J. theor. Biol. (2000) **202,** 65–76
Article No. jtbi.1999.1044, available online at http://www.idealibrary.com on IDEAL®

Natural Selection and Sex Differences in Morbidity and Mortality in Early Life

JONATHAN C. K. WELLS*

Childhood Nutrition Research Centre, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, U.K.

(*Received on* 24 *May* 1999, *Accepted in revised form on* 5 *November* 1999)

Both morbidity and mortality are consistently reported to be higher in males than in females in early life, but no explanation for these findings has been offered. This paper argues that the sex difference in early vulnerability can be attributed to the natural selection of optimal maternal strategies for maximizing lifetime reproductive success, as modelled previously by Trivers and Willard. These authors theorized that males and females offer different returns on parental investment depending on the state of the environment. Natural selection has therefore favoured maternal ability to manipulate offspring sex in response to environmental conditions in early life, as shown in variation in the sex ratio at birth. This argument can be extended to the whole period of parental investment until weaning. Male vulnerability in response to environmental stress in early life is predicted to have been favoured by natural selection. This vulnerability is most evident in the harsh conditions resulting from pre-term birth, but can also be seen in term infants, and manifests as greater morbidity and mortality persisting into early childhood. Malnutrition, interacting with infection after birth, is suggested as the fundamental trigger mechanism. The model suggests that whatever improvements are made in medical care, any environmental stress will always affect males more severely than females in early life.

Introduction

Both morbidity and mortality are higher in males than in females in early life, with this difference persisting after adjustment for gestational age and body size, and being more marked in low birthweight and pre-term subjects (Bawkin, 1929; Ciocco, 1940; Sabin *et al.*, 1958; Hammoud, 1965; Washburn *et al.*, 1965; Froeschle *et al.*, 1966; Abramowicz & Barnett, 1970; Glezen *et al.*, 1971; Naeye *et al.*, 1971; Paneth *et al.*, 1982; Khoury *et al.*, 1985; Resnick *et al.*, 1989; Hoffman & Bennett, 1990; Zhang *et al.*, 1991; Copper *et al.*, 1994; Msall *et al.*, 1993, 1994; Synnes *et al.*, 1994; La Pine *et al.*, 1995; Fanaroff *et al.*, 1995; Read *et al.*, 1997; Stevenson *et al.*, 1998; MacDorman & Atkinson 1998; Stoll *et al.*, 1998). The degree of sex difference in morbidity is not consistent between disease states, but some of this inconsistency may be due to variation between diseases in the symptomatic-to-asymptomatic infection ratios, since a sex difference is predicted to be harder to detect when the symptomatic-to-asymptomatic infection ratio is high (Green, 1992).

Aside from effects of specific sex-chromosome factors, the increased disease stress in males is poorly understood (Green, 1992; Synnes *et al.*, 1994). The increased susceptibility of males to nutritional insult in early life, reported in both

* E-mail: j.wells@ich.ucl.ac.uk

0022–5193/00/010065 + 12 $35.00/0

humans and other animals (Smart, 1977, 1986; Katz, 1980; Lucas *et al*., 1990, 1998), is also generally assumed to be an unresolved biological issue (Lucas *et al*., 1998). Evolutionary theory has previously been used to link selective male mortality and biased sex ratios at birth (Trivers & Willard, 1973). However, despite referring to sex differences in survival, the significance of this theory for the epidemiology of disease in early life has not adequately been realized. The aim of the present paper is to expand the Trivers–Willard hypothesis and explore its significance for the early-life association between sex and disease in greater detail.

Evolutionary Theory

Differential sex mortality in early life is consistent with aspects of evolutionary theory which model maternal strategies for the maximization of reproductive success during the period of parental investment (PI). In general, natural selection favours parents who invest equally in sons and daughters (Fisher, 1930). If parents invested the same in an average son as in an average daughter, then natural selection would favour a sex ratio of 1.0 at conception, since if the ratio deviated from this value, selection would always favour the rarer sex. However, evidence from humans consistently indicates an excess of males at conception (Robinette *et al*., 1957), and it is ratio of 1.0 at weaning that is actually predicted by evolutionary theory (Maynard Smith, 1978).

Under certain conditions, natural selection favours subsequent manipulation of the sex ratio following conception, leading to variation in the secondary ratio at birth (Trivers & Willard, 1973). Natural selection is not the only model which has been proposed to account for variation in the human sex ratio at birth (James, 1998), but the effects of different mechanisms will be additive, and for the purposes of this article, it is the natural selective mechanism that is relevant.

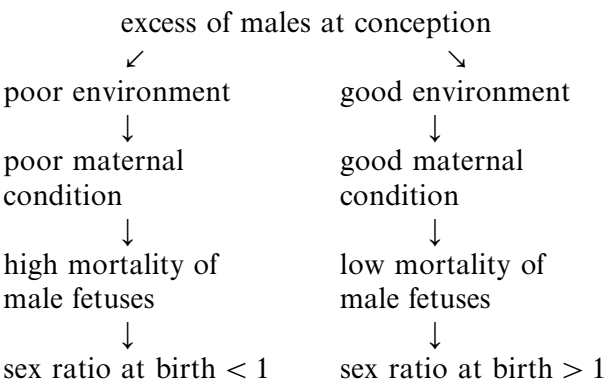
The Trivers–Willard argument may be summarized as follows. In vertebrates in general, nearly all females mate successfully, with the females in the best condition producing the healthiest offspring. In contrast, larger stronger males mate at a high frequency while their smaller weaker peers may fail to mate at all. Evolutionary theory predicts that a female in good condition would maximize her reproductive success if she gave birth to sons, who are themselves likely to have high reproductive success on reaching adulthood. A female in poor condition who gave birth to unhealthy sons might expect a poor reproductive return from them and so she is predicted to maximize her reproductive success by giving birth to daughters who will at least mate, even if not as successfully as their healthier and fitter peers.

The hypothesis rests on three assumptions: (1) that at the end of PI, the condition of the offspring reflects the condition of the mother during PI; (2) that differences in condition at this time endure into adulthood; and (3) that condition in adulthood differentially affects reproductive success more in males than in females. Whether all three of these assumptions invariably hold true in contemporary human populations is debatable, but they can be assumed to have characterized our evolutionary history (Trivers & Willard, 1973).

