The rise and fall of excess male infant mortality

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The male disadvantage in infant mortality underwent a surprising rise and fall in the 20th century. Our analysis of 15 developed countries shows that, as infant mortality declined over two centuries, the excess male mortality increased from 10% in 1751 to >30% by approximately 1970. Remarkably, since 1970, the male disadvantage in most countries fell back to lower levels. The worsening male disadvantage from 1751 until 1970 may be due to differential changes in cause-specific infant mortality by sex. Declines in infant mortality from infections and the shift of deaths to perinatal conditions favored females. The reduction in male excess infant mortality after 1970 can be attributed to improved obstetric practices and neonatal care. The additional male infants who survived because of better conditions were more likely to be premature or have low birth weight, which could have implications for their health in later life. This analysis provides evidence of marked changes in the sex ratio of mortality at an age when behavioral differences should be minimal.

birth weight | sex differences | mortality trends

Males have higher mortality than females at every age in most countries (1). However, the magnitude of the male disadvantage varies depending on environmental, social, and economic conditions. Throughout much of the 20th century, as overall mortality declined, and causes of death shifted from infections to chronic degenerative diseases, the male disadvantage in life expectancy continued to increase in many industrialized countries (2). But since the 1970s, the gender gap in life expectancy has narrowed (3).

Changes in the size of the male disadvantage in life expectancy can be partially attributed to sex differences in infant mortality. Sex differences in mortality are due to a combination of biological, social, and environmental factors. Although lifestyle and behavioral factors contribute importantly to sex differences in adult mortality (4, 5), they are unlikely to explain sex differences in mortality among infants. The present analysis shows that historical changes in the size of the male disadvantage in infant mortality are remarkably similar across 15 countries despite varying social, demographic, and epidemiological circumstances. From 1751 to approximately 1970, these countries showed a consistent pattern of progressively rising relative male infant mortality, which was followed by an abrupt fall in the excess male disadvantage in recent decades. This rise and fall occurred during the major continuing decline in overall infant mortality. To account for the pattern of change in sex differences, we examine trends in cause-specific infant mortality and changes over time in obstetrical and neonatal care practices.

Preston (6) has noted that the male disadvantage over time and across countries is most consistent in infancy and that sex ratios of death rates at all ages tend to increase with declines in mortality. Others also noted that sex ratios in infant mortality showed a more pronounced male disadvantage in the middle of the 20th century than earlier (7, 8). Environmental and medical factors related to the decline in mortality are also likely to be related to changes in the sex ratio of mortality. Early historical decreases in infant death rates are partly attributable to improvements in hygiene, water quality, and living conditions that reduced the spread of infections. Development of the germ theory in the 1870s led to expanded public health measures and to the use of antitoxins and vaccines. The 20th century contributions to declining infant mortality include the practice of antiseptic delivery and increasing availability of pasteurized milk, followed midcentury by the availability of antibiotics and further developments in perinatal medicine (9). A time line of public health and medical advances in relation to the progressive decline of infant mortality since the late 18th century is shown in supporting information (SI) Fig. 6.

The period of mortality decline was also a period of major shifts in the causes of infant deaths. As infant mortality declined, infectious diseases became less important, whereas the relative importance of complications of childbirth and prematurity increased. Although male infants have higher mortality from most causes of death, the sex differential varies by cause (10). The decline in deaths from infection is likely to affect males and females differently. Because females have more vigorous immune responses and greater resistance to infection (11), female infants have lower mortality from infections (12) and respiratory ailments (13). The male disadvantage begins *in utero* (14), when gonadal steroid production already differs strongly by sex. Males are more likely to be born prematurely and to suffer from respiratory conditions in the perinatal period (15, 16). Thus, an increase in survival among premature infants may affect the sex balance of mortality.

