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 5 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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Declines in Male Proportion, 1950-1995

Country	Years	Difference in Male Proportion	*P* Value
Canada	1970-1990	0.0022	<.001
United States	1970-1990	0.001	<.001
Denmark	1960-1995	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]

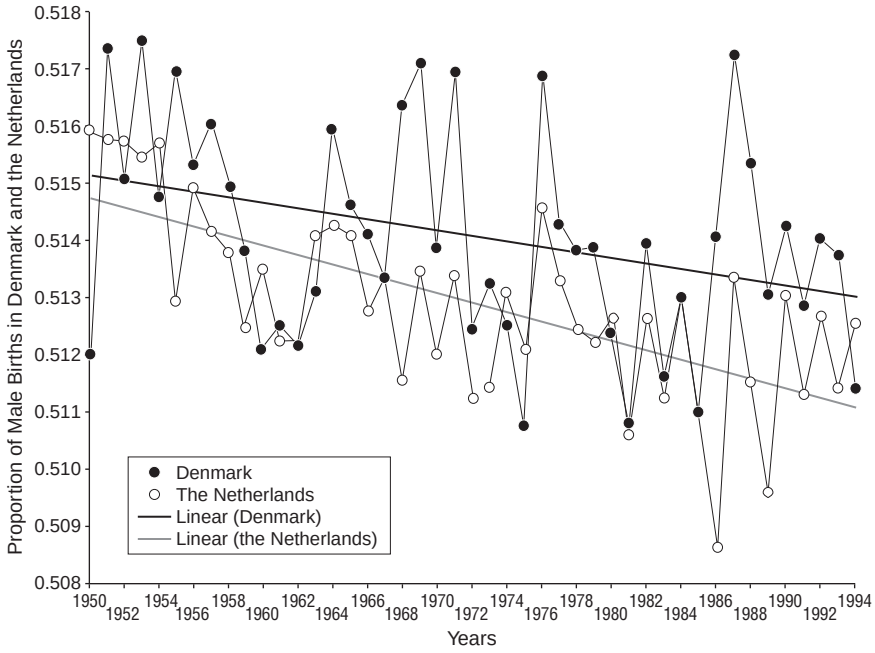

Figure 1.—Proportion of male births in Denmark and the Netherlands, 1950-1994. Data are from van der Pal-de Bruin et al[6] and Moller.[7]

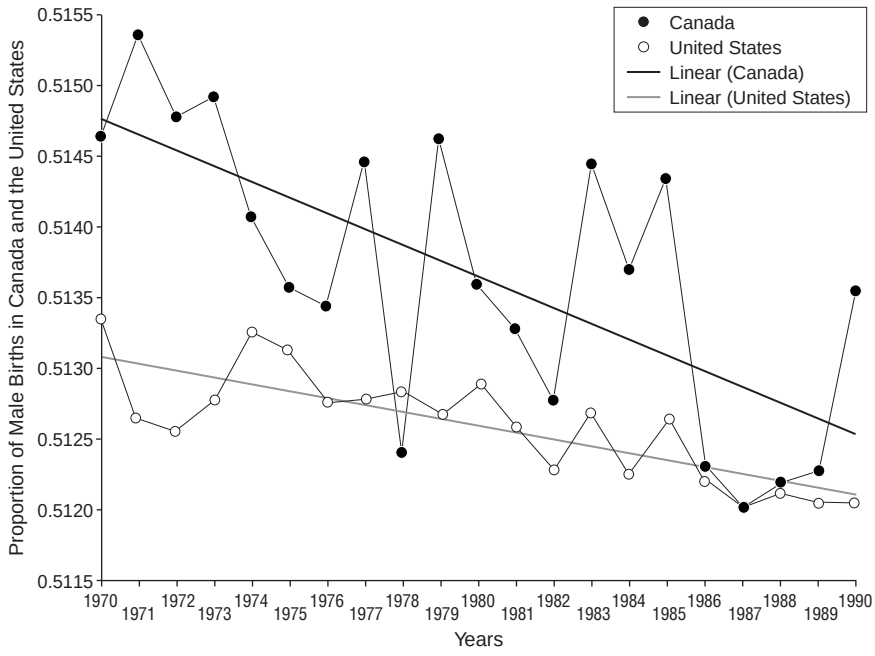

Figure 2.—Male proportion of newborns in Canada, 1970-1990. Data from Allan et al.[8]

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]

POSSIBLE ENVIRONMENTAL CAUSES OF ALTERED SEX RATIO

Dioxin in Seveso, Italy

A striking illustration of the apparent ability of environmental exposures to influence male proportion comes from recent epidemiologic reports on the population most highly exposed to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) from a chemical plant explosion in Seveso. In July 1976, an explosion released a large cloud dispersing many kilograms of this toxic agent into the atmosphere. A recent assessment of children born to the small number of highly exposed adults on whom data are available in this region found that for 7 years after this explosion, twice as many females as would be expected were born and overall fertility was markedly reduced.[31]