Females therefore are predicted to manipulate the sex ratio of their offspring during the period of PI, skewing the sex ratio towards more daughters when the environment is poorer. There is evidence from both human and animal studies that such manipulation takes place—adverse environmental conditions are associated with a reduced male : female sex ratio at birth in deer (Robinette *et al*., 1957; Clutton-Brock *et al*., 1986), rabbits (Maurer & Foote, 1971), sheep (Rasmussen, 1941) and humans (Shapiro *et al*., 1968; Williams & Gloster, 1992; Chacon-Puignau & Jaffe, 1996; Andersson & Bergstrom, 1998). Experimental evidence of the mechanism has recently been demonstrated in birds (Nager *et al*., 1999), and human studies have provided evidence of the mechanism extending to other aspects of differential PI besides birth sex ratio variation (Gaulin & Robbins, 1991). High social status, most notably in European royal families, has been associated with sex ratios of up to 1.37, which is attributed to the minimization of early male mortality (Winston, 1932; Bernstein, 1948).

Since it is the male gamete which determines sex in mammals, it is through differential mortality of offspring by the female that the sex ratio at

birth is determined (Trivers & Willard, 1973). Hence, differential male mortality during the period of PI is predicted to be "part of the mechanism by which a female adjusts the sex ratio of her young in such a way as to maximize her eventual reproductive success" (Trivers & Willard, 1973). The chain of events may be conceptualized as follows:



The significance of this mechanism for variation in the birth ratio was explicitly realized by the authors of the hypothesis. The relevance of the theory to the epidemiology of neonatal and infant disease has apparently been neglected however, and is discussed below.

Making the Manipulation

Manipulation of the sex ratio must be achieved by a mechanism which transmits given environmental effects differentially onto males and females. Genes are successful in evolution simply if they maximize their survival in the gene pool over time. The Trivers–Willard theory argues that genes achieve this best if the offspring is male when the early environment is good, and female when it is poor. Therefore, genes which favour male health when the environment is good, and genes which favour early male morbidity and mortality when the environment is bad, will both be selected over time.

These selective forces have two effects. Firstly, they have favoured genes for greater birthweight in males in good environments. A mother has a finite quantity of PI to divide among her total offspring, but in a good environment she invests proportionally more in a male than in a female fetus during the second half of pregnancy, resulting in the male being heavier at birth. This greater energy deposition is disproportionately in the form of lean tissue, since female infants though smaller are fatter than males at birth (Copper *et al*., 1993).

Similarly, but in the opposite direction, the selective forces have favoured the spread of genes for male vulnerability in poor environments. These genes may increase susceptibility to disease in a poor environment, or increase the severity of a given disease, compared to females. Male infants show delayed lung maturation compared to females equivalent to >1 week of gestational age (Torday *et al*., 1981), and so remain more vulnerable despite their greater size. Thus, we may consider both the heavier birthweight of males, and their increased vulnerability in early life, to be two sides of the same coin, the product of natural selection acting on genes which contribute to the maximization of maternal reproductive success.

This model predicts that any disease, that affects males to a greater extent than females, will play a role in the mechanism underlying selective mortality. However, it may be useful to distinguish between diseases which act on general vulnerability, and those which have been selected more actively due to their enhanced susceptibility to nutritional insult. This issue will be dealt with in greater detail below.

The Period of Parental Investment

The Trivers–Willard hypothesis aimed to account for differences in the sex ratio at birth, but as these authors mentioned, extending the period over which selective mortality can occur would confer greater flexibility on the mother. Environmental conditions may deteriorate at any stage of PI, and birth does not represent a PI endpoint. Most differential mortality is predicted to occur in early pregnancy, so that the potential PI resources can be redirected to another pregnancy, but it would be wrong to assume that selective mortality can no longer benefit the mother in late pregnancy and early infancy. If the environment were consistently poor, the optimum time for selective mortality would indeed be early in pregnancy and the highest frequency of selective mortality would be expected at this time.

However, if the environment worsened after conception, selective mortality would continue to remain of value to the other as long as PI could not be offered to a future, potentially better value, offspring until the requirements of the present offspring were terminated.

Central to the Trivers–Willard hypothesis is the concept that the strategy which maximizes the mother's reproductive fitness is not the same as that which maximizes the offspring's. Because mother and offspring share only 50% of their genes, and the mother typically divides her total PI among different offspring, there is a conflict of interest between mother and any one offspring. Inclusive fitness of the mother is maximized by a lower level of PI in any one offspring than that which would maximize the inclusive fitness of that offspring (Trivers, 1974), as has been demonstrated for birthweight (Karn & Penrose, 1952; Blurton Jones, 1978). This conflict of interest changes with offspring age, and manifests in older offspring as a steady but relatively benign withdrawal of PI, initiated by weaning. However, in younger offspring, the conflict of interest may be sufficiently dramatic for the mother to benefit from selective mortality of her offspring.

Maternal manipulation of the sex of her offspring could involve differential mortality either of embryos, fetuses or infants. Different mechanisms may be assumed to have evolved for these different stages of growth, and this article is concerned with the offspring only after it has reached the minimal stage of development compatible with extra-uterine life. Prior to this age, manipulations of the sex ratio will manifest through miscarriage rather than neonatal or infant disease, with an increased prevalence of males in stillborn fetuses again reported (Bawkin, 1929; Strandskov & Bisaccia, 1949; Hammoud, 1965; Jakobovits *et al*., 1987). Post-natally, the sex ratio may be deliberately manipulated according to cultural values, the most obvious method being infanticide which has often been used to skew the ratio towards males (Dickemann, 1979). Such practices ultimately contribute to the differential success of genes in the gene pool, but this article is concerned only with morbidity and mortality which may be attributed to natural, rather than artificial, selection.

Humans are characterized by a relatively long period of PI extending well beyond birth, and because birth occurs when the offspring is still at a comparatively vulnerable stage of development, post-natal maternal investment, especially nutrition, is a major factor affecting long-term survival and reproductive fitness. Exclusive breast-feeding may inhibit reconception for up to four years post-partum (Blurton-Jones, 1986), such that the period of intensive post-natal PI is potentially much greater than that of pregnancy. Whether the mother can invest in another conception at the same time as feeding an infant by lactation is determined by her own energy stores, which are themselves an index of environmental conditions. Below a certain level of maternal body-fat, breast-feeding results in lactational amenorrhoea, ensuring that while the infant continues to suckle, the mother cannot reconceive (Fitzgerald, 1992). When higher maternal body fat is present, reconception is possible, and interbirth interval is thus a direct function of environmental conditions mediated by maternal nutritional status (Fitzgerald, 1992).