Several factors, including declines in infection, an increase in hospital births, medical advancements to improve birth outcomes, and better nutrition, have contributed to lower infant mortality. As infections were being minimized, there were also increases in the proportion of births taking place in hospitals and the spread of new obstetrical practices. For example, in 1900, <5% of U.S. babies were delivered in hospitals (17); by 1938, hospital delivery reached 55% (18) and soared to 99% by 1963 (19). European countries show similar trends. Hospital births were 99% in Sweden by 1960 and 94% in Norway by 1962, whereas other European countries lagged: England and Wales, 60% (1958); Denmark, 54% (1962); and Netherlands, 29% (1960–1962) (19).

Improving nutrition of mothers and babies also helped lower infant mortality. For example, in England, better nutrition is considered responsible for 40% of the decline in mortality between 1800 and 1980, with most of the effect in infant mortality (20). Conversely, inadequate nutrition *in utero* adversely affects organ and cell growth as well as insulin sensitivity and other metabolic set-points, which may increase chronic disease risk throughout the life span (21). With improving nutrition and declining infection, both maternal stature and fetal size increased (22). Although the increases in average birth weight were generally a positive influence on infant mortality, large babies (macrosomia, >4,500 g) are at higher risk of birth injury and mortality because of fetopelvic disproportion (23–25). Difficult labor is more common for male infants because of their larger average body size and head circum-

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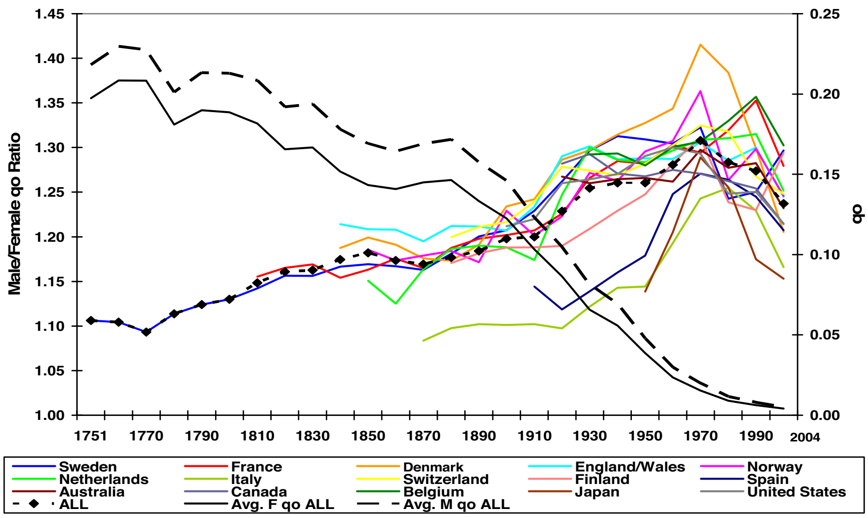

Fig. 1. q_0^M/q_0^F averaged over 10-year intervals, 1751–2004, for each of the 15 countries and for all countries available at a given date (left axis). Average over 10-year intervals of, q_0^M and q_0^F for all countries available in each time period (right axis). Data source: Human Mortality Database (www.mortality.org).

ference (26), which would exacerbate the male infant mortality disadvantage. In the last several decades, medical-technical advances, such as the increased use of Cesarean delivery (C-section) and the spread of neonatal intensive care units (NICUs), have further lowered infant mortality, particularly among small and premature babies, which would disproportionately benefit males (27).

Results

Trends in Sex Ratios of Infant Mortality. A worsening male disadvantage occurred during the major historical decline in infant mortality in these 15 countries (Fig. 1). From 1800 to 1900, the declines in infant mortality for both sexes averaged 33% across eight European countries; from 1900 to 2000, infant mortality in all 15 countries declined even faster, by 96%. In 1751, Swedish males had 10% higher probability of dying in infancy than females, which gradually climbed to 32% in 1970. For the other countries, excess male q_0 approximates Sweden at the same date (SI Tables 1 and 2). By 1900, excess male infant mortality averaged 20%, which was followed by a surge in the male disadvantage. The timing of changes differs somewhat for Italy, Spain, and Japan, where the male disadvantage is initially lower and rises later. Most countries in Fig. 1 (10 of 15) reached a peak of excess male q_0 in 1970–1980 (1.30 average q_0^M/q_0^F across all 15 countries). After 1970, excess male infant mortality declined in most countries to an average of 1.24 in 2000. Exceptions to this pattern include: Canada, for which there was little change until recently; the U.S., with an early rise and a long peak; and France, the Netherlands, and Belgium, which show later declines in q_0^M/q_0^F after 1990.

