Maternal and Neonatal Characteristics and Sex Ratios in Humans

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Scholarly Report Title: Maternal and Neonatal Characteristics and Sex Ratios in Humans

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TITLE: Maternal and Neonatal Characteristics and Sex Ratios in Humans

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PURPOSE: To understand the correlation of sex ratio at birth and maternal health and social characteristics, and neonatal characteristics.

METHODS: We obtained data from the state of Massachusetts and analyzed births that occurred in the state and births that occurred to the residents of the state from 1987-2015 with about 80,000 births per year in each set. We analyzed categories such as the mothers' marital status, hypertension (chronic and gestational), diabetes (chronic and gestational), Apgar scores at 1 and 5 minutes, and birthweight of the offspring.

RESULTS: We found a higher sex ratio correlated with a higher birthweight ($p < 0.001$). Higher sex ratio at birth also correlated with lower Apgar scores at 1 and 5 minutes ($p < .001$). Higher sex ratio was correlated with diabetes (gestational and chronic, $p = 0.04495$) in births occurring in MA, but no association was found in births to MA residents. Higher sex ratio was also found in gestational diabetes ($p = 0.01151$). There was no correlation between sex ratio at birth and chronic hypertension, but a higher sex ratio was found to be associated with gestational hypertension. Marital status of the mother did not show any association with sex ratio at birth.

CONCLUSIONS: Maternal health is correlated with sex ratio at birth with higher sex ratio associated with gestational diabetes, and gestational hypertension. Higher sex ratio is also correlated with neonatal qualities such as higher birthweights and lower Apgar scores. These results suggest that male offspring may be associated with increased risks to the mother during pregnancy and intrapartum period. However, it is unclear how these findings correlate to the widely known Trivers-Willard hypothesis, suggesting the necessity for further research.

Abbreviations:

MDPH: Massachusetts Department of Public Health

GDM: Gestational Diabetes Mellitus

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INTRODUCTION:

Mothers are speculated to adjust the sex ratio of their offspring depending on the reproductive fitness of their future sons and daughters (Trivers and Willard 1973). This effect has been documented in insects and mites (Wrensh and Ebbert 1993) and hermaphrodites (Warner 1975). The Trivers-Willard effect explains how females will have higher reproductive success if they have male offspring with higher than average fitness than female offspring of average fitness. For instance, Clutton-Brock, Albon and Guinness found that higher ranking female red deer were more likely to sire male offspring as they had greater access to resources and would pass their rankings to their offspring (1984).

In human populations, the average sex ratio at birth is 1.03:1 (male:female) (Maconochie and Roman 1997). However, a range from 1.06:1 (Asian newborns) to 1.028:1 (Native American newborns) is seen (Quddus 2005). Further, it was widely believed that there was a higher male to female sex ratio at conception. However, Orzack et al. (2015) found that the ratio was 1:1 at conception with changes in ratio throughout the pregnancy.

Higher male sex ratios were found in Venezuela for cohabitating and married couples, while the male sex ratio decreased when single mothers were caring for the children (Chacon-Puignau and Jaffe 1996). In addition, a meta-analysis noted the decrease in male sex ratio following the decline in the annual consumption of goods and services by individual households in Sweden (Margerison Zilko 2010).

Maternal stress, physical and psychological, are considered as risk factors for spontaneous miscarriage, preterm birth, low birthweight (Witt et al. 2014). As mentioned earlier, Trivers-Willard's theory noted mothers would spontaneously abort male fetuses in times of stress as it was likely the suboptimal quality male offspring would produce fewer offspring compared to a suboptimal quality female offspring. Shifotoka and Fogarty (2013) found a decreased sex ratio globally in areas with high prevalence of HIV and tuberculosis. One could, therefore, speculate that in cases of resource limitations and environmental constrain, female fetuses are more likely to survive.