In humans therefore, pregnancy is only the first part of a period of PI during which the mother is predicted to benefit from being able to manipulate the sex ratio of her offspring: when the environment is poor, selective mortality may benefit the mother well into her offspring's infancy. As Dawkins & Carlisle (1976) have argued, the value to the mother of selective mortality is not related to her previous investment in a given offspring. At any one time, whatever the age of the offspring, either continuing to invest in an existing offspring or investing in a new offspring may maximize maternal reproductive success. Natural selection is predicted to have favoured mechanisms that allow selective mortality in conditions where the second option is better, no matter how much investment has been directed to the offspring previously.

Evolutionary theory therefore predicts that natural selection will favour the persistence of male vulnerability until weaning occurs and maternal reconception is possible. Following this age, the cost to the mother of any one offspring is markedly lower, and the selective pressure on male vulnerability will relax. Indeed, there is some evidence that early male vulnerability

disappears, so that by 7–15 yr morbidity has been reported to be higher in females (Sweeting, 1995). In the first half of the century, Bawkin (1929) demonstrated that in both U.S. and U.K. populations, excess male mortality steadily declined from birth to 4 yr of age, when the sex difference disappeared. This four-year time point matches approximately the interbirth interval in pre-industrial societies (Lee & Devore, 1968; Blurton-Jones, 1986), and is highly consistent with the theory that mechanisms for differential male mortality would be favoured until the time point at which an offspring was sufficiently independent to allow maternal investment in further offspring.

Triggering the Mechanism

Environmental deterioration may take many forms, including physical damage to the uterus, the presence of specific toxins, the absence of certain essential nutrients or the lack of adequate energy and protein for growth. This latter category is likely to be of most relevance to the Trivers–Willard hypothesis, since whether a male represents a better or worse strategy for maximizing maternal reproductive success is primarily a function of early growth. The other factors, which are likely to exert more severe life-threatening effects, are predicted to act more equally on the two sexes.

During pregnancy, when growth is at its most rapid and hence most vulnerable to nutritional insult, specific nutrients may additionally play an important role: essential fatty acids, for example, have been suggested as a limiting factor for brain growth (Crawford *et al*., 1987). Following birth however, energy tends to be the limiting nutrient for early growth and development (Wells *et al*., 1993), and there is little evidence of micronutrient intakes restricting growth (Allen, 1994). Studies of human infants indicate that optimal growth is a good proxy for general fitness (Kow *et al*., 1991), while poor early growth is of course directly related to the outcome of interest, adult size. These facts indicate that the trigger for selective male mortality is likely to be general malnutrition, especially after birth, but the causes of this malnutrition are several, and vary with age of the offspring.

During pregnancy, the foetus may experience malnutrition either if the mother is poorly nourished, or if placental function is impaired. Post-natally, the term infant may experience malnutrition if lactation is sub-optimal (Bailey, 1965), or if the weaning diet is poor (Rowland *et al*., 1978). Further, disease may either reduce infant appetite (Tomkins, 1985), adversely influence intestinal absorption (Lunn *et al*., 1993) or increase energy requirements through the costs of infection (Butte *et al*., 1993). The link between infection and malnutrition is complex, but there is ample evidence that malnutrition both increases the likelihood of infection, and compromises the infant's ability to survive the illness (Rowland *et al*., 1981; Schroeder & Martorell, 1997). The net result of all these effects is an inadequate supply of energy and protein for optimal growth, and an inability to develop protective energy stores by which subsequent health may be maintained.

Whatever be the state of the environment, pre-term birth inevitably inflicts harsher conditions on the offspring, including simultaneous loss firstly of thermal homeostasis, secondly of protection from pathogens and physical injury, and thirdly of placental nutrition. Survival of pre-term infants is a relatively modern phenomenon, associated with intense development of medical technology. As the scientific understanding of pregnancy, and the technological ability to simulate the required conditions artificially, have improved, the minimum stage of development at which life is possible has been extended further back into pregnancy. Nevertheless, practical difficulties continue to impose limitations and the earlier the pre-term birth, the cruder the simulated conditions, the harsher the resulting environment, and the higher the morbidity and mortality.

Pre-term birth itself is characterized by an increased number of males, with studies consistently showing a male excess, compared to all births, of 4.4–8.8% (Cooperstock & Campbell, 1996). This sex difference is too small to have implications for health care, but is highly significant statistically, and indicates that the effects of male vulnerability are observable both in the incidence and the consequences of pre-term birth.

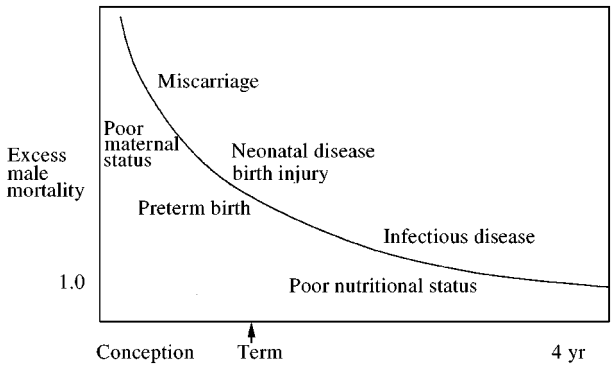


FIG. 1. Development of the pattern of excess male mortality in early life in relation to different environmental stresses. The cause of malnutrition is given below the curve, and the associated cause of mortality above it. By approximately 4 yr the sex difference in mortality disappears.

Pre-term birth is therefore the most extreme example of a wider range of patterns of malnutrition that may develop in early life. All such patterns are predicted to expose the greater male vulnerability, but pre-term birth will have a particularly severe impact, both because optimum growth at this time is faster than post-natally, and because the environmental deterioration is more extreme. The development of the general pattern, by which malnutrition of the mother or offspring is related to excess male mortality, is illustrated in Fig. 1 and discussed in relation to different disease states below.

The Pattern of Disease in Early Life

According to the theory described above, worsening of environmental conditions is predicted to trigger the mechanisms underlying selective mortality of male offspring. Such mechanisms may be divided into two broad types, general susceptibility to malnutrition and diseases, and diseases actively selected through their differential effect by sex.