Preston's (6) analysis of mortality change at all ages in national populations showed that, as mortality declines, sex differences in death rates tend to decrease, whereas sex ratios of death rates tend to increase. The observed increases in sex ratios of infant mortality (Fig. 1) occurred during a period of rapid decline in infant mortality. However, the downturn in sex ratios after the 1970 peak also occurred during a period of declining infant mortality. Following Preston and Wang (4), we further clarify the sex-specific pattern of change in infant mortality by calculating the sex differences of rates of change in q_0. The sex differences (male–female) in percentage change of q_0 over 10-year intervals for 15 countries are shown in SI Fig. 7. Positive values indicate worsening male mortality relative to females, with negative values indicating faster improvement for males than females. Values tend to be positive before 1965–1974 (approximating the peak male disadvantage in infant mortality sex ratios) and negative after this period. On a country-by-period basis, 70% of values are positive (worse for males) before 1965–1974 and 71% of values are negative (better for males) after 1965–1974. This calculation of rates of change in q_0 provides results consistent with the trend in mortality ratios: male infants did increasingly worse than females before the peak, after which they began to close the gap.

Declines in infant mortality are correlated with rising sex ratios until the level of mortality becomes relatively low, after which the relationship between the level of mortality and sex differences disappears (Fig. 2). When the probability of dying in infancy is <0.02 (vertical line), the relationship between q_0 and q_0^M/q_0^F does not hold. The date when q_0 falls to <0.02 is close to the period of peak excess male mortality in 11 of 15 countries. This link between the level of infant mortality and the sex ratio helps explain the later timing of change in the sex mortality ratios

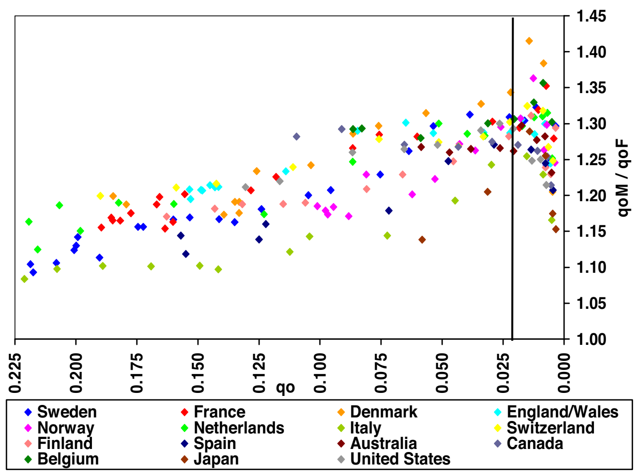

Fig. 2. Scatterplot of infant mortality (q_0) versus sex ratio of infant mortality (q_0^M/q_0^F) for 15 countries averaged over 10-year intervals. Data source: Human Mortality Database (www.mortality.org). q_0^M/q_0^F was regressed on q_0 for both sexes combined. When $q_0 \geq 0.02$, R^2 is 66%. When $q_0 < 0.02$ (dark vertical line), the relationship between q_0 and the sex ratio of infant mortality largely disappears (R^2 = 20%).

