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Natural variation in the human sex ratio

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Analysis of the effect of multiple birth, birth order, age of parents and the sexes of preceding siblings on the secondary sex ratio was performed for 815 891 children, born in Denmark, 1980–1993. The proportion of males was analysed as a function of multiple birth, birth order, age of parents and the sexes of preceding siblings, using contingency tables, χ^2 tests and logistic regression analysis. The secondary sex ratio decreased with increased number of children per plural birth and with paternal age, whereas no independent effect was observed for maternal age, birth order, the sex of the preceding child, or the combination of sexes of previously born children in the family.

Key words: birth order/parental age/sex composition/sex ratio/twins

Introduction

The variation in the sex ratio among newborn infants (often expressed as the proportion of males or as the number of males per 100 females) has been of interest to investigators for years (reviewed in James, 1987), and has found increased attention with the independent observations of decline in the sex ratio in several populations during recent decades (Dickinson and Parker, 1996; Møller, 1996, 1998; Allan *et al.*, 1997; Parazzini *et al.*, 1998). Explanations for the decline in sex ratio has led to speculations that stresses from environmental toxic agents of the male reproductive system could result in low sex ratios, and even natural stress factors have been identified (e.g. earthquakes; Fukuda *et al.*, 1998). However, some doubt on the impact of pollution on the decline in sex ratios has been expressed, as urban and rural areas in European countries do not seem to have the expected differences in sex ratios (James, 1998).

The largest natural variation in the human sex ratio is found between ethnic groups, where Asian populations have the highest sex ratio and black populations the lowest (James, 1984, 1985a; Ruder, 1985). The intra-population variation in the sex ratio is generally smaller in magnitude (Ullizzi and Zonta, 1995) and has been associated with various natural factors such as maternal parity ('Poisson association'), paternal age, maternal age, the sexes of previously born children in the family (James, 1975) and season (e.g. Lerchl, 1998). Most large-scale studies on parity and parental ages suggest an effect on the sex ratio of birth order and paternal age, and in some studies, also of maternal age (Table I). One possible biological explanation for the decrease in sex ratio with maternal age and birth order is an increase in female gonadotrophin concentration with age (James, 1980a,b, 1985b). The decline in sex ratio with paternal age is suggested to be due to decreasing coital rates with age (James, 1980b).

An association with the sexes of previously born children in the family could either be due to in-utero interaction with the sex of the previous children affecting the sex of the current child ('Markov association') or to a predisposition of individuals or couples to have predominantly children of a particular sex ('Lexis association'). One case of Markov association has been suggested (Edwards, 1961) in which Markovian dependency is postulated to be due to interactions between the sex of the fetus and that of its predecessor, with the sex of the predecessor child influencing the probability of survival of the current child. We will use Edward's concept of Markovian dependency in this article. Different studies addressing the hypothesis of Markov association find different results. Some authors (Edwards, 1966) found a positive association between adjacent sibs in sibships, whereas others (Greenberg and White, 1967; Maconochie and Roman, 1997) did not. The Lexis association is difficult to distinguish from Markov association because both phenomena result in a higher than expected number of boys or girls in some sibships. Indeed, many conclusions on Lexis association could have been explained as well by the hypothesis of Markov association (James, 1975).

Children from multiple births have been shown to have a lower sex ratio than singletons (Pollard, 1969). The proportion of multiple births has increased in Denmark in the period, 1980–1994 (Westergaard *et al.*, 1997) and we were therefore curious to examine the sex ratio among Danish multiple born children.

In the present study, using data on more than 800 000 births in Denmark, 1980–1993, we address the hypothesis that sex ratio in the Danish population varies with multiple birth, birth order, ages of parents and with the sexes of preceding siblings.

Materials and methods

All live-born children (815 891) in the period 1980–1993 were identified in the Danish Fertility Database (Knudsen, 1998). For each child we obtained information on the sex of the child, the number of children per multiple birth, maternal parity, maternal age, paternal age and the sexes of previous children of the same mother.

To examine the sex ratio of multiple born infants, 795 027 singletons

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Table I. Overview of articles examining the effect of maternal age, birth order and paternal age

Study size in millions	Effects recognized			Reference	Study population	Type of analysis
	Maternal age	Birth order	Paternal age			
0.5				Arnold and Rutstein (1997)	12 sub-developed countries 1992–1997	Multivariate
0.6			NA	Maconochie and Roman (1997)	Scotland, 1975–1988	Univariate
0.8			–	Present study	Denmark, 1980–1993	Multivariate
1.5		–	–	Garfinkel and Selvin (1976)	New York Whites, USA	Multivariate
1.7	–		–	Ruder (1985)	USA, 1975	Multivariate
6	–	–	–	James and Rostron (1985)	England and Wales, 1968–1977	Multivariate
7.3	–	NA	–	Pollard (1969)	Australia, 1914–1963	Multivariate
14.6	+	–		Takahashi (1954)	Japan, 1937–1943	Univariate

NA = not analysed, – = significant decrease, + = significant increase.

and 18 991 multiple born children representing 9406 pregnancies were compared. For 1873 children, there was no information on the mother or on number of children per multiple birth. Information on zygocity of the multiple born children was not available. Therefore the comparison with singletons was done on an expected sex ratio among the multiple born similar to singletons, while keeping in mind that we were making an underestimation of the expected sex ratio for twins, triplets and quadruplets.