GENERAL VULNERABILITY

Firstly, natural selection is predicted to have favoured increased male vulnerability to general factors such as infectious disease, injury or malnutrition. Such factors may be inflicted on either sex at any age, and the model merely predicts that in early life, natural selection has favoured greater vulnerability of males to these insults. Observational data are consistent with the model. Throughout the 20th century, a greater incidence of male mortality in the post-natal months has been noted for a wide range of diseases, including diarrhoeal diseases, measles, diphtheria, tuberculosis, pneumonia and syphilis (Bawkin, 1929), respiratory distress syndrome (Khoury *et al.*, 1985), haemorrhages (Naeye *et al.*, 1971), birth injuries (Khoury *et al.*, 1985) and sudden infant death syndrome (Kraus *et al.*, 1989; Mitchell *et al.*, 1992). In a recent large study of over 18 million births where infectious disease was the fourth leading cause of infant mortality, accounting for 9% of all deaths, mortality from this source was highly significantly greater in males (58% of deaths from this source) (Read *et al.*, 1997).

Though less widely researched, a similar pattern can be seen for morbidity with regard to various diseases, including rickets (Bawkin, 1929), meningitis and septicaemia (Washburn *et al.*, 1965), enterovirus (Sabin *et al.*, 1958; Froeschle *et al.*, 1966) and acute lower respiratory disease (Glezen *et al.*, 1971). It should be noted that sex differences in morbidity are not always easy to identify, due to their being less obvious when the symptomatic-to-asymptomatic infection ratio is high (Green, 1992). Finally, males have been shown to be more vulnerable to malnutrition in early infancy, in terms of subsequent cognitive performance (Lucas *et al.*, 1990, 1998).

I have argued above that nutrition is the ultimate trigger for selective mortality and morbidity, as it is this aspect of the environment that is most directly related to adult size and hence male reproductive fitness. However, nutrition is clearly not the primary cause of all early disease, and its role in differential morbidity and mortality is more subtle. Two points need to be borne in mind.

Firstly, as discussed above and argued in greater detail below, male physiology in early life is inherently less robust than of females. This difference is assumed to have evolved under strong selective pressure from nutritional stresses, but the vulnerability in contemporary populations is now more general and, for any given level of nutritional status, environmental stresses

are likely to be more associated with greater morbidity and mortality in males than in females.

Secondly, with regard to infectious diseases it is their interaction with nutrition that is critical. Poor nutritional status at birth has been associated with an increased risk of subsequent mortality (Morris *et al*., 1998) including that from infectious disease (Read *et al*., 1997), and it remains associated with greater morbidity and mortality from infectious disease throughout infancy (Pelletier *et al*., 1994; Fawzi *et al*., 1997; Yoon *et al*., 1997; Genton *et al*., 1998). Mortality risk is increased even when malnutrition is only moderate, and decrements in nutritional status increase mortality risk in an exponential fashion (Pelletier *et al*., 1994). In turn, most infectious diseases in early life impair nutritional efficiency, by reducing appetite, compromising intestinal function or increasing energy requirements through the costs of infection.

Hence, poor nutritional status predisposes to infection, and even where nutrition is not the primary cause of post-natal disease, most infectious diseases adversely affect nutritional status, creating a vicious cycle (Schroeder & Martorell, 1997). The inherent vulnerability of males, combined with the role of nutrition in the process, therefore predisposes them to greater morbidity and mortality from a wide range of infectious diseases and other general stresses in early life.

ACTIVELY SELECTED DISEASES

Secondly, natural selection is predicted to have favoured the genes for specific early-life diseases in males which are caused by poor environmental conditions. According to the most simple model, a non-infectious disease caused by exposure to poor environmental conditions ought to be selected out of the gene pool, since it is directly related to low reproductive success. However, the Trivers–Willard hypothesis indicates that if a disease has a differential effect according to infant sex, it will play a more complex role in maximizing reproductive success, and may be actively selected under certain conditions. In evolutionary terms, early-life diseases may be either beneficial to the mother (when the environment is poor, by permitting manipulation of the sex ratio) or neutral to the mother (when the environment is good, in which case the disease fails to develop). Under these conditions, genes for such diseases will spread and become common, or even universal, in the population gene pool. If the genes become universal, the trait will manifest as a invariable feature of human biology, such that any individual will display the symptoms if the required environment is provided. Equally, if the environmental risk factors can be avoided, then the chances of developing the disease can be minimized.

Again, observational data are consistent with the model. Neonatal diseases are consistently more serious in pre-term than in term infants (Read *et al*., 1997), and occur more often in small-for-gestational age infants compared to appropriate-for-gestational-for-age infants (Minior & Divon, 1998), indicating that environmental deterioration plays a role in their aetiology. Likewise, male sex is usually an independent risk factor. Little research has been directed to investigating the origins of such diseases, but I suggest that any neonatal disease, that arises neither from infection nor specific injury but is characterized by a sex difference, may prove to be a member of this group.

For example, respiratory diseases [respiratory distress syndrome (RDS) and chronic lung disease (CLD)] are a common cause of early mortality with a high male excess mortality risk of 1.57 (Khoury *et al*., 1985). These authors argued that the excess male mortality from RDS was due to a higher incidence of the disease, rather than the illness being more severe, and that the higher incidence was consistent with the retarded lung maturation of males (Torday *et al*., 1981). Intrauterine growth retardation is a contributory factor in the aetiology of CLD (Ryan, 1998), but malnutrition typically worsens following birth due both to reduced energy intake (Ryan, 1998) and to raised energy expenditure from the respiratory distress (Frank & Sosenko, 1988): thus the disease process itself enhances the malnutrition. These findings suggest that nutrition plays an important role in the aetiology of neonatal lung disease, but that females are to some extent protected from this vicious cycle through their greater lung maturity.

