EDC #92
Sex Ratio

# Reduced Ratio of Male to Female Births in Several Industrial Countries

## A Sentinel Health Indicator?

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**Context.**—The sex ratio of 1.06:1, the ratio of male to female births, has declined over the past decades. Recent reports from a number of industrialized countries indicate that the proportion of males born has significantly decreased, while some male reproductive tract disorders have increased.

**Objectives.**—To examine the evidence for declines in the male proportion at birth and suspected causes for this decline, and to determine whether altered sex ratio can be considered a sentinel health event.

**Data Sources.**—Birth records were analyzed from national statistical agencies.

**Study Selection.**—Published analyses of trends in ratio of males to females at birth and studies of sex determinants evaluating epidemiological and endocrinological factors.

**Data Extraction.**—Proportion of males born: 1950-1994 in Denmark; 1950-1994 in the Netherlands; 1970-1990 in Canada; and 1970-1990 in the United States.

**Data Synthesis.**—Since 1950, significant declines in the proportion of males born have been reported in Denmark and the Netherlands. Similar declines have been reported for Canada and the United States since 1970 and parallel declines also have occurred in Sweden, Germany, Norway, and Finland. In Denmark, the proportion of males declined from 0.515 in 1950 to 0.513 in 1994. In the Netherlands, the proportion of males declined from 0.516 in 1950 to 0.513 in 1994. Similar declines in the proportion of males born in Canada and the United States are equivalent to a shift from male to female births of 8600 and 38 000 births, respectively. Known and hypothesized risk factors for reduced sex ratio at birth cannot fully account for recent trends.

**Conclusion.**—Patterns of reduced sex ratio need to be carefully assessed to determine whether they are occurring more generally, whether temporal or spatial variations are evident, and whether they constitute a sentinel health event.

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THE SURVIVAL of the species depends on the ability of males and females to reproduce successfully. Reproduction is a complex process, involving multiple stages of vulnerability for parents prior to conception and birth of their offspring. Few established risk factors have been identified for failures that occur during many of these reproductive stages. In industrialized countries, about 1 of every 6 couples experiences difficulty reproducing.[1] Exposures of pregnant females to a variety of foreign substances may pose a threat to the health of offspring. In addition, exposures of males and females to foreign substances prior to conception can affect both their ability to conceive and the health of their offspring.[2] Timing of exposure to such substances may be more critical than the total dose rate in determining a broad array of outcomes.[3]

A sentinel health event has been defined as an unusual pattern of health in a population that signals changes in avoidable factors.[4] Thus, changes in either a relatively common health occurrence, such as childhood asthma, or a relatively rare disease, such as pulmonary hypertension, can reflect changes in avoidable exposures. To assess whether shifts in the ratio of males to females born, defined as the *sex ratio*, constitute a sentinel health event, it is necessary to determine the expected pattern of sex ratio in light of known modifying conditions. It is also crucial to determine whether known causes of alteration in this rate could theoretically account for recently reported changes.

This article reviews evidence that the ratio of male to female births is declining in several industrial countries, discusses known and suspected causes of sex determination and altered sex ratio, speculates about possible environmental factors that could be involved, and considers whether altered sex ratio is a sentinel health event.

Births of males to females can be reported in different ways. Sex ratio is measured as the ratio of male to female births. For instance, for every 100 female births, there are believed to be 106 male births.[5] This yields a sex ratio of 1.06. Frequently, however, the relationship between male and female births is reported as the male proportion, or the number of male births divided by total

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| Country | Years | Difference in Male Proportion | P Value |
|---|---|---|---|
| Canada | 1970-1990 | 0.0022 | <.001 |
| United States | 1970-1990 | 0.001 | <.001 |
| Denmark | 1980-1995 | 0.002 | .01 |
| The Netherlands | 1950-1994 | 0.003 | .001 |

births (106 male births divided by 206 total births equals 0.515). This can be easily understood as the percentage of males born out of all births combined; in the above example, 51.5% of the births are male. Recent analyses (the logistic regression analysis for the United States and Canada and the linear regression analysis for Denmark and the Netherlands) of trends in male births have been reported as male proportion, which we generally employ throughout this article.

