the effect of consanguinity differ under different circumstances? This question was addressed by Khoury and others who found indications of smaller effects due to consanguinity in populations with high vs low mortality rates. In his analysis, the measures of association were relative risks, and public health impact was measured as population-attributable risks. The results were interpreted as possible support for the theory of ‘washing out’ of deleterious recessive genes over generations of inbreeding. By definition, relative risks are dependent on the occurrence of the condition in the control group representing the general or the non-consanguineous population, and will, therefore, necessarily be lower when baseline rates are higher. Consequently, analysis of the effects of consanguinity (or any other exposure for that sake) should not rely solely on the comparison of relative risks. An analysis of excess risks of pre-reproductive death for offspring of first cousin parents revealed that the absolute effect of consanguinity on stillbirth (from ~24 weeks of gestation) and childhood mortality (children followed up to a median of 10 years) was constant (4.4%) across a wide range of population risks of pre-reproductive death. A limitation of Bittles’ and Neel’s study was that there was no adjustment for socio-economic differences between the consanguineous and non-consanguineous groups within each population. This may have inflated the estimates of the excess risk for children with consanguineous parents, particularly in populations with large mortality differences between socio-economic groups. In some Norwegian studies of consanguinity we have used a multivariate model that adjusts for other variables and estimates the adjusted excess risk. Hence, adjusted excess risks may replace relative risks (or odds ratios) as measures of association, allowing for comparisons between populations with different background risks. A comparison of data from Pakistan, The Middle East, Britain and Norway showed that the excess risks for infant death among children of first-cousin parents were similar (excess risks were 18, 15, 12 and 12 per 1000 live births, respectively), whereas the relative risks pointed in the opposite direction and varied according to the overall mortality in the population (relative risks were approximately 1.3, 1.5, 2 and 2, respectively), evidently with lower relative risks in the population (Pakistan) with high infant mortality rates in the non-consanguineous group. The proportion of infant deaths that could be contributed to consanguinity in Pakistan was ~15% (with an overall infant mortality rate of 99/1000), whereas the corresponding proportion in Norway was 41% (among immigrants from Pakistan with an infant mortality rate of 14/1000). This illustrates that relative risks, excess risks and population-attributable risks should all be considered when the effects of consanguinity are assessed.

**New opportunities**

There are at least three good reasons for increasing the scientific focus on consanguinity. First, cousin marriages are very common in the world today; secondly, the evidence for the detrimental biological effects of consanguinity is strong but not well documented and evaluated in large human populations; and thirdly, new genetic technologies provide opportunities for studies in consanguineous populations aiming at discovering genetic factors in human traits and disease in general. For example, homozygosity mapping is a technique which is used to identify recessive mutations in consanguineous families. Morrow and co-workers used this technique to identify autism genes in consanguineous families, demonstrating the usefulness of such families in genetic studies of common complex diseases.

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