A further example is provided by cerebral palsy, which is associated with pre-natal or

peri-natal deterioration of the uterine environment, and is much more common in males than in females (Spinillo *et al*., 1997). The true incidence of cerebral palsy is impossible to estimate, because fetuses dying *in utero* cannot be diagnosed. However, over the last two decades, the absolute incidence of cerebral palsy has increased due to increased survival of pre-term infants (Spinillo *et al*., 1997), while the incidence in term infants has remained unchanged (Stanley & Watson, 1992). This pattern of incidence is equivalent to a direct relationship between environmental deterioration and disease incidence, and suggests that the trait is common if not universal. There is also evidence that improved nutrition following pre-term birth can reverse this trend (Lucas *et al*., 1998), and that maternal hypertension during pregnancy, which increases placental transfer to the foetus (Churchill *et al*., 1997), is associated with a protective effect against the disease (Gray *et al*., 1998). These findings are all consistent with the hypothesis that malnutrition plays a crucial role in determining the incidence of the disease, with the effect more noticeable in males.

Further work is required, to consider a greater range of neonatal non-infectious diseases. However, the model presented in this paper predicts that such diseases may have been actively selected during our evolutionary history, so that they comprise, along with general vulnerability, the mechanism by which selective mortality is achieved.

The Evolution of Programming

The last decade has seen resurgence of interest in the link between early environment and subsequent development. The idea of critical early windows, during which a stimulus exerts a long-lasting and irreversible effect, was first suggested by Davison and Dobbing (1968) in their critical period hypothesis and subsequently refined as the concept of programming by Lucas (1991). Extensive epidemiological evidence of programming has been put forward by Barker (1993), and experimental evidence is also emerging rapidly (Waterland & Garza, 1999).

Despite the realization of the potential impact of early programming on later health, the evolutionary origins of the vulnerability of animals to early environmental stresses have been ignored. A simplistic model would predict strong selection for effective strategies to protect the foetus from environmental insult, so that PI is rewarded by the birth of healthy offspring. However, the significance of the Trivers–Willard hypothesis is that it acknowledges the benefits to the mother of being able to predict subsequent reproductive fitness of her offspring. In order for the mother to be able to maximize her total reproductive success, by manipulating offspring sex in relation to environmental conditions, there must be potential vulnerability in the offspring on which the environmental stress can act. Such vulnerability must comprise physiological mechanisms which have been favoured by natural selection.

The Trivers–Willard hypothesis assumes that maternal fitness is used as a proxy for future fitness of her offspring, and that the information carried by her during pregnancy is used to determine her optimum reproductive strategy. In extreme conditions, it may benefit the mother to terminate investment in an offspring regardless of the sex of offspring. This may involve failure to implant the embryo *in utero*, spontaneous termination of the foetus subsequently, or even infanticide after birth. In less extreme but still adverse conditions, the Trivers–Willard hypothesis predicts that selective mortality of male offspring will be favoured. In good environments, such selective mortality will not be favoured, and investment in the offspring regardless of sex is maximized, with males programmed to receive more PI than females, and the skewed sex ratio at conception reflected in the ratio remaining above 1.0 at birth. This model explains why vulnerability is present in both sexes, and is merely greater in males.

Maternal reproductive success may be maximized by selective mortality, but clearly it is also highly dependent on PI both before and after birth. It can safely be assumed that natural selection has strongly favoured the evolution of maternal behavioural patterns which permit efficient distribution of PI to offspring. The mechanism for selective mortality must therefore be buried in physiological mechanisms which can exert their effect independently of maternal care: the model predicts only that in adverse environments, basic physiological mechanisms promoting foetal

and infant growth may be superseded by other mortality-inducing mechanisms triggered by the environmental conditions.

That early nutritional programming plays a fundamental role in the mechanism by which selective mortality is achieved is supported by the fact that it is overwhelmingly an early-life phenomenon. Whereas hormonal programming of growth continues to operate during childhood, there is little evidence for later critical windows in which nutrition is the key influence. Rather, nutritional effects of both over- and under-feeding in childhood and adulthood are generally reversible, with the exception of the period following puberty during which peak bone mass is determined. *In utero* and in infancy however, nutrition is a major limiting factor for growth and development, and early insults cause permanent adverse effects. The existence of programming in humans and other animals may partially be viewed as the consequence of evolutionary selection for early vulnerability. From the opposite perspective, the Trivers–Willard scenario only exists because, unless the subsequent environment improves drastically, poor early growth cannot be ameliorated by catch-up growth (Golden, 1994). It is precisely because early-life nutrition is a limiting factor for later size that vertebrate mothers in general benefit from the ability to manipulate offspring sex.

Morbidity vs. Mortality

Reproductive strategies and the physiological mechanisms underlying them will spread in the gene pool if they are successful compared to alternative strategies, regardless of their effects on individual infants. Natural selection has acted to increase the likelihood of maternal sex ratio manipulation, but the optimum outcome is not guaranteed in every individual. The model simply predicts that the degree of male vulnerability is stabilized at a level higher than that which would be predicted if there was no sex difference in potential return on PI. Some long-term effects of early male vulnerability, such as reduced motor ability, are detectable statistically but may be too minor in terms of lifetime reproductive success to be strongly selected against.

Most congenital non-infectious diseases which today cause serious morbidity in the pre-term or low birthweight infant would in the past almost invariably have led to death. Severe diseases of mental development would have led to feeding difficulties, thus jeopardizing post-natal survival. Thus, during our evolutionary history, the critical window during which nutrition programs development would have acted as an efficient filter, selecting out a proportion of offspring who did not represent optimal reproductive investment for the mother. The filter would have been most efficient for pre-term infants, who cannot survive without modern technology, but would also have exerted harsh selective effects throughout infancy. Injury and infectious disease would have continued to trigger the filter throughout infancy, acting ultimately through nutritional mechanisms, with the effects fading only towards the period of weaning at four years of age.

As improved medical care leads to decreased mortality and the efficiency of the filter is reduced, morbidity is predicted not only to increase but also to exhibit an enhanced rather than reduced sex difference. This pattern has already manifested during the present century with regard to mortality, whereby as the total infant mortality rate steadily declined, the mortality sex ratio increased (Bawkin, 1929; Abramowicz & Barnett, 1970). These findings indicate that as the environment improves and mortality in both sexes declines, males remain more vulnerable to both severe and moderate environmental stresses.

Conclusions

Morbidity and mortality in early life are the consequence of many inter-related factors. However, insufficient attention has been paid to the distinctive pattern of disease following birth. Applying the Trivers–Willard hypothesis of differential PI by sex, I have argued in this paper that the nature of the post-natal disease spectrum can partially be attributed to natural selection of physiological traits which maximize maternal reproductive fitness. Male vulnerability in poor environments has been selected because of its role in optimizing maternal reproductive strategies. This vulnerability is now exposed by environmental stresses acting in early life. According to this theory, mortality and morbidity are

predicted to remain greater in males than in females for any given degree of early environmental stress, especially following pre-term birth. Furthermore, reductions in mortality which translate into increases in early morbidity may directly increase the sex-difference in disease prevalence.