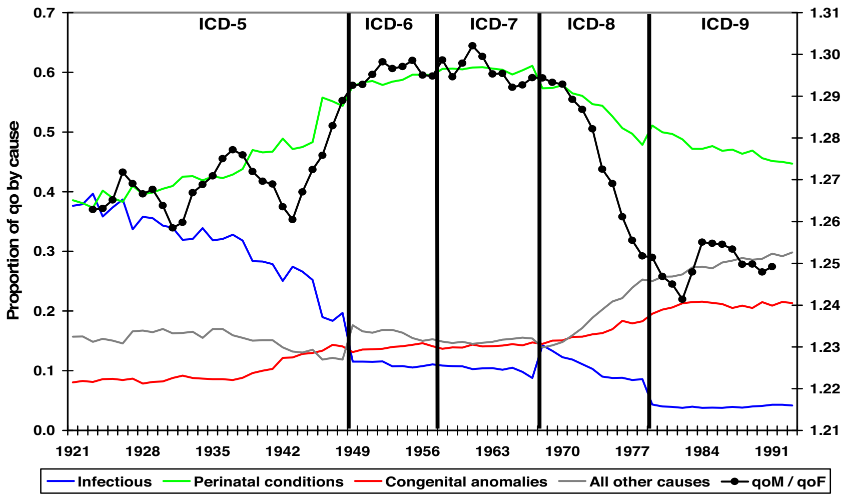

Fig. 3. Proportion of infant deaths attributable to specified causes of death (left axis), U.S., 1921–1993. Annual sex ratio of infant mortality (q_0^M/q_0^F, right axis). Dark vertical lines separate periods covered by revisions of the International Classification of Disease. For data sources, see references in *SI Text*.

observed in Italy, Spain, and Japan in Fig. 1. These three countries have relatively high infant mortality when data become available, which accounts for their lower sex ratios early on. For example, q_0 and q_0^M/q_0^F for Italy in 1870 resemble Sweden 100 years earlier. Spain and Japan also have higher infant mortality than the other countries when data are first available.

Factors in the Rising Relative Male Disadvantage. From 1900 until the approximate peak of the male disadvantage in 1970, infant mortality declined by 87% (average of all countries). During this enormous reduction in infant mortality, the male disadvantage grew further (all-country average q_0^M/q_0^F increased from 1.20 in 1900 to 1.31 in 1970). As the infant mortality declined and the male disadvantage increased, the leading causes of infant mortality also changed. During 1900–1964, the proportion of infant deaths from infectious diseases for all 15 countries combined dropped 4-fold (from 44% to 11%), whereas the proportion due to perinatal conditions more than doubled (from 24% to 58%). These shifts in causes of infant death worsened the male disadvantage. The sex mortality ratio for infectious disease mortality increased from 1.15 in 1900 to 1.25 in 1964, whereas the ratio for perinatal causes increased from 1.18 in 1900 to 1.38 in 1964. This combination of changes increased the average q_0^M/q_0^F by 0.2.

We assessed the relative influence of perinatal conditions and infectious diseases on changes in the sex mortality ratio by regressing q_0^M/q_0^F on the percentage of infant deaths attributable to each cause of death (28). We estimated separate models for infectious diseases, perinatal conditions, and all other causes combined for all country–year observations during 1861–1964. The negative slope coefficient for infectious diseases on q_0^M/q_0^F (-0.24, $R^2 = 35\%$) indicates that, as the importance of these diseases declined, the male disadvantage increased. Conversely, the positive slope coefficient for perinatal conditions on q_0^M/q_0^F ($+0.28$, $R^2 = 35\%$) indicates that the male disadvantage increased as these conditions became more important.[§]

The link between cause of death and the sex ratio of infant mortality was further analyzed with detailed annual data for the U.S. during 1921–1993, which includes information on death from congenital anomalies. In 1921, infectious diseases and perinatal conditions contributed equally to infant deaths (Fig. 3). Paralleling the international data, as infectious disease mortality declined in importance, perinatal conditions comprised an increasingly larger share of infant deaths: from 39% in 1921 to 60% in 1964 (the peak of male infant disadvantage). Congenital anomalies also become an increasingly important cause of infant death after 1970. These results indicate that, during this period, males had a disadvantage in mortality from both infectious disease and perinatal conditions, but the male disadvantage is greater for perinatal conditions (hence the rise in infant mortality sex ratios).

