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Running Title: *Sex ratios: heritability and theory*

Does the lack of heritability of human sex ratios require a rethink of sex ratio theory? No: a response to Zietsch *et al*. 2020

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Zietsch et al. (2020) estimated the heritability of the sex ratio at birth in humans by measuring the association between the sex ratios produced by over 14 million Swedish sibling pairs. The heritability estimate was 0.00058, with a 95% confidence interval of -0.00076 - 0.00196. They concluded that the sex ratio differences observed among the families of siblings are not due to genetic differences in the tendency to produce one sex more than the other. Zietsch et al. also concluded that this result renders (p.1) "Fisher's principle untenable … [as a framework] for understanding human offspring sex ratio". Here, we discuss why the latter conclusion is incorrect.

Düsing (1884) created the theoretical framework from which our understanding of sex ratio evolution derives. This framework was then elaborated in important ways by, among others, Fisher (1930), Shaw and Mohler (1953), Shaw (1955, 1958), Kolman (1960), MacArthur (1965), Hamilton (1967), Leigh (1970), Charlesworth (1977, 1994), Kahn et al. (2015) and Argasinski and Broom (2020). Overviews of the current state of theory and its empirical application can be found in Charnov (1982), Bull and Charnov (1988), Karlin and Lessard (1986), Wrensch and Ebbert (1993), Hardy (2002) and West (2009). A key result of this theory is that there can be an "equal investment" equilibrium resulting from the action of natural selection in a randomly-mating population. It occurs when the cumulative resource invested in female offspring and the cumulative resource invested in male offspring are equal at the end of parental investment. If the ratio of resource investments is 1 and females and males have identical mortality rates, the equilibrium occurs when there are equal proportions of females and males in the mating pool of adults. This is often referred to as the 1:1 sex ratio equilibrium. If the cumulative resource investments are not equal, the evolutionary equilibrium is an unequal numerical sex ratio, with the more costly sex being in the minority.

What is the evolutionary process that can result in the evolution of the equal investment equilibrium? Consider the case when females and males are equally costly to produce and have identical mortality rates. If equal proportions of females and males are not present in the mating pool, parents that produce more of the rarer sex will leave more descendants. If the tendency to produce the rarer sex is inherited, these descendants will also produce more offspring of the rarer sex. This decreases the sex ratio bias in the mating pool formed by these offspring, which means that the advantage of producing the rarer sex decreases. This dynamic attains an evolutionary equilbrium only when both sexes have equal proportions in the mating pool. This equilibrium is consistent with the absence or presence of genetic variation influencing the sex ratio (see below).

Empirical investigations confirm that this process of "frequency-dependent" natural selection can result in the attainment of this evolutionary equilibrium (e.g., Conover and Van Voorhees 1990; Basolo 1994). Additional theory describes the conditions under which the equilibrium sex ratio produced by the population is predicted to be produced by each individual or mated pair (see Orzack and Hines 2005 and references therein). Zietsch et al. denote as "Fisher's principle" the process by which individuals producing the rarer sex have an evolutionary advantage, which thereby increases the frequency of the sex they produce: we refer to it as the "Düsing-Fisher principle".

For the Düsing-Fisher principle to cause the sex ratio to evolve, offspring sex ratio must be inherited from parents to offspring, at least in part, and there must be inherited variation among individuals or couples in regard to the offspring sex ratio they produce (the latter condition is that the trait be "heritable", see Falconer and Mackay 1996 for the distinction between this condition and the condition that a trait be inherited). However, contrary to the claims of Zietsch et al. (2020), the Düsing-Fisher principle makes no inference that the sex ratio be heritable *at the evolutionary equilibrium*. For example, a 1:1 sex ratio equilibrium is consistent with, say, each individual having a genotype that causes them to produce the same 1:1 sex ratio (not heritable) or with half of them having a genotype that causes them to produce all daughters and half of them having a genotype that causes them to produce all sons ("maximally" heritable; cf., Patterson 1928). No implication about the realized importance of the Düsing-Fisher principle as an evolutionary explanation for the human sex ratio can be drawn from the fact that the sex ratio is not heritable in the Swedish sample. The evolutionary equilibrium arising from the Düsing-Fisher principle is like those arising in many other evolutionary contexts: the attainment of the equilibrium erases the evidence of the causal process that led to its evolution (e.g., Hartl et al. 1985). Therefore, Zietsch et al.'s results do not render the Düsing-Fisher principle inherently untenable as a framework for understanding the evolution of the human offspring sex ratio. In this context, we note that Zietsch et al. appear to assume that the absence of genetic variation for the sex ratio at birth implies that there is no genetic variation for the human sex ratio at any age, especially the later age at which the evolutionary equilibrium attained by the Düsing-Fisher principle might be attained. There is no reason that this assumption must be true, especially given the age-specificity of the expression of many traits (e.g., Leips et al. 2006).