REFERENCES

ABRAMOWICZ, M. & BARNETT, H. L. (1970). Sex ratio of infant mortality. *Am. J. Dis. Child.* **119,** 314–315.

ALLEN, L. H. (1994). Nutritional influences on linear growth: a general review. *Eur. J. Clin. Nutr.* **48** (Suppl. 1), S75–S89.

ANDERSSON, R. & BERGSTROM, S. (1998). Is maternal malnutrition associated with a low sex ratio at birth? *Hum. Biol.* **70,** 1101–1106.

BAILEY, K. V. (1965). Quantity and composition of breast-milk in some New Guinean populations. *J. Trop. Pediatr.* **11,** 35–49.

BARKER, D. J. (1993). *Fetal and Infant Origins of Adult Disease.* London: BMJ Press.

BAWKIN, H. (1929). The sex factor in infant mortality. *Hum. Biol.* **1,** 90–116.

BERNSTEIN, M. E. (1948). Recent changes in the secondary sex ratio of upper social strata. *Hum. Biol.* **20,** 182–194.

BLURTON JONES, N. (1978). Natural selection and birth-weight. *Ann. Hum. Biol.* **5,** 487–489.

BLURTON JONES, N. (1986). Bushman birth spacing: a test for optimum birth intervals. *Ethol. Sociobiol.* **7,** 91–105.

BUTTE, N. F., VILLALPANDO, S., WONG, W. W., FLORES-HUERTA, S., HERNANDEZ-BELTRAN, M. & SMITH, E. O. (1993). Higher total energy expenditure contributes to growth faltering in breast-fed infants living in rural Mexico. *J. Nutr.* **123,** 1028–1035.

CHACON-PUIGNAU, G. C. & JAFFE, K. (1996). Sex ratio at birth deviations in modern Venezuela: the Trivers–Willard effect. *Soc. Biol.* **43,** 257–270.

CHURCHILL, D., PERRY, I. J. & BEEVERS, D. G. (1997). Ambulatory blood pressure in pregnancy and fetal growth. *Lancet* **349,** 7–10.

CIOCCO, A. (1940). Sex differences in morbidity and mortality. *Quart. Rev. Biol.* **15,** 59–73.

CLUTTON-BROCK, T. H., ALBON, S. D. & GUINESS, F. E. (1986). Great expectations: maternal dominance, sex ratios and offspring reproductive success in red deer. *Anim. Behav.* **134,** 460–472.

COOPERSTOCK, M. & CAMPBELL, J. (1996). Excess males in preterm birth: interactions with gestational age, race, and multiple birth. *Obstet. Gynecol.* **88,** 189–193.

COPPER, R. L. GOLDENBERG, R. L., CLIVER, S. P., DUBARD, M. B., HOFFMAN, H. J. & DAVIS, R. O. (1993). Anthropometric assessment of body size differences of full-term male and female infants. *Obstet. Gynecol.* **81,** 161–164.

COPPER, R. L. GOLDENBERG, R. L., CREASY, R. K., DUBARD, M. B., DAVIS, R. O., ENTMAN, S. S., IAMS, J. D. & CLIVER, S. P. (1994). A multicenter study of preterm birth weight and gestational age-specific neonatal mortality. *Am. J. Obstet. Gynecol.* **170,** 960–961.

CRAWFORD, M. A. DOYLE, W. & MEADOWS, N. (1987). Gender differences at birth and differences in fetal growth. *Hum. Reprod.* **2,** 517–520.

DAWKINS, R. & CARLISLE, T. R. (1976). Parental investment, mate desertion and a fallacy. *Nature* **262,** 131–133.

DICKEMANN, M. (1979). The ecology of mating systems in hypergynous dowry societies. *Soc. Sci. Inf.* **18,** 163–195.

DAVISON, A. N. & DOBBING, J. (1968). The developing brain. In: *Applied Neurochemistry* (Davison, A. N. & Dobbing, J., eds), pp. 253–286. Oxford: Blackwell.

FANAROFF, A. A., WRIGHT, L. L. & STEVENSON, D. K. *et al.* (1995). Very-low-birth-weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, May 1991 through December 1992. *Am. J. Obstet. Gynecol.* **173,** 1423–1431.

FAWZI, W. W., HERRERA, M. G., SPIEGELMAN, D. L., EL AMIN, A., NESTEL, P. & MOHAMED, K. A. (1997). A prospective study of malnutrition in relation to child mortality in the Sudan. *Am. J. Clin. Nutr.* **65,** 1062–1069.

FISHER, R. A. (1930). *The Genetical Theory of Natural Selection.* Oxford: Clarendon.

FITZGERALD, M. H. (1992). Is lactation nature's contraceptive? Data from Samoa. *Soc. Biol.* **39,** 55–64.

FRANK, L. & SOSENKO, I. R. S. (1988). Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. *Am. Rev. Respir. Dis.* **138,** 725–729.

FROESCHLE, J. E., FEORINO, P. M. & GELFAND, H. M. (1966). A continuing surveillance of enterovirus infection in healthy children in six United States cities. *Am. J. Epidemiol.* **83,** 455–469.

GAULIN, S. J. & ROBBINS, C. J. (1991). Trivers–Willard effect in contemporary North American Society. *Am. J. Phys. Anthropol.* **85,** 61–69.

GENTON, B., AL-YAMAN, F., GINNY, M., TARAIKA, J. & ALPERS, M. P. (1998). Relation of anthropometry to malaria morbidity and immunity in Papua New Guinean children. *Am. J. Clin. Nutr.* **68,** 734–741.

GLEZEN, W. P., LODA, F. A., CLYDE, W. A., SENIOR, R. J., SHEAFFER, C. I., CONLEY, W. G. & DENNY, F. W. (1971). Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J. Pediatr.* **78,** 397–406.

GOLDEN, M. (1994). Is complete catch-up possible for stunted malnourished children? *Eur. J. Clin. Nutr.* **48** (Suppl 1), S58–S71.