Falling Male Disadvantage Since 1970. The surge in excess male infant mortality in the U.S. closely tracks the proportion of deaths due to perinatal conditions up through the peak of q_0^M/q_0^F, but not afterward (Fig. 3). We hypothesize that improvements in obstetric practices and neonatal care were the main factors in the fall of excess male infant mortality. The increasing use of C-section and improvements in neonatal medicine further reduced infant mortality, particularly among small and premature infants, which disproportionately benefited males.

Because few births took place in hospitals until well into the 20th century, it is impossible to fully document historical trends in sex differences in birth weight or infant mortality by birth weight. National data on birth weight for the U.S. are not available until 1950 (29). Examination of the neonatal sex mortality ratio by birth weight shows (Fig. 4) that, in 1950, males had higher mortality at every birth weight except at the extremes (<1,000 g and >4,501 g). The neonatal sex mortality ratio in 1950 was highest (1.8) for babies weighing 2,001–2,500 g, and at least 1.2 over the entire range of 1,001–4,000 g. Between 1950 and 2000, the neonatal sex mortality ratio greatly decreased for births weighing 1,501–3,500 g, which includes the range of normal birth weights (Fig. 4).

C-sections were increasingly used for risky births as techniques and survival rates improved. Very few infants were delivered by C-section before 1970 (≈5% in countries with available data); by 2003, the C-section rate increased 4-fold (average 20%; rates vary widely by country) (Fig. 5). Male fetuses are more likely to experience complications during pregnancy (30, 31), with C-sections being 20% more common for males (26, 31). Very large and very small babies are more likely to be delivered by C-section, which reduces mortality risks at both weight extremes, <1,500 g (32) and >4,500 g (33). C-section rates for the U.S. in

§We also estimated the same models with country-specific fixed effects to account for the nonindependence of observations in each country. In each model, interpretations were unchanged, although slope coefficients were attenuated, and R^2 values were higher.

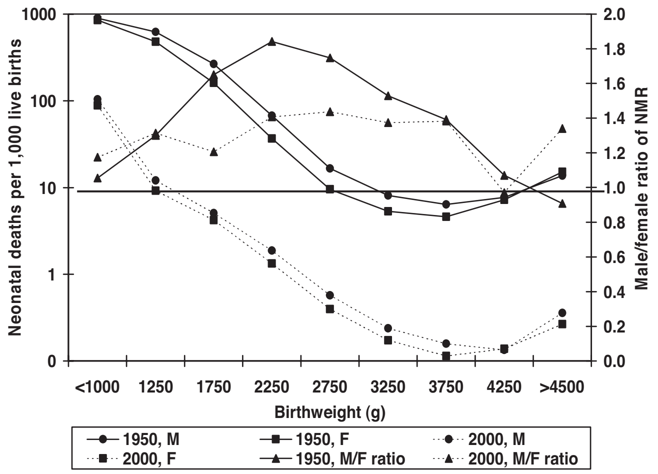

Fig. 4. Neonatal mortality rates by sex and birth weight (left axis) and male (M)/female (F) neonatal mortality ratios by birth weight (right axis), U.S. 1950 and 2000. For data sources, see references in *SI Text*.

1993 were highest for the low birth weights (<1,500 g, 45.8%; 1,500–2,499 g, 32.5%) and for high birth weights (≥4,000 g, 28.4%) versus 19.6% for the normal birth weights (2,500–3,999 g) (34). Among births with fetopelvic disproportion, C-section delivery has become almost universal (96% in the U.S., 89% in Canada, and 83% in Sweden) (34, 35), reducing infant mortality from this complication to very low levels.

To evaluate the similarity of the timing of the increase in C-section delivery and the change in the sex ratio of infant mortality, we conducted a regression of q_0^M/q_0^F on the percentage of births delivered by C-section for available years, controlling for the effect of country using a fixed-effects model. The data combined for 15 countries during 1970–2004 yield a slope coefficient for percentage of C-sections of −0.0065 [$P = 0.0007$, $R^2 = 0.156$, intercept = 1.376; data range from 28 observations (Sweden) to single years (Finland, 2000; Spain, 1985)]. For example, as C-section rates increased from 5% to 20%, this effect size would predict a 26% decrease in the male disadvantage in infant mortality, showing that higher C-section rates are associated with lower male excess infant mortality.

