



Invited Commentary

Invited Commentary: Natural Versus Unnatural Sex Ratios—A Quandary of Modern Times

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The typical dilemma with sex-ratio findings is that when they are real, they aren't interesting, and when they are interesting, they aren't real. In this issue of the *Journal*, Fernández et al. (*Am J Epidemiol.* 2011;174(12):1327–1331) describe a deviation of the sex ratio that is apparently both large and real. There was a temporary but distinct spike in the proportion of boys born in Cuba around the time of the collapse of the national economy during the 1990s. Although an excess of boys does not fit the prevailing biologic theory regarding maternal stress and the sex ratio, the data are consistent with results from the Dutch famine (where population-level deprivation was even more extreme). A new quandary arises in the modern era with interpretation of the sex ratio: If the decision to abort a pregnancy is influenced by the sex of the fetus, a change in the behavior of even a small proportion of women could influence the sex ratio at birth. The possible role of sex selection in the Cuban context is discussed.

abortion; sex ratio

The natural sex ratio at birth (51 boys to 49 girls) is a topic that manages at once to be highly accessible, scientifically intriguing, and of questionable importance. Believable deviations in the natural sex ratio (such as the shifts that have occurred over time) are usually miniscule, while the dramatically large deviations that get into news reports are seldom replicated. (The distortion of sex ratio by prenatal sex selection (1) is a different matter, as discussed further below.)

In humans, the sex of the baby is determined by the fertilizing sperm. A spermatozoon carrying a Y chromosome produces a boy, while one carrying an X chromosome produces a girl. Given that the ratio of X- and Y-carrying human sperm is 50:50 (2), the slight shift to a preponderance of boys by the time of delivery is a minor biologic mystery. Perhaps Y sperm have more success in the female reproductive tract or in fertilization of the ovum (although there is no evidence of this, based on the limited data available (2)). Another possibility is that female conceptuses have higher mortality during early pregnancy. This doesn't seem to fit, however, with the higher male mortality at the later (observable) stages of pregnancy.

Our cultural preoccupation with sexual identity makes infant gender the cardinal piece of information recorded at birth. This produces a vast cornucopia of human sex-ratio data—with all the inevitable possibilities for robust but trivial

differences in large samples and for dramatic but spurious differences in small samples. With large samples, researchers have strained themselves to attach importance to “highly statistically significant” changes in the sex ratio that are nearly invisible—for example, a shift from 51.6% to 51.3% boys (3). Small samples are more entertaining. They offer opportunities for splashy results, such as the observation that 60% of the offspring of billionaires are sons (4).

A recurring theme of sex-ratio studies is the publication of positive findings followed by failure to replicate. This cycle of discovery and disappointment has accelerated in recent times with the advent of online publication. A record was set in 2005, when a *BMJ* report of more boys among infertile women (5) was followed 6 days later by null results from a study 10 times bigger with higher-quality data (6).

In this issue of the *Journal*, Fernández et al. (7) show a marked rise in the proportion of male births in Cuba in 1995–1996. This is a striking finding that bears closer inspection. The authors began with a general hypothesis that mothers who have been subjected to severe living conditions are more likely to produce girls. Known as the Trivers-Willard hypothesis, this proposition was developed from evolutionary theory and data from nonprimate mammals (8). Fernández et al. examined the sex ratio in Cuba during the collapse of the Cuban economy in the mid-1990s. The results

are captured in their figure 2: The economy crashed in 1991, followed by a spike in the proportion of boys. (The authors express this value as the ratio of boys to girls, which reaches a maximum of 1.18.) At its peak, this sex ratio is both substantial (54 boys to 46 girls) and beyond what can plausibly be attributed to chance.

If we can exclude the possibility of recording errors or other reporting artifacts during this time of extreme social distress, the finding is impressive. The challenge then becomes one of interpretation. The first thing to note is that the change in sex ratio was not in the direction predicted by theory. However, as the authors discuss, the change is consistent with results from the Dutch famine of World War II, in which mothers exposed to famine had an excess of sons (9).

What else can we glean from these data? Ecologic data don't provide much opportunity to pursue specific etiologic questions, but a closer look at the time sequence may be instructive (figure 2) (7). If 1960–1985 is considered as a baseline, the sex ratio was substantially elevated for 7 years before the spike and 4 years afterwards (a matter not discussed by the authors). Although not as dramatic as the 1995–1996 spike, this rise seems unlikely to have occurred by chance (judging from the 95% confidence intervals). This shift toward boys before the start of the crash complicates conjectures about causation.

The spike itself did not begin until 2 years after the lowest point of the economic collapse. Even allowing 9 months' gestation, that seems like a long time for a biologic response. What sequence of physiologic events in the mother or father—through nutritional deprivation, emotional stress, behavioral changes, or things not yet defined—might have produced this pattern? Were other reproductive processes involved? Might the authors be able to find data in Cuba from this period on changes in sperm quality, fecundability, or miscarriage that would support a biologic interpretation?

As we explore interpretations, there is one other possibility. The authors dismiss the suggestion that prenatal sex selection might have played a role in the observed pattern—but can we be sure? All the necessary elements for an influence of sex selection seem to be present: Cuba is a country where abortion is easily available and perceived by many as an acceptable method of birth control (10). Prenatal ultrasound examination (with the opportunity for early diagnosis of fetal gender) is routinely provided as part of the national health program (11). Birth rates typically decline in periods of economic deprivation, and Cuba around this time was no exception (figure 1 (7)). If pregnancies are less welcome during an economic collapse, might fetal gender become an element in a woman's decision to abort? In times of societal hardship and uncertainty, might it be harder to decide to abort a boy than a girl?

With a few assumptions, it is possible to estimate the fraction of women who would have to make such a choice in order to produce the observed percentage of boys. This fraction can be expressed as follows:

$$x = (z - 0.51) / [(0.49z)(1 + a)],$$

where x is the percent of female fetuses that would have to be aborted in order to produce the observed sex ratio (z), and

a is the ratio of induced abortions to livebirths without sex selection. This formula assumes a sex ratio of 0.51; minor perturbations in this baseline have minor effect on the calculations. The value of x is also relatively insensitive to the quantity of a , which we estimate as 0.45 based on the reported abortion ratio in Cuba in the early 1980s (12). Plugging in the observed peak sex ratio ($z = 0.54$), we calculate that 8% of female fetuses would have had to be selectively aborted to produce the observed spike. This amount of selective abortions is not trivial, but neither does it seem beyond the realm of possibility.

In the end, these data from Cuba suggest a remarkably large deviation in the sex ratio, related in time to a period of acute economic deprivation, for which possible pathways of effect remain obscure. The consistency of this finding with data from the Dutch famine invites the possibility of a real biologic effect—albeit one that requires a different biologic theory than the one prevailing. At the same time, it does not seem possible to rule out the alternative hypothesis that the sex ratio changed through human intent. Indeed, the possibilities for unnatural variations in sex ratio have only just begun (13).

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