GRAY, P. H., O'CALLAGHAN, M. J., MOHAY, H. A., BURNS, Y. R. & KING, J. F. (1998). Maternal hypertension and neurodevelopmental outcome in very preterm infants. *Arch. Dis. Child.* **79,** F88–F93.

GREEN, M. S. (1992). The male predominance in the incidence of infectious diseases in children: a postulated explanation for disparities in the literature. *Int. J. Epidemiol.* **21,** 381–386.

HAMMOUD, E. I. (1965). Studies in fetal and infant mortality II. Differentials in mortality by sex and race. *Am. J. Public Health* **58,** 1152–1163.

HOFFMAN, E. L. & BENNETT, F. C. (1990). Birth weight less than 800 grams: changing outcomes and influences of gender and gestation number. *Pediatrics* **86,** 27–34.

JAKOBOVITS, A. JAKOBOVITS, A. A. & VISKI, A. (1987). Sex ratio of the stillborn fetuses and neonates dying in the first week. *Early Hum. Dev.* **15,** 131–135.

JAMES, W. H. (1998). Hypotheses on mammalian sex ratio variation at birth. *J. theor. Biol.* **192,** 113–116.

KARN, M. N. & PENROSE, L. S. (1952). Birthweight and gestation time in relation to maternal age, parity and infant survival. *Ann. Eugen.* **16,** 147–164.

KATZ, H. B. (1980). The influence of undernutrition on learning performance in rodents. *Nutr. Abstr. Rev.* **50,** 767–783.

KHOURY, M. J., MARKS, J. S., MCCARTHY, B. J. & ZARO, S. M. (1985). Factors affecting the sex differential in neonatal mortality: the role of respiratory distress syndrome. *Am. J. Obstet. Gynecol.* **151,** 777–782.

KOW, F., GEISSLER, C. & BALASUBRAMANIAM, E. (1991). Are international standards appropriate for developing countries? *J. Trop. Pediatr.* **37,** 37–44.

KRAUS, J. F., GREENLAND, S. & BUTTERYS, M. (1989). Risk factors for sudden infant death syndrome in the US collaborative perinatal project. *Int. J. Epidemiol.* **18,** 113–120.

LA PINE, T. R., JACKSON, J. C. & BENNETT, F. C. (1995). Outcome of infants weighing less than 800 grams at birth: 15 years' experience. *Pediatrics* **96,** 479–483.

LEE, R. B. & DEVORE, I. (1968). *Man the Hunter*. Chicago: Aldine Publishing Co.

LUCAS, A. (1991). Programming by early nutrition in man. *Ciba Found. Symp.* **156,** 38–50.

LUCAS, A., MORLEY, R. & COLE, T. J. (1998). Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ* **317,** 1481–1487.

LUCAS, A., MORLEY, R. & COLE, T. J. GORE, S. M., LUCAS, P. J., CROWLE, P., PEARSE, R., BOON, A. J. & POWELL, R. (1990). Early diet in preterm babies and developmental status at 18 months. *Lancet* **335,** 1477–1481.

LUNN, P. G., NORTHROP-CLEWES, C. A. & DOWNES, R. B. (1993). Long-term growth faltering in Gambian infants is related to intestinal damage but not diarrhoeal prevalence. *Trans. Roy. Soc. Trop. Med. Hyg.* **87,** 371.

MACDORMAN, M. F. & ATKINSON, J. O. (1998). Infant mortality statistics from the linked birth/infant death data set-1995 period data. *Mon. Vital Stat. Rep.* **46** (Suppl 2), 1–22.

MAYNARD SMITH, J. (1978). *The Evolution of Sex*. Cambridge: Cambridge University Press.

MAURER, R. R. & FOOTE, R. H. (1971). Maternal aging and emryonic mortality in the rabbit. 1. Repeated superovulation, embryonic culture and transfer. *J. Reprod. Fer.* **25,** 329–341.

MINIOR, V. K. & DIVON, M. Y. (1998). Fetal growth restriction at term: myth or reality? *Obstet. Gynecol.* **92,** 57–60.

MITCHELL, E. A., TAYLOR, B. J. & FORD, R. P. K., STEWART, A. W., BECROFT, D. M., THOMPSON, J. M., SCRAGG, R., HASSALL, I. B., BARRY, D. M. & ALLEN, E. M. (1992). Four modifiable and other major risk factors for cot death: the New Zealand study. *J. Paediatr. Child Health* **28,** S3–S8.

MORRIS, S. S., VICTORIA, C. G., BARROS, F. C., HALPERN, R., MENEZES, A. M., CESAR, J. A., HORTA, B. L. & TOMASI, E. (1998). Length and ponderal index at birth: associations with mortality, hospitalisations development and postnatal growth in Brazilian infants. *Int. J. Epidemiol.* **27,** 242–247.

MSALL, M. E., BUCK, G. M., ROGERS, B. T., DUFFY, L. C., MALLEN, S. R. & CATANZARO, N. L. (1993). Predictors of mortality, morbidity, and disability in a cohort of infants $\leq$ 28 weeks' gestation. *Clin. Pediatr.* **32,** 521–527.

MSALL, M. E., BUCK, G. M., ROGERS, B. T., MERKE, D. P., WAN, C. C., CATANZANO, N. L. & ZORN, W. A. (1994). Multivariate risks among extremely premature infants. *J. Perinatol.* **14,** 41–47.

NAEYE, R. L., BURT, L. S., WRIGHT, D. L., BLANC, W. A. & TATTER, D. (1971). Neonatal mortality, the male disadvantage. *Pediatrics* **48,** 902–906.

NAGER, R. G., MONAGHAN, P., GRIFFITHS, R., HOUSTON, D. C. & DAWSON, R. (1999). Experimental demonstration that offspring sex ratio varies with maternal condition. *Proc. Nat. Acad. Sci. U.S.A.* **96,** 570–573.

PANETH, N., WALLENSTEIN, S., KIELY, J. L. & SUSSER, M. (1982). Social class indicators and mortality in low birth weight infants. *Am. J. Epidemiol.* **116,** 364–375.

PELLETIER, D. L. FRONGILLO, E. A., SCHROEDER, D. G. & HABICHT, J.-P. (1994). A methodology for estimating the contribution of malnutrition to child mortality in developing countries. *J. Nutr.* **124** (Suppl). 2106S–2122S.