Between April 1977 and December 1984 (corresponding to 1 half-life of TCDD in the body), 74 children were born to parents in the zone of greatest exposure. Of these, 48 were female and 26 male, for a male proportion of 0.351. In 1976, serum samples were taken from the exposed populations; based on an assay (that was not available at the time of the explosion), it has been determined that for 7 years after the explosion, no boys were born to parents with the highest levels of dioxin in their blood. The proportion of female offspring proved to be highest among parents with the highest levels of serum TCDD. In fact, none of the 9 couples with the highest serum TCDD levels (at least 100 parts per trillion) bore a single male child.

Since 1985, the male proportion in this population has returned to expected levels and overall fertility has increased. This resumption of a normal pattern in the Seveso population further strengthens the argument that unusual environmental exposures can be the primary cause of reduced sex ratio in some circumstances.

Other Possible Environmental Causes

Several researchers have assessed whether general environmental exposures to materials linked to alterations in sex at birth in highly exposed workers might also produce alterations in children conceived in neighborhoods with similar exposures.[32] The evidence on this matter remains incomplete, but provocative. Five different retrospective studies of heavily polluted Scottish residential areas revealed significantly impaired sex ratio.[33] The pollutants included some highly visible emissions from acrid smelters, steel foundries, and incinerators in Scotland between 1975 and 1983.

INCREASED PRENATAL VULNERABILITY OF THE MALE

There are compelling biological reasons for deducing that whatever factors may be altering phenotypic sex at birth could also be involved in producing other adverse effects in males. Disorders of the reproductive tract, such as hypospadias and cryptorchidism, are reported to have increased in many industrial countries.[34] A recent analysis in the United States showed that the rate of hypospadias had nearly doubled in all 4 regions of the United States from 1970 to 1993.[35] During this same period, testicular cancer rates have also increased.[36] A recent study reports a link between exposure to polyvinyl chloride and testicular cancer.[37] A number of reports have recently reviewed this evidence and speculated that these phenomena are biologically connected to critical exposures to xenohormones that occur immediately before and early in the process of reproduction.[38,39]

Both human and animal evidence demonstrate that prenatal exposures may be far more important to the overall health and development of the organism than those that occur later in life.[40] Thus, exposures during the period of organogenesis and differentiation of the genitals during weeks 6 and 9 chemically imprint rapidly growing reproductive tract cells for later developmental disorders, ranging from testicular cancer to reproductive difficulties.[41]

Recent innovative analysis of geographic patterns of cryptorchidism suggests that parental exposure to hormone-disruptive chemicals increases the risk of this disorder.[42] Cryptorchidism is a birth defect of the male reproductive tract that is typically corrected surgically through cryptorchidopexy. This study compared rates of male reproductive tract defects in different regions of the Spanish province of Granada. Although fruit and vegetable crops in this region take up only 4.65% of Spain's farmland, they are treated with 51% of the pesticides used in the country. In much of the area along the Mediterranean coast, greenhouse crop farming under plastic-encased systems is widespread. In the enclosed greenhouses, workers (including pregnant women) are exposed to high levels of pesticides, many of them organochlorine compounds that have been shown to damage the endocrine system. When districts within Granada were categorized based on pesticide use, it was found that rates of cryptorchidopexy in the population were highest in those districts where pesticide use was high. In these areas, the level of cases was 2.32 times the rate in areas not exposed to pesticides ($P<.05$).

Further evidence of a link between defects in male reproductive outcomes and reduced male proportion is provided by recent observations from rural Minnesota.[43] Increased rates of birth defects have occurred in male children of workers who apply pesticides, suggesting that the developing male fetus may be especially vulnerable to hormone-disrupting substances. Compared to the general population, children born to workers who apply pesticides, herbicides, and fungicides were 1.57 times as likely to have birth defects of the circulatory and/or respiratory, urogenital, and musculoskeletal and/or integumental systems. In agricultural areas, increased rates of birth defects were also seen in the general population. For example, in western Minnesota where spring wheat production predominates and fungicides are aerially applied, 2.6% of live births showed anomalies, as compared with 1.83% of births in noncrop regions. The increase was especially pronounced for infants conceived in the spring, when chlorophenoxy herbicides were routinely applied.