## RECENT PATTERNS IN SEX RATIO

Recent reports from several industrial countries, including the Netherlands,[6] Denmark,[7] Canada, and the United States,[8] indicate that the proportion of males has declined significantly in the past 3 decades (Table). As with most complex biological phenomena, explanations for this decline are likely to be multifactorial. The male proportion among newborns in Denmark and the Netherlands have both declined in a parallel manner from the 1950s to the 1990s. In Denmark, the proportion of males declined from 0.515 in 1950 to 0.513 in 1994 (Figure 1). In the Netherlands, the proportion of males declined from 0.516 in 1950 to 0.513 in 1994 (Figure 1). Figure 2 shows similar trends in Canada and the United States for the period 1970 to 1990.

In Canada, the proportion of males has decreased significantly from 1970 to 1990, following a west-east gradient in 4 main regions. For Canada during this period, there was a declining trend, with a cumulative loss of 2.2 male births per 1000 live births. Between 1970 and 1990, the decline was greatest in the Canadian Atlantic region, where average socioeconomic status is lowest, reaching 5.6 fewer male births per 1000 live births. In the United States, the declines were also significant overall and individually in 4 of the 9 regions (East-North Central, West-North Central, South Atlantic, and Pacific). The overall change in the United States throughout the 20 years represented a cumulative decrease of 1.0 male births per 1000 live births. It has been observed that in some Latin American countries the male proportion[9] has also declined since the 1970s, from 0.513 to 0.512. Similar trends have recently been reported in other Nordic countries.[10]

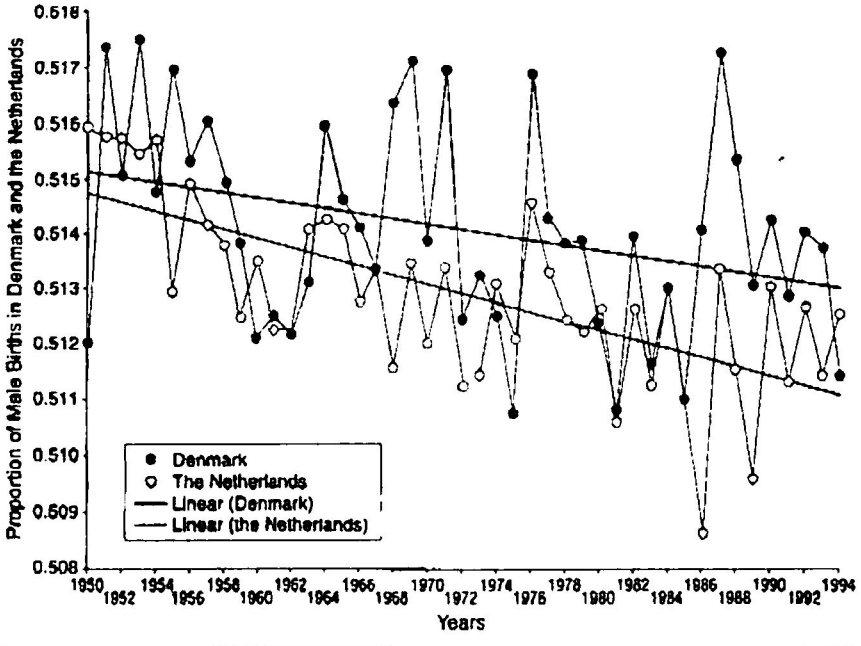


Figure 1.—Proportion of male births in Denmark and the Netherlands, 1950-1994. Data are from van der Pal-de Bruin et al[6] and Møller.[7]