However, out of the several studies investigating the Trivers-Willard hypothesis in human populations, Lazarus (2002) found that only 48% of the studies he analyzed supported the Trivers-Willard effect. Since then, other studies have found the male gender to be "an independent risk factor for adverse pregnancy outcome" (Di Renzo et al. 2007). Supporting literature includes data showing a correlation between higher rates of abnormal fetal heart tracing patterns during the first and second stages of labor with higher sex ratios at birth in humans (Yahai et al. 2017).

For my pursuing inquiry in medicine project in 2015, we sought to understand the importance of the mothers' health on possible resource allocation to the fetus and how that would impact the survival of male versus female offspring. We used the Kessner Index for adequacy of prenatal care and obtained data for years 1989-2013 from the Massachusetts Department of Public Health. We found that mothers who had adequate care were more likely to have female offspring at birth compared to male offspring with 51.1% of births siring male offspring versus "other" prenatal care (including inadequate, intermediate, unknown care), where the percent of male offspring was 51.6% ($p=10^{-8}$), which contradicted our initial hypothesis.

We speculated that perhaps the Kessner Index was not a good indicator of maternal health as the Index only accounts for the number of prenatal visits during pregnancy, it was possible that mothers who received "adequate" care during pregnancy were the ones who needed increased monitoring due to a poorer state of health.

Regardless of the reason behind our findings, it was apparent that environmental factors can impact the reproductive success in human populations in a gender specific manner. The hypothesis of this research project was the presence of an impact of maternal and neonatal characteristics on male to female sex ratio in humans at birth.

STUDENT ROLE: The student was the primary author of this paper, took charge of the IRB approval process, obtained data from MDPH, and communicated with the statisticians for data analysis.

METHODS:

The project was determined as "Not a Humans Subject Research" by Harvard IRB due to the lack of identifying factors of the individuals of population studied. We obtained data from the Massachusetts Department of Public Health and analyzed birth records from 1987 to 2015 (with estimated birth around 80,000 per year). We had two sets of data from MDPH including resident births (births to residents of the state of Massachusetts, regardless of the location of birth) and occurrence births (births that occurred in the state of Massachusetts, regardless of the residency of the mother).

The sex ratio at birth in those years were analyzed in terms of categories as follows: Apgar scores at 1 minute, Apgar scores at 5 minutes, birthweight (very low (<1500g), low (1500-2499g), normal (2500-4000g), overweight (>4000g)), marital status of mother, chronic diabetes, chronic hypertension, gestational diabetes, and gestational hypertension.

We worked with Dr. David Steinsaltz and Dr. Maria Christodoulou at Oxford University as our expert statistical consult to analyze our data.

Diabetes, hypertension, and marital status were analyzed using chi-squared tests for 1 degree of freedom to study the association between sex of offspring and membership to category (e.g. suffering from diabetes or not). As birthweights and Apgar scores are ordered categories (e.g. "very low birthweight" versus "overweight") they were analyzed using Cochran-Armitage tests to explore any association between sex of offspring and category membership. Statistical analysis was performed using base R (R Core Team, 2017) and the "coin" package (Hothorn et al., 2008) in through RStudio (R Studio Team, 2016).

RESULTS:

Birthweights:

After combining the study years for births occurring in Massachusetts, a Cochran Armitage test for association between sex and birthweight-category resulted in a significant result ($Z=107.36$, $p<2.2 \times 10^{-16}$). Residuals indicate that males are overrepresented in the "Overweight" category, and females are overrepresented in the "Low" and "Normal" categories (Figure 1). This pattern and significance level persist when each year is studied independently. Births to Massachusetts' residents between 1987 and 2015 present a similar pattern for association between sex and birthweight category ($Z=105.99$, $p<2.2 \times 10^{-16}$), which persists in the year-by-year breakdown.