In addition to changes in delivery practices, improvements in neonatal intensive care also may have benefited malesmore than females. After 1950, the pace of improvement in infant mortality slowed in the U.S. and other developed countries (19). However, the ensuing development and spread of neonatal intensive care units (NICUs) with advanced equipment and highly trained staff (27) introduced major benefits for premature babies with complications and lower chances of survival. The NICUs allowed infants to further develop and survive medical crises until they could tolerate a normal environment. Thus began a new period of rapid decreases in infant mortality, with higher survival of small and frail infants at the same time deaths were increasingly concentrated among low-birth-weight infants. For example, U.S. birth weights of <1,500 g comprised only 1.1% of all births in 1950 and 37% of all neonatal deaths (29); in 2003, babies weighing <1,500 g comprised 1.5% of all births and 72% of all neonatal deaths (36).

Until 1970, mechanical and assisted ventilators were used for respiratory difficulties in normal or low-birth-weight babies, who were 60% more likely to be male (37, 38). Implementation of continuous positive airway pressure by the NICUs in 1971 further increased survival of very low-birth-weight and premature infants (39). As survival improved, the typical NICU patient became even smaller (40). Other developments favoring survival of preterm small births included increased use of antenatal steroids and the availability of surfactant therapy (16). Because males are at higher risk of prematurity and prematurity-related conditions, including respiratory distress syndrome (RDS), the recent advances in therapy and management may be inferred to favor boys (37, 41). The largest declines in male excess neonatal mortality occurred among very premature infants and resulted from a faster decrease in male deaths from RDS (16).

Discussion

Unlike adult mortality, explanations for sex differences in infant mortality are dominated by biological rather than lifestyle factors (42). Our analysis illuminates an unappreciated major shift of sex mortality differences in the first year of life when biology is the prominent factor. Although one might expect that innate biological differences between males and females would result in a constant level of the excess vulnerability of males, our analysis shows that biological differences are highly sensitive to both the medical-technical and epidemiological contexts. During the great historical improvements in infant mortality, the rising male disadvantage in infancy revealed a level of unexpected male vulnerability. Although males are more susceptible to both infections and conditions associated with prematurity and development, there are marked changes over time in how these

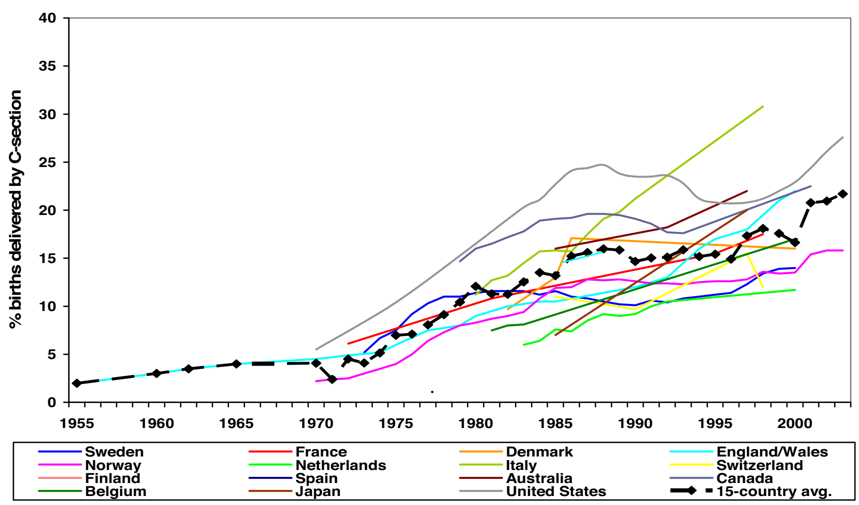

Fig. 5. Historical increases in Cesarean delivery for 15 countries, 1955–2003. For data sources, see references in *SI Text*

conditions are related to mortality. The fall in excess male infant mortality after approximately 1970 is a clear indicator of this. Thus, the relative biological vulnerability of males shows plasticity depending significantly on the environmental context.