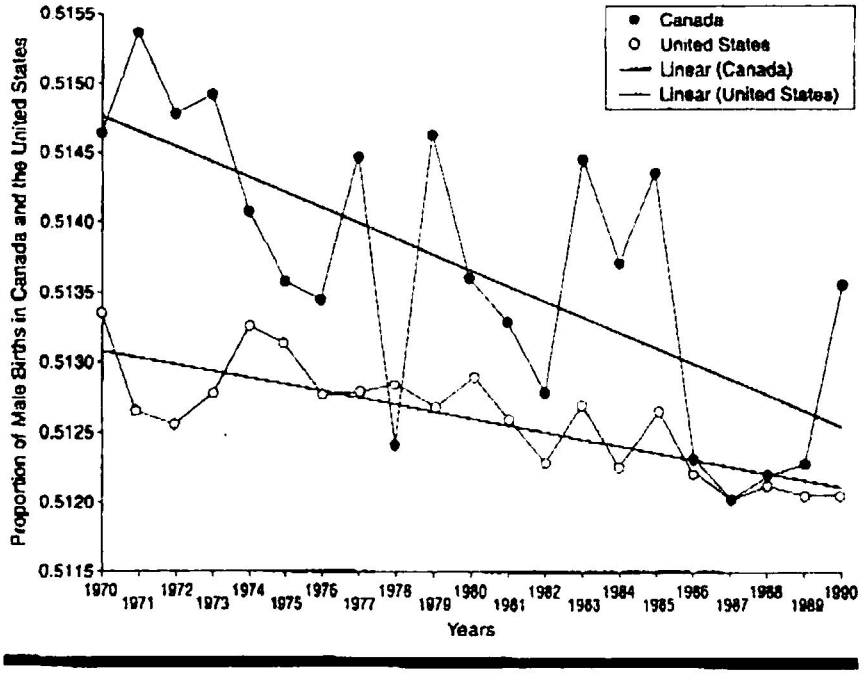


Figure 2.—Male proportion of newborns in Canada, 1970-1990. Data from Allan et al.[8]

## ESTIMATED IMPACT OF ALTERED SEX AT BIRTH

In all of the analyses of changes in male proportion throughout time in industrial countries, reported variation occurs in fractions of percentage points. Such small changes, however, can have profound implications for large populations, where hundreds of thousands or millions of births occur each year. For example, the reported statistically significant decrease of 2.2 males per 1000 births in a country the size of Canada with an annual average of 333 159 births represents a cumulative decline of about 8600 male births since 1970. During the same period, the US decline of 1 male birth per

1000 corresponds to approximately 38 000 male births.[8]

## SEX AT BIRTH: KNOWN AND HYPOTHESIZED CAUSES OF ALTERATIONS

Both timing of exposure to hormones, or to toxicants that affect hormones, as well as dose of exposure to these materials, appear to be critical determinants of a wide range of outcomes that are determined early in embryogenesis, including sexual and terminal cell differentiations. These outcomes range from cryptorchidism, hypospadias to testicular cancer, and possibly, early onset of breast cancer. The link between disorders of the reproductive tract, sexual differentiation, and malignancy is well established.[11] Events that cause somatic mutation in the *SRY*, the sex determining gene on the Y chromosome, might also lead to female sex predominance of offspring, as would events that damage or impair Y chromosome–bearing sperm cells.[12]

Susceptibility to any toxicant is a function of the rate of cell division and the timing and extent of exposure.[2] Rapidly dividing cells have a greater potential to incorporate and replicate errors than do those that grow more slowly. Fetal gonadal tissue, which is among the most rapidly growing of all, is especially vulnerable to exposures that may result in abnormalities, including those that could affect sex determination.

Prenatal sexual development involves a complex process. Absent some form of androgen stimulation, all embryos appear to be female.[13] Insufficient androgens can produce a feminized male that appears to be a normal female.[14] Sexual differentiation takes places between weeks 6 and 9 of human life, during which time Sertoli cells of the testis or follicular cells of the ovary become active.[15] At this point, the embryo has a unisex pair of gonads and 2 sets of ducts that are referred to as wolffian and müllerian ducts (mesonephric and paramesonephric ducts). In an XY embryo, the gonads will specialize into testes. The testes will then produce male hormones such as testosterone, which drives the further masculine development of the fetus. Testosterone cues the development of the wolffian ducts into the ductus deferens and the descent of the testes into the scrotal sac. The müllerian inhibitory hormone that is induced by the Sertoli cells triggers the disappearance of the müllerian ducts. In the female, the wolffian ducts disappear absent any hormonal instructions, and the müllerian ducts develop into the oviducts. Normal differentiation of the testes depends on the Sertoli cells not being disrupted at the critical stage. Thus, disruptions during this critical period of sexual differentiation could affect the phenotypic determination of sex as well as subsequent development of offspring.[16]