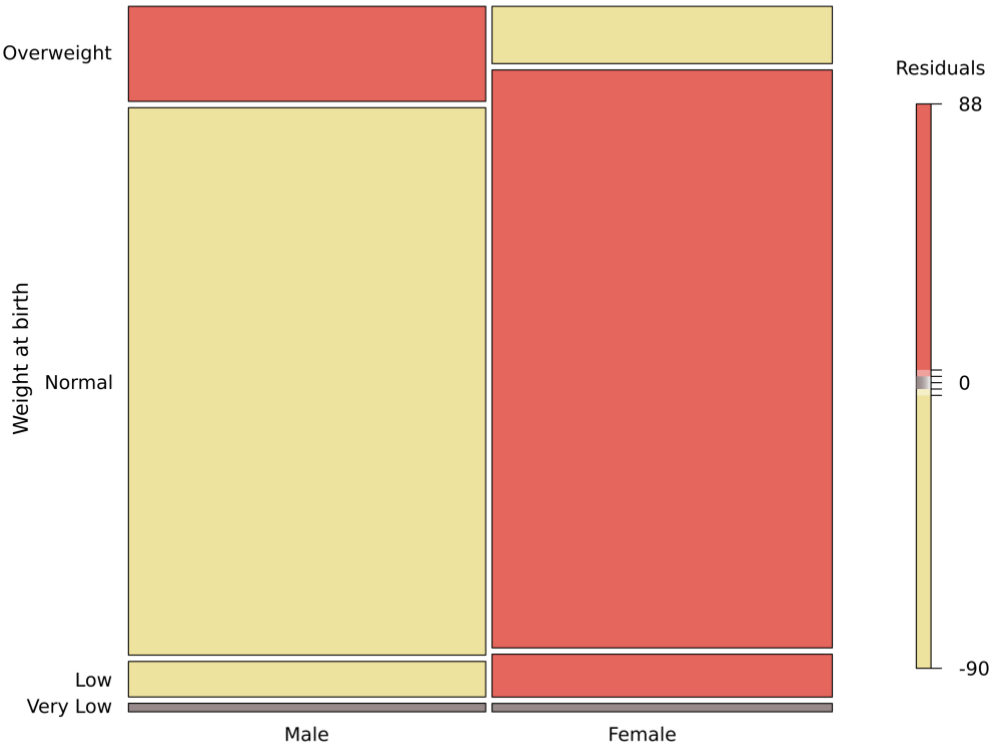

Figure 1: Association of sex and weight at birth categories for births that occurred in Massachusetts between 1987 and 2015. Residual colors indicate weight-sex combinations that are as expected (in grey), overrepresented (in red), and underrepresented (in yellow). Males are overrepresented in the "Overweight" category and underrepresented in all other categories except "Very low". Contrasting this, females are underrepresented in the "Overweight" category and overrepresented in all other categories except "Very low".

Diabetes – All Types

A chi-squared test for association between sex and diagnosis of any type of maternal diabetes for births occurring in Massachusetts between 1987 and 2015 indicated a significant difference ($\chi2$=4.0205, df=1, p=0.04495). Residuals indicate that boys are slightly underrepresented for mothers that do not suffer by any type of diabetes, and girls are slightly underrepresented for mothers that do. Analysis in a year by year basis resulted in non-significant associations for all years except 1988 ($\chi2$=3.9687, df=1, p=0.04635), 2005 ($\chi2$=8.9094, df=1, p=0.002837), and 2013 ($\chi2$=10.924, df=1, p=0.0009491). Of interest was the observation that even though the residuals for 1988 and 2013 suggest the same pattern as the overall analysis (with girls underrepresented for mothers that suffer from diabetes), in 2005 the pattern is inverted, with girls overrepresented and boys underrepresented for diabetes. Births to Massachusetts' residents between 1987 and 2015 did not present a significant association between sex and maternal diabetes.

