



Can sex ratios at birth be used in the assessment of public health, and in the identification of causes of selected pathologies?

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A B S T R A C T

This paper will consist of two parts. In the first, further support is given to the proposal that offspring sex ratios (proportions male) may usefully be regarded as indicators of public health. In the second, it is shown that sex ratios may help in the identification of the causes and effects of several pathologies that seriously impinge on public health viz. autism, testicular cancer, hepatitis B and toxoplasmosis.

1. Part 1 sex ratios and the assessment of public health

Recently it has been proposed that the human live birth sex ratio (proportion male, males divided by total births, M/T), may be a useful indicator of public health. Here that idea is given added credibility by describing the evolutionary context of two established causes of M/T variation. The suggestion is that the hormones which are hypothesized to cause M/T variation at birth are also associated with health in individuals - both men and women. In short, M/T, to some extent, may reflect the health of the breeding population as well as of the public at large.

1.1. Introduction

M/T occupies a curious place within science. It has been known for more than 300 years that it normally exceeds 0.5 (equal numbers of male and female births), and that it varies very slightly around a value of about 0.51 [1]. M/T is intrinsically relevant to several branches of science and medicine (demography, genetics, physiology, endocrinology, obstetrics and gynaecology, epidemiology and probability theory). But, until recently, practitioners in none of these specialties have taken the lead in unravelling the causes of that variation. So progress has been slow. However, over the last few decades, two causes of M/T variation have been identified. These causes will now be described.

1.2. Acute M/T variation. Maternal stress-related male-biased miscarriages

For many years, it had been thought (but with a deficit of firm evidence) that when pregnant women are stressed, they are more likely

to miscarry, and that such miscarriages are more likely to be of the male sex. Over the last two decades, that deficit has now been rectified by Catalano and colleagues, and by others, and it has also been shown that these changes may have varying temporal effects.

Time series analyses have shown that M/T may be acutely, abruptly and very temporarily depressed following unexpected (so-called “exogenous” [2]) catastrophic events. These include not only natural events (such as earthquakes [3], temperature oscillations [4], floods and heavy fog [5]), but also man-made events such as severe economic stress [6], mass layoffs [7], and terrorist attacks [8]. The latter was first demonstrated in the United States following the September 11 attacks [9,10], where it was also shown that the dips were due to an excess of male foetal losses [11].

The time interval between the catastrophic event, and the M/T dip is of the order of 4–5 months, suggesting that male mid-trimester foetuses are particularly at risk. It seems likely that the causal factor in these male-biased miscarriages is stress-induced maternal adrenal androgens, including testosterone [12].

1.3. Secular and seasonal M/T influences

M/T may also demonstrate long-term cyclical changes [13]. Long-term trends have also been shown in various countries, such that, for example, M/T has been shown to be declining in most industrialized countries over the past 50 decades [14]. This is because M/T may be influenced not only by environmental but also by social factors [15,16].

Indeed, the observed secular trends and geographical variations in M/T in different countries and regions often demonstrate mixed and often contradictory results [14]. The multitude of environmental, social, economic, demographic and other factors that have been proposed

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to putatively influence M/T thus further complicate the interpretation of both secular trends and geographical variations. For this reason, long M/T time series analyses, searching for temporal cycles and random components, have been proposed as superior approaches than the disingenuous establishment of simple linear trends [14].

The extent of this culling of male fetuses is of comparable intensity to estimates of perinatal mortality, potentially making it a public health issue [17]. It has further been shown that these male fetuses are selected for frailty, rather than at random [2,18,19]. This was done by showing that male survivors of low-M/T cohorts have low mortality. This was interpreted by these workers as evidence for evolutionary adaptation as contrasted with dysregulated gestation [20–22].

If this claim were true, it is important. However, the validity of such a claim is difficult to assess. Indeed, the ease with which such claims may be made has been satirised [23]. This review will now elaborate on the argument that the above cause of M/T variation (sex-selective miscarriage) has health-related evolutionary precursors. This reasoning will then be supplemented with evidence on the health-related evolutionary context of a second cause of M/T variation.

1.4. Population-level measurements and caveats thereupon

It is first worth noting that the use of M/T as a possible health indicator has been illustrated, with rising M/T correlated with a decline in important health metrics such as infant mortality, and vice versa [24,25]. Large samples of national M/T have shown that this correlates positively with life expectancy [25], and cognitive ability [26], and negatively with parasite stress [27], and, in particular, with prevalence of infection by the parasite *Toxoplasma gondii* [28]. However, such claims must be interpreted with caution since aggregate data, while convenient and incorporates large numbers, cannot explicate any effects of or effects upon subgroup M/T, as will be amplified below.