## POSSIBLE MEDICAL DETERMINANTS OF SEX AT BIRTH

General medical factors and conditions documented to reduce the male proportion of offspring include older age of fathers, in vitro fertilization, non-Hodgkin lymphoma, hepatitis, and use of fertility drugs, such as clomiphene.[17] In addition, the sex ratio for children of men and women with multiple sclerosis could be linked to the parents' stress levels, giving birth to more female and male babies, respectively.[18] Historically, rates of stillbirths declined with improvements in obstetrical care from the beginning of this century until the 1950s. As stillbirths tend to occur more in male babies, reductions in stillbirths have been deduced to account for the increasing trend of sex ratio that occurred during the first half of this century.[17,19]

Other factors that have been hypothesized to affect the sex of offspring include stress, which increases pituitary secretion of corticotropin (adrenocorticotropic hormone). In men and women, elevated levels of corticotropin produce paradoxical effects on gonadotropin, which is consistent with this hypothesis. In men, increased corticotropin levels lower the endogenous levels of testosterone and increase the relative proportion of estrogen, which, in turn, leads to the production of more female offspring. In women, increased corticotropin levels activate the adrenal cortex, yielding relatively elevated levels of testosterone, and create a hormonal milieu that yields more male offspring.[20] High maternal gonadotropin levels are associated with the production of females. Dosing with testosterone prior to conception has been shown to increase the male offspring in humans as well as in experimental animals.[20] In one study, men who were given methyltestosterone therapy sired 45 boys and 17 girls.[21]

Parental age has also been hypothesized to affect sex at birth, although findings appear inconsistent. Male proportion has been observed to decline with increases in paternal[22] and maternal age.[18] One recent study of births in 301 families found that the difference in age between parents was a significant predictor of the sex of the first child.[23] The age of either one of the parents had only a weak effect on the sex of the offspring, while parents with a greater difference between their ages gave birth to an excess of boys. In contrast, a small age difference between husbands and wives was associated with more female births.

## POSSIBLE OCCUPATIONAL DETERMINANTS OF SEX AT BIRTH

### Dibromochloropropane

Several studies have identified occupational and environmental exposures that influence sex at birth. In one study of workers who apply the nematocide dibromochloropropane, exposed men were found to have diminished sperm counts.[24] Although testosterone levels remained normal, gonadotropin levels were elevated. Of importance, those who were able to have children produced 3 times as many daughters as expected. Of the 12 births that occurred in wives of exposed men who had been oligospermic, 10 were female, for a male proportion of 0.167. Further analysis of this cohort provided additional evidence that male births were reduced. The proportion of male infants conceived prior to exposures of these same men to dibromochloropropane was 0.529, in contrast to 0.352 for those conceived during the periods when their fathers were working with this compound. When the conception rate was calculated only for the exposed azoospermic and oligospermic groups, an even lower proportion of 0.162 male infants was evident.[25] Further evidence is provided in this study for the gonadotropin hypothesis in that elevated levels were reported in those who fathered disproportionately more female babies.

### Other Occupational Exposures

Under some unusual workplace conditions, male proportion has been found to be radically altered. One analysis from the state of Washington found that fathers who worked in the aluminum industry from 1980 to 1990 as carbon setters, anode setters, or carbon changers had 53 male and 86 female births, for a proportion of male births of 0.381 ($P = .003$).[26] Other factors that have been reported to reduce male proportion significantly include workplace exposures to organochlorine pesticides[27] and waste anesthetic gases.[28] One study in the Netherlands of offspring born from 1978 to 1990 revealed a remarkable shift toward more daughters, and a male proportion of 0.248, in children conceived by men who had received workplace exposure to pesticides. This report also found that time to conception was significantly longer for fathers who were estimated to have incurred greater exposures, as measured in terms of the number of days of pesticide spraying. Other workplace exposures have also been linked to lowered male proportion, including other types of pesticides, *inorganic borates*,[29] alcohol, lead, and solvents.[30]