Diabetes – Gestational

A chi-squared test for association between sex and gestational diabetes for births occurring in Massachusetts between 1996 and 2015 indicated a significant difference ($\chi2$=6.3843, df=1, p=0.01151). Residuals indicate that fewer girls and more boys than expected were born to mothers that suffered from gestational diabetes. In a year by year breakdown significant differences were only found in three years: 1997 ($\chi2$=5.0209, df=1, p=0.02504), 2001 ($\chi2$=8.9895, df=1, p=0.002715), and 2004 ($\chi2$=3.8441, df=1, p=0.04992). In every case, girls were underrepresented and boys overrepresented in the gestational diabetes category. Births to Massachusetts residents followed the same pattern. Pooled births from 1996 to 2015 showed significant differences ($\chi2$=7.5147, df=1, p=0.00612), as did the data from 1997 ($\chi2$=6.5374, df=1, p=0.01056), 2001 ($\chi2$=7.8381, df=1, p=0.005116), and 2004 ($\chi2$=4.0063, df=1, p=0.04533).

Hypertension – All Types

No significant differences were detected between sex and hypertension for births occurring in Massachusetts ($\chi2$=0.9191, df=1, p=0.3376) and births to Massachusetts residents between 1987 and 2015 ($\chi2$=0.28131, df=1, p=0.5958).

Hypertension – Gestational

Significant association was detected between sex and gestational hypertension for births occurring in Massachusetts ($\chi2$=7.8336, df=1, p=0.005128). Residuals indicate that fewer girls and more boys are born to mothers suffering from gestational hypertension than expected. Pattern similar for births to Massachusetts residents between 1989 and 2015 ($\chi2$=6.3819, df=1, p=0.01153).

Apgar: 1 minute

Apgar scores 1 minute after birth were analyzed for association with sex for all births occurring in Massachusetts using a Cochran Armitage test, with significant results

(Z=-39.097, p<2.2 X 10^(-16)). Residuals indicate that males are underrepresented for score category 9 and overrepresented for scores 0-7, and females are overrepresented for score category 9 and underrepresented for scores 0-7 (Figure 2). Pattern was consistent for births to all Massachusetts residents during the same period (Z=-35.97, p<2.2 X 10^(-16)).