Zietsch et al. conclude (p. 6) that their results are consistent with "the simple explanation that variation in offspring sex ratio in humans is due to unbiased Mendelian segregation of sex chromosomes during spermatogenesis and unbiased fertilization". This is correct, although it does not have precedence over the Düsing-Fisher principle as an evolutionary explanation. In human spermatogenesis, meiosis results in the production of statistically-equal proportions of gametes containing an X chromosome and of those containing a Y chromosome and equal numbers of females and males appear to be conceived (see results and discussion in Orzack et al. 2015). These outcomes could be the result of natural selection for "honest meiosis" (Leigh 1977) and thereby not arise from natural selection on the sex ratio in a direct sense. However, both processes of natural selection could operate or have operated simultaneously. It is also possible that the XY process of sex determination is an outcome of natural selection for a 1:1 sex ratio. Even if natural selection on the sex ratio was the sole evolutionary influence on the human sex ratio in the past, it is arguable that the extent to which the Düsing-Fisher principle, or other adaptive sex ratio processes, can operate currently is greatly limited by the presence of chromosomal sex determination (Williams 1979). We note in this context that investigators seeking an adaptive explanation for the human sex ratio sometimes implicitly assume that it has evolved via natural selection within *Homo sapiens*. There is no compelling reason to think that this is true and there is evidence to indicate that it is not. For example, estimates of the sex ratio at birth vary among primates, but many are statistically similar to the male-bias observed in many human populations or to a 1:1 sex ratio at birth (Sugiyama 2004; White 2009; Bronikowski et al. 2016). Similarly, post-birth age-specific mortality rates are lower for females than for males in several primate species, just as in humans (Bronikowski et al. 2011). Evolutionary explanations for the sex ratios observed among primate species remain controversial (e.g., Schino 2004; Silk et al. 2005). Whatever the conclusion about the adaptive significance of sex ratios in other primates, it is essential to assess the influence of evolutionary history when attempting to understand the evolution of human sex ratios. Even if one assumes that the Düsing-Fisher principle is the evolutionary explanation for the human sex ratio, this does not identify when this process of natural selection occurred. It could, for example, have occurred when mammals evolved in the Mesozoic, when primates evolved in the Paleocene, or more recently when apes evolved in the Oligocene. If so, the sex ratio of *Homo sapiens* would be at least in part a result of past evolution, instead of being entirely a result of current evolution in human populations, and indeed this potential influence of past evolution is mentioned by Zietsch et al. (p. 7). Consideration of the influence of such "phylogenetic inertia" (Felsenstein 1985; Hansen and Orzack 2005) is rare among analyses that attempt to compare the predictions of sex allocation theory to data from humans and other vertebrates and can render their conclusions ambiguous.

Finally, we comment more broadly on what is and is not known about the evolution of the human sex ratio. The sex ratio at birth in most populations is slightly, but significantly, biased towards males (Garenne 2002, 2008; Mathews and Hamilton 2005; Chao et al. 2019; Zietsch et al. 2020) and thereafter is statistically equal for only a small portion of a cohort's existence. Neither fact can be interpreted as evidence for or against the Düsing-Fisher principle, and sex allocation theory more generally, given the absence of evidence about the empirical validity of the assumptions underlying the equal investment equilibrium. For example, there is extensive evidence for non-random mating within and between human populations but its influence on the evolutionary success of individuals or couples producing different sex ratios remains unclear. In addition, the age at which resource investment by parents ends is poorly known at best for humans and many other species. To this extent, the age(s) at which the observed sex ratio should be compared with the sex ratio predicted by the Düsing-Fisher principle are unknown.

Conclusion

Attaining a full understanding of the evolutionary basis for human sex ratio biology is challenging at best and is likely unattainable. Important reasons for this are the subtle sex ratio effects predicted for humans by sex ratio theory, cultural practices, such as son preference (e.g., Malpani et al. 2002) and sex-balancing of families (e.g., Pennings 1996) that can obscure the influence of natural selection, plus ethical constraints on experimentation (Lazarus 2002; Mace and Jordan 2005; West and Burton-Chellew 2013; Hardy and Maalouf 2017; Gellatly 2020)

The substantial evidence provided by Zietsch et al. (2020) leaves little doubt that differences among siblings in regard to the sex ratio at birth of offspring they produce are not due to inherited differences. However, this absence of inherited variation is not evidence against the claim that Düsing-Fisher frequency-dependent selection has influenced the human sex ratio. Nonetheless, if and when this process of natural selection has influenced the human sex ratio remains unresolved.

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