For example, the United States constitutes a natural experiment insofar as four races are demographically represented in national statistics, and these are American Indian or Alaska Native, Asian or Pacific Islander, Black or African American and White. It has been shown that M/T is Asian or Pacific Islander > White > American Indian or Alaska Native > Black or African American. The perinatal mortality rate is an important indicator of quality of health care delivery. The rate is expected to approximate 6/1000 births [29]. The lower baseline M/T of Indian or Alaska Native and Black and African American is equivalent to a constant reduction of 3.5–4/1000 male births when compared to White M/T. Race remains the most significant variable associated with wealth inequality in this country and may be partially responsible for the observed male deficit due to chronic socio-economic stress [30], which is known to reduce M/T [6].

Sex-selective abortion is widespread in Asia and its immigrants, and in this race, [31] in this study, was equivalent a constant loss of 3.5 female fetuses per 1000 live births when compared to Whites [30]. Indeed, a recent study concluded that the number of missing women due to this phenomenon was 126 million in 2010, and this number is expected to peak at 150 million by 2035. The annual number of newly missing females was estimated at 3.4 million in 2010 and is expected to remain above 3 million annually until 2050 [32].

However, the analysis of the aggregates of large populations is potentially fraught confounding factors that may be erroneously ignored. For example, it has been shown that for 1970–2002, Filipino mothers (which in the above study would have been incorporated in Asian/Pacific Islander births, albeit these studies had differing timeframes) had the highest M/T, but there were years in which Japanese mothers had the lowest M/T and Japanese and Hawaiian M/T was identical to White, while Black was identical to American Indian [33]. Thus, the aggregation of populations for the purposes of M/T analysis may lead to inaccurate conclusions, including about M/T secular gradients and consequently, the cause of any contributing public health issues.

It is worth noting that while the observed US decline in M/T was

predominantly due to White births, but not African Americans [34], it has been observed that factors that are somehow lowering M/T in the former may be unable to lower it in the latter which is already chronically depressed [30]. It is thus possible that M/T at national or even major group level may be artefactual and a result of M/T dynamics at lower levels since the ratio may be effected by different causes such as parental age structure, birth orders and so and aggregates are therefore uninformative of the processes occurring in subgroups and individuals.

All of this is superimposed on broad secular M/T trends which must also be taken into account along with the potential cyclicity of these trends [14–16]. While the public health aspects of the M/T ratio are thus abundantly clear, it is equally clear that analysis should take therefore take place at the lowest level of available data possible. And even then, statistical significance may not be the ideal metric for the assessment of M/T changes of public health import – trends may be a more important measurement. Once such changes are detected, it is important to remember the dictum that correlation does not automatically imply causation [14].

In this paper, in analyzing the geographical variation in M/T, two different levels of analysis are distinguished (global and local), and two different sets of factors affecting M/T are proposed accordingly. Some key guidelines and future research directions are also proposed.

1.5. The hypothesis of Trivers and Willard (1973)

Most studies of the evolutionary setting of M/T variation have been based on the hypothesis of Trivers & Willard (TW). The background to this will now be described. It has been reported in many species (including man) that the variance of male reproductive success exceeds that of female reproductive success. In other words, for instance, most women have average numbers of children whereas, in contrast, some men have many children while an appreciable number of other men have no children. TW noted that, under these circumstances, women would maximise their numbers of grandchildren if women in good ‘condition’ were to produce more sons, and women in poor ‘condition’ were to produce more daughters. Accordingly, in an intuitive coup, these authors predicted that this actually happens. Their paper has been influential, having attracted more than 2000 citations (according to the Web of Science in September 2017) [35]. It is true that some of these citations were by authors who claimed to have failed to find supporting evidence for the hypothesis. However, it is suggested here that these claims are based on failures to test the hypothesis as it was originally formulated (by failing to observe TW’s stipulated criteria for ‘condition’). Moreover, it has been reported that the TW hypothesis was consistently supported if the measure of ‘condition’ was made around the time of conception [36,37]. Lastly, and seemingly unnoticed by Trivers and Willard themselves, there was very strong pre-existing direct evidence for their hypothesis. This is that in very large samples, under conditions of natural fertility, the most fertile human parents reportedly have the most male-biased M/T [38,39]. Further credibility accrues to the TW hypothesis when it is considered in the context of James’ hormonal hypothesis [40]. This proposes a second cause of sex ratio variation and it will now be described.

1.6. M/T variation cause 2. Parental hormone levels around the time of conception

It has been hypothesized that M/T is partially controlled by the hormone levels of both parents around the time of conception [41–48].

Ex hypothesi, high levels of testosterone (in either parent) and/or of estrogen (in the mother) are associated with subsequent male births. And high levels of gonadotrophins (in either parent) are associated with subsequent female births. Many papers offering empirical support to this hypothesis have been published [49]. The hypothesis has also recently been described by Spiegelhalter as ‘the most coherent’ known to

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