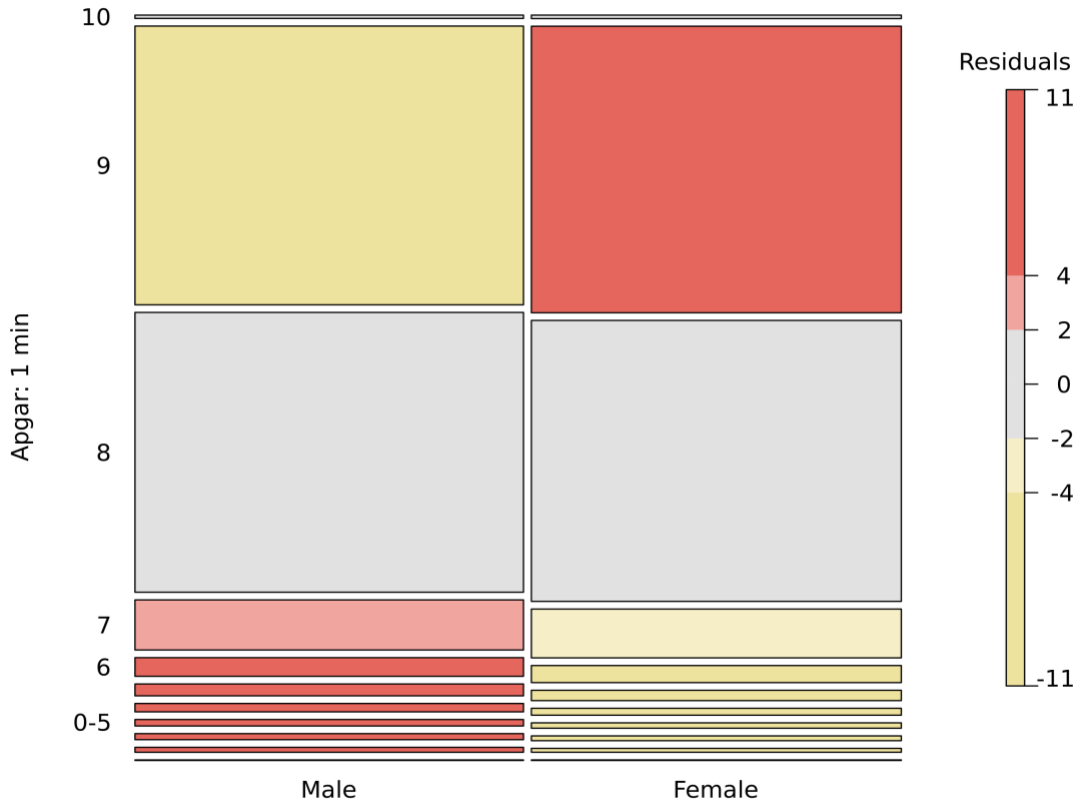

Figure 2: Association of sex and Apgar score 1 minute after birth for births that occurred in Massachusetts between 1987 and 2015. Residual colors indicate score sex combinations that are as expected (in grey), overrepresented (in red), and underrepresented (in yellow). Males are overrepresented in scores of 7 and below and underrepresented for score 9. Females are underrepresented in scores of 7 and below and overrepresented for score 9.

Apgar: 5 minutes

Apgar scores 5 minute after birth were analysed for association with sex for all births occurring in Massachusetts using a Cochran Armitage test, with significant results

(Z=-26.404, p<2.2 X 10^(-16)). Male and female individuals have overall higher scores in Apgar 5 min than they did in Apgar 1, with category 9 having the highest percentage of individuals. Residuals indicate that males are underrepresented for score categories 9 and 10 and overrepresented for scores 0-8. Females are overrepresented for score categories 9 and 10 and underrepresented for scores 0-8 (Figure 3). Pattern consistent for births to all Massachusetts residents during the same period (Z=-26.508, p<2.2 X 10^(-16)).