RASMUSSEN, K. (1941). A note on the effect of multiple births on the sex ratio in sheep. *Sci. Agric.* **21,** 759–760.

READ, J. S., TROENDLE, J. F. & KLEBANOFF, M. A. (1997). Infectious disease mortality among infants in the United States, 1983 through 1987. *Am. J. Public Health* **87,** 192–198.

RESNICK, M. B., CARTER, R. L. & ARIET, M. (1989). Effects of birthweight, race, and sex on survival of low-birthweight infants in neonatal intensive care. *Am. J. Obstet. Gynecol.* **161,** 184–187.

ROBINETTE, W. L., GESHWILER, J. S., LOW, J. B. & JONES, D. A. (1957). Differential mortality by sex and age among mule deer. *J. Wildlife Manag.* **21,** 1–16.

ROWLAND, M. G. M., BARRELL, R. A. E. & WHITEHEAD, R. G. (1978). Bacterial contamination in traditional weaning foods. *Lancet* **i,** 136–138.

ROWLAND, M., PAUL, A. A. & WHITEHEAD, R. G. (1981). Lactation and infant nutrition. *Br. Med. Bull.* **37,** 77–82.

RYAN, S. (1998). Nutrition in neonatal chronic lung disease. *Eur. J. Pediatr.* **157** (Suppl 1), S19–S22.

SABIN, A. B., KRUMBIEGEL, E. R. & WIGAND, R. (1958). ECHO type 9 virus disease. *Am. J. Dis. Child.* **96,** 197–219.

SCHROEDER, D. G. & MARTORELL, R. (1997). Enhancing child survival by preventing malnutrition. *Am. J. Clin. Nutr.* **65,** 1080–1081.

SHAPIRO, S., SCHLESINGER, E. R. & NESBITT, R. E. L. (1968). *Infant, Maternal, and Childhood Mortality in the United States*. Cambridge, MA: Harvard University Press.

SMART, J. L. (1977). Early life malnutrition and later learning ability: a critical analysis. In: *Genetics, Environment and Intelligence* (Oliviero, A., ed.), pp. 215–235. Amsterdam: Elsvier/North-Holland.

SMART, J. L. (1986). Undernutrition, learning and memory: review of experimental studies. In: *Proceedings of XIII International Congress of Nutrition* (Taylor, T. G. & Jenkins, N. K., eds), pp. 74–78. London: John Libbey.

SPINILLO, A., CAPUZZO, E., ORCESI, S., STRONATI, M., DI MARIO, M. & FAZZI, E. (1997). Antenatal and delivery risk factors simultaneously associated with neonatal death and cerebral palsy in preterm infants. *Early Hum. Dev.* **48,** 81–91.

STANLEY, F. J. & WATSON, L. (1992). Trends in perinatal mortality and cerebral palsy in Western Australia 1967 to 1985. *BMJ* **304,** 1658–1663.

STEVENSON, D. K. WRIGHT, L. L., LEMONS, J. A., OH, W., KORONES, S. B., PAPILE, L. A., BAUER, C. R., STOLL, B. J., TYSON, J. E., SHANKARAN, S., FANAROFF, A. A., DONOVAN, E. F., EHRENKRANZ, R. A. & VERTER, J. (1998). Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. *Am. J. Obstet. Gynecol.* **179,** 1632–1639.

STOLL, B. J., HOLMAN, R. C. & SCHUCHAT, A. (1998). Decline in sepsis-associated neonatal and infant deaths in the United States, 1979 through 1984. *Pediatrics* **102,** e18.

STRANDSKOV, H. H. & BISACCIA, H. (1949). The sex ratio of human stillbirths at each month of uterogestation and at conception. *Am. J. Phys. Anthropol.* **7,** 131–143.

SWEETING, H. (1995). Reversals of fortune? Sex differences in health in childhood and adolescence. *Soc. Sci. Med.* **40,** 77–90.

SYNNES, A. R., LING, E. W., WHITFIELD, M. F., MACKINNON, M., LOPES, L., WONG, G. & EIFFER, S. B. (1994). Perinatal outcomes of a large cohort of extremely low gestational age infants (twenty-three to twenty-eight weeks of gestation). *J. Pediatr.* **125,** 952–960.

TOMKINS, A. M. (1985). Nutrient intake during diarrhoea in young children. In: *Proceedings of XIIIth International Congress of Nutrition* (Taylor, T. G. & Jenkins, N. K., eds), pp. 110–113. London: John Libbey.

TORDAY, J. S., NIELSEN, H. C., FENCL, M. DE M. & AVERY, M. E. (1981). Sex differences in fetal lung maturation. *Am. Rev. Respir. Dis.* **123,** 205–208.

TRIVERS, R. L. (1972). Parental investment and sexual selection. In: *Sexual Selection and the Descent of Man* (Campbell, B., ed.), pp. 136–179. Hawthorne, NY: Aldine.

TRIVERS, R. L. (1974). Parent-offspring conflict. *Am. Zool.* **14,** 247–262.

TRIVERS, R. L. & WILLARD, D. E. (1973). Natural selection of parental ability to vary the sex ratio of offspring. *Science* **179,** 90–92.

WASHBURN, T. C., MEDEARIS, D. N. & CHILDS, B. (1965). Sex differences in susceptibility to infections. *Pediatrics* **35,** 57–64.

WATERLAND, R. A. & GARZA, C. (1999). Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am. J. Clin. Nutr.* **69,** 179–197.

WELLS, J. C. K., DAVIES, P. S. W. & LEE, P. C. (1993). Patterns of infant weight gain in developing countries. *J. Trop. Pediatr.* **19,** 214–218.

WILLIAMS, R. J. & GLOSTER, S. P. (1992). Human sex ratio as it relates to caloric availability. *Soc. Biol.* **39,** 285–291.

WINSTON, S. (1932). Birth control and sex at birth. *Am. J. Sociol.* **38,** 225–231.

YOON, P. W., BLACK, R. E., MOULTON, L. H. & BECKER, S. (1997). The effect of malnutrition on the risk of diarrheal and respiratory mortality in children < 2 yr age in Cebu, Phillippines. *Am. J. Clin. Nutr.* **65,** 1070–1077.

ZHANG, J., CAI, W. W. & CHEN, H. (1991). Perinatal mortality in Shanghai: 1986–1987. *Int. J. Epidemiol.* **20,** 958–963.