Interestingly, more male than female infants were affected by birth defects in Minnesota regions with elevated rates of use of some herbicides and fungicides. Among all births with anomalies, the proportion of males was 0.579. In areas of high use of chlorophenoxy herbicides and/or fungicides, the male proportion among children born with defects to workers who apply pesticide was 0.735, compared with 0.607 for births with anomalies in the general population. In areas of low pesticide usage, the male proportion born with defects was 0.682 for children of fathers who were pesticide appliers compared with 0.633 for the general population. Thus, it appears that the male fetus is more vulnerable to paternal exposures that take place prior to conception and that may be linked with birth defects.[2]

COMMENT

With respect to the quality of data and record keeping on sex at birth, all of the countries reported here have no known cultural biases regarding reporting or selection of sex through elective abortion. This suggests that recorded trends in sex at birth are likely to reflect real patterns rather than artifacts of measurement or cultural bias.

The ratio of human males to human females at birth is not static. Between 1900 and 1950, the proportion of males rose significantly in several industrial countries, beyond the range of historical variation. This was chiefly due to general improvements in obstetrical care, which produced a decline in stillbirths,[7,44,45] that

disproportionately affect males. In general, male fetuses appear to be more susceptible to reproductive hazards, as they also experience higher rates of many birth defects than do females. Since 1970, a significant downward trend has occurred in the proportion of males in the Netherlands, Denmark, Canada, and the United States, and recent reports indicate that parallel declines also have occurred in Sweden, Germany, Norway, and Finland.[10] It is distinctly possible that the causes of these trends, however, are not benign. Rather, the reduction of the proportion of males born may be a sentinel health event that some, as yet, unrecognized environmental health hazards are affecting the sex ratio of births as well as other unexplained defects in male reproduction.

Provocative theories about shifting parental hormonal milieus have been devised to account for some reported alterations in sex at birth. Some observers have speculated that increases in male proportion after major wars are due to an increase in coital frequency.[20] Increased sexual activity appears to result in earlier fertilizations within the cycle and in more males being conceived and born.[17] The recent decline in the proportion of male births has been explained by some as a return to normal after a wartime high. However, our analysis indicates that this proportion continues to decline several decades after the wartime high, suggesting that other factors must be contributing to the trends.

Recent trends and geographic patterns in sex ratio cannot be attributed to documented causes of altered sex ratio, such as physiological conditions and medical treatments. Known causes of altered sex ratio, such as older age of father, use of in vitro fertilization, and stress of mothers, appear unlikely to account for trends that have persisted throughout the past 2 decades. In fact, the decline in Canada is greatest in those regions where known medical causes of reduced male proportion such as in vitro fertilization are likely to be lowest. In Canada overall, in vitro fertilization only accounts for some fraction of the recent reductions in male births each year.[30] Infertility affects about 7% to 8% of all couples. Based on survey data, it appears that about 8% of infertile couples undergo ovulation induction. If about 25% of these succeed in producing live births, far fewer than 1% of live births annually in Canada could be due to ovulation induction. If induction decreases the proportion of male births to 46%, then as many as 350 fewer male births would result annually in recent years. But, this explanation cannot account for the overall declines in male proportion observed in the 1970s and early 1980s, when in vitro fertilization was not widely available.

The study of sex determination remains a field full of speculation and with limited empirical evidence. As a consequence, factors that affect the sex ratio remain poorly understood. Many of the causes of reduced male births that have been identified, such as stress of fathers, in vitro fertilization, less frequent intercourse, and multiple sclerosis, are unlikely to account for the time trends that have recently been observed in several industrial countries. Several specific workplace and environmental exposures have altered the sex ratio in those who were highly exposed to some pesticides and other general environmental contaminants. Whether these agents could account for some of the recently observed patterns is a matter of considerable concern.

CONCLUSIONS

We propose that reduced male proportion at birth be viewed as a sentinel health event that may be linked to environmental factors. To determine the value of this suggestion, it will be important to answer a number of questions: Do the trends in sex ratio reported for the United States, Canada, Denmark, and the Netherlands parallel similar changes in other countries? Are regional differences in the proportion of males consistent with environmental factors or other known causes of alterations? Does other evidence confirm that occupational cohorts with exposures to smelting operations, pesticides, inorganic borates, lead, solvents, alcohol, and other such workplace hazards have produced children with reduced male proportion?

To resolve these matters, it will be important for public health researchers to conduct a number of assessments, examining patterns, and time series of state, regional, and national birth registries. Information on sex ratio has the virtue of being easy to obtain in countries with limited resources for health and environmental research. In contrast to studies of morbidity, sex ratio is not susceptible to diagnostic bias or changes in ascertainment. Geographic monitoring of changes in sex ratio could prove a useful tool for assessing whether specific, avoidable medical or environmental exposures are occurring in specific regions.

Relatively small reductions in male proportion over the past 2 decades in the United States and Canada theoretically account for decreases in about 38 000 and 8600 male births, respectively.[8] The potential repercussions of conditions that may alter the ratio of the sexes at birth should be considered a matter of utmost concern. The extent to which other adverse health consequences are linked to this phenomenon is a matter of grave importance for public health.

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