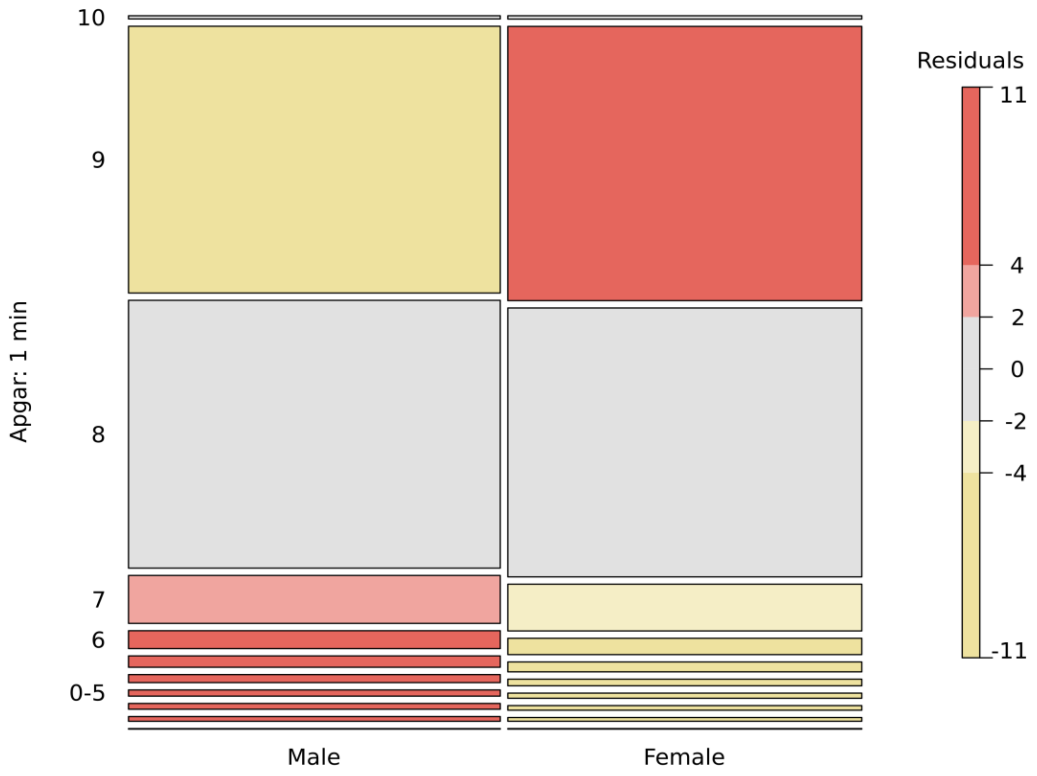

Figure 3 Association of sex and Apgar score 5 minutes after birth for births that occurred in Massachusetts between 1987 and 2015. Residual colors indicate score/sex combinations that are as expected (in grey), overrepresented (in red), and underrepresented (in yellow). Males are

overrepresented in scores of 8 and below and underrepresented for scores 9 and 10. Females are underrepresented in scores of 8 and below and overrepresented for scores 9 and 10.

Marital status:

Association of marital status with sex for all births occurring in Massachusetts between 1987 and 2015 was studied using a chi-squared test. No significant differences were found between married and not married mothers ($\chi 2$=0.004591, df=1, p=0.946). No association was found for marital status and sex for births to Massachusetts resident for the same period ($\chi 2$=0.12735, df=1, p=0.7212).

DISCUSSION:

Some of our findings were consistent with published data. We found a significantly higher number of male offspring at birth who were overweight (>4000g) compared to female offspring (p <.001). It is known that male offspring weigh more than their female counterparts worldwide (de Zegher et al. 1999). Women pregnant with male embryos had 10% greater daily energy consumption compared to women who were pregnant with female embryos (Rulla 2003), and higher weight gain during pregnancy was shown to correlate with higher sex ratio at birth (Navara 2014).

Interestingly, we also found a significantly higher sex ratio at birth in mothers with gestational diabetes (p = 0.012) and slightly significantly elevated sex ratio at birth in mothers with all types of diabetes (gestational and chronic). Sheiner et al (2004) had found a higher sex ratio at birth correlating with GDM, fetal macrosomia and shoulder dystocia. The correlation between the diagnosis of GDM and higher sex ratio at birth and the relationship between higher gestational weight gain and higher sex ratio posits the question of higher energy required by male embryos, leading to more gestational weight gain and risk of GDM in mothers.

Along similar lines, although we did not find a significant difference in sex ratio for mothers with "all" types of hypertension (chronic and gestational), there was a significantly higher sex ratio at birth correlated in mothers with gestational hypertension (P=0.0051). Our findings are consistent with Di Renzo et al.'s (2007) speculation that the male sex is a risk factor for adverse pregnancy outcomes.

We found a higher sex ratio at birth correlating with lower Apgar scores (p<0.001) at 1 and 5 minutes. This was consistent with the thought that male fetuses were likely to be at a higher risk for complications during the perinatal period and our other findings in this study. Bekedam et al. (2002) also noted lower Apgar scores for males compared to females and increased risk of perinatal death in males.

Marital status of the mother has been shown to impact sex ratio at birth (Chacon-Puignau, and Jaffe, 1996; Norberg 2004) with a higher ratio for cohabitating and married couples. However, in our study, we did not find a significant difference in the sex ratio at birth for

married and unmarried mothers during their pregnancy. Fellman and Eriksson (2010) also found no correlation between marital status and sex ratio at birth in twins.

From our findings, it was evident that sex ratio at birth in human populations is not straightforward and it does not neatly follow the Trivers-Willard hypothesis. Although we found significant results in the differences in sex ratio at birth for certain maternal and neonatal characteristics, it is apparent that we need to further understand the complexities of the effects of these qualities on the sex ratio at birth in order to understand the enigma of sex ratios at birth at the level of evolutionary biology. For future studies, we may need to explore the effects of multigenerational epigenetic inheritance, or the impact of paternal characteristics on sex ratio at birth.

Finally, as Darwin noted in regards to sex ratios, "but I now see that the whole problem is so intricate that it is safer to leave its solution to the future," we must continue to work to understand this "intricate" challenge (1871).

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