Others have noted a growing male disadvantage in infant mortality during the first half of the 20th century (7, 8), and our analysis confirms that the worsening disadvantage occurred in 15 countries spanning three continents; that the timing of the changes was very consistent across countries; and that the sex difference is related to the overall level of mortality. However, the subsequent, highly consistent pattern of falling male excess infant mortality in the last few decades of the 20th century has not been noted previously. Again this pattern of decline is consistent in Europe, North America, and Japan.

These 15 developed countries experienced similar changes in causes of infant death as declines in infectious disease mortality shifted the causes of infant deaths to perinatal conditions. As infant deaths became even more concentrated among these causes, the excess vulnerability of boys increased. Data for all countries show that, whereas the distribution of cause of death was changing, the male/female ratio of mortality in both of these causes increased over time. Our regression results suggest that, as infectious disease mortality decreased, males became even more disadvantaged because of their even greater vulnerability to mortality from perinatal conditions. We assume that this results from the fact that, as infant mortality falls to very low levels, infant deaths become increasingly concentrated among those who are initially born with some weakness. In the last few decades of the 20th century, even infant deaths due to infection were rarely due solely to some external cause. Changes in obstetrical practice and neonatal medicine that saved all but the weakest babies have benefited boys more than girls because boys were more vulnerable across the entire range of birth weights.

We must note that it seems unlikely that the changes in excess male infant mortality could be accounted for by shifting gender preferences demonstrated by preferential infant care in these industrialized countries. That is, there is no evidence that boys became devalued and then revalued in all of these countries within a generation. Although there may be differences in preferences for sons across the 15 countries, the patterns of change in male versus female mortality are remarkably similar.

The sex difference in life expectancy at birth reached a peak in 1970 and 1980 in these 15 countries. At this time, the higher male infant mortality contributed ≈0.5 year to this difference. Currently, the sex difference in life expectancy at birth has shrunk in most countries, and the sex difference of infant mortality contributes much less to this difference, because both the effect of infant mortality on life expectancy and the sex difference have decreased.

The changing sex differences in infant mortality during the 20th century share environmental factors that we have also associated with major improvements in growth and longevity. In particular, improving infant mortality in cohorts was strongly linked to increased adult height and life expectancy at the later ages after 1800 in both genders (43, 44). These findings may also be considered in terms of the links of early and later life health to adult disease (45). The strong association of prematurity with later lung dysfunction and cardiovascular risk (46, 47) implies that a subgroup of the rescued male babies may experience earlier onset of later-life diseases. It is also possible that these improvements have relaxed selection against vulnerable genotypes. Further analysis of the sex differences in adult mortality may reveal additional medical and environmental factors that differentially affect males and females.

Materials and Methods

Using data from the Human Mortality Database (www.mortality.org) from 1751 to 2004 for most countries and additional data sources for France and the United States (48, 49), we examined male/female ratios of the probability of dying in infancy (q_0^M/q_0^F) for 15 developed countries: Sweden, France, Denmark, England/Wales, Norway, The Netherlands, Italy, Switzerland, Finland, the U.S., Spain, Australia, Canada, Belgium, and Japan. Data for Sweden are available from 1751; other national data are limited to the 19th century (nine countries) or 20th century (five countries). Details on the dates used for specific countries are included in *SI Text*. We also use data on infant mortality by cause of death for the same 15 countries for selected years from 1861 to1964 in Preston, Keyfitz, and Schoen (28). The country-year observations range from as few as two for Belgium (1960 and 1964) to 12 for England/Wales (every 10 years from 1861 to 1960, plus 1964). We supplement this with annual data on infant mortality by cause of death for the United States for 1921–1993 (50, 51).

Based on the International Classification of Disease (ICD), broad categories of cause of death were created: infectious diseases, perinatal conditions (including complications of pregnancy, childbirth and infections acquired during the first month of life, immaturity and postmaturity, and respiratory distress syndrome), congenital anomalies, and all other causes of death. Additional details are found in *SI Text*.

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