For the 795 027 singletons, the effects of maternal and paternal ages and birth order were analysed by logistic regression. The proportion of males born was calculated as a function of the sexes of preceding siblings with the same mother for 204 815 second, 40 433 third and 5279 fourth born children. Only firstborn children and their siblings within the period 1980–1993 were used in the analysis on the sexes of preceding siblings, due to missing information on the children born before 1980. For the rest of the analysis inclusion of children with siblings born before 1980 were included, as information on the previous siblings did not have any influence on the analysis. The analyses of the proportion of males as a function of the sex of previous siblings were done by contingency tables, χ^2 tests and by logistic regression.

From all logistic regression analyses, odds ratios and 95% confidence intervals were calculated; a statistical test (two-sided) for trend over categories was performed by assigning values 1, 2, 3, etc. to successive categories and including the resulting variable in the analysis.

Results

The whole population of registered live-born children in the period 1980–1993 was 815 891 with a male proportion of 51.3% corresponding to 105 males per 100 females.

Multiple born children

Table II presents the comparison between singletons and children from different categories of multiple births. Overall, the sex ratio decreased with increasing number of children per plural birth, and the sex ratios for twins and triplets were significantly lower than that of singletons ($P < 0.05$). Same-sexed twins had a sex ratio close to that of singletons (51.1 versus 51.3). Twins with different sex had a lower sex ratio than singletons (50, $P = 0.04$; Table II) and the overall sex ratio for twins was 50.6. If only one of the twins was alive at the time of birth, the sex ratio was 47.9. Overall, triplets had a significantly lower ($P < 0.05$) sex ratio than singletons (47.0 versus 51.3). This was due to a lower sex ratio for all groups

Table II. Sex ratio of singletons compared to children in multiple births

Type of birth	Number of children	Sex ratio	P-value[a]
Multiple births	18 991	50.5	0.02
Twins	18 450	50.6	0.05
Both alive	18 216	50.6	NS
Same sex	12 516	51.1	NS
Different sex	5700	50.0	0.04
One dead	234	47.9	NS
Triplets	513	47.0	0.05
All alive	477	47.4	NS
Same sex	168	42.8	0.03
Different sex	309	49.8	NS
One or two dead	36	41.7	NS
Quadruplets	28	42.9	NS
Singletons	795 027	51.3	–

[a]Compared with singletons.
NS = not significant.

of triplets. Triplets with different sex had the highest sex ratio within triplets (49.8), same-sexed triplets the second (42.8) and triplets with one or two dead in the birth the lowest (41.7). The seven sets of quadruplets had an apparently lower sex ratio than singletons (42.9 versus 51.3), but this was not significant.

Parental ages, birth order and sexes of preceding siblings

There was no significant effect of maternal birth order or maternal age on the sex ratio (Table III). The sex ratio decreased with the paternal age from 51.6 in fathers $<$25 years to 51.0 in fathers aged $\geqslant$40 years. The effect of paternal age remained significant when adjusted for maternal age and maternal birth order.

The results from the logistic regression analysis on the sex ratio as a function of the sexes of preceding siblings are shown in Tables IV and V. Logistic regression analysis showed no significant effect on the proportion of males as a function of the sex of the immediately preceding sibling when adjusted for paternal age (Table IV). The highest adjusted sex ratio was 51.7 for the third birth following a girl and the lowest was 50.9 for the fourth births following a boy. No statistically significant association between sex of a child and the sex combination of preceding children in the family was found (Table V) as the sex ratio following three previously born boys was apparently lower than following three girls (52.0

Table III. Crude and adjusted sex ratios for having a boy (i.e. male proportion) by parental ages and birth order

Variable	Number of children	Sex ratio (univariate analysis)	Odds ratio (95% confidence interval) Univariate analysis	Adjusted sex ratio[a] (multivariate analysis)	Adjusted odds ratio[a] (95% confidence interval) Multivariate analysis
Father's age (years)					
13–24	111 522	51.6	1.01 (1.00–1.03)	51.7	1.02 (1.00–1.03)
25–29	280 396	51.3	1.00[b]	51.3	1.00[b]
30–34	246 599	51.4	1.01 (1.00–1.02)	51.4	1.00 (0.99–1.02)
35–39	115 312	51.0	0.99 (0.98–1.01)	51.0	0.99 (0.97–1.01)
⩾40	52 615	51.0	0.99 (0.97–1.01)	51.0	0.99 (0.97–1.01)
NA	9447				
Trend[c]		$P = 0.02$		$P = 0.02$	
Mother's age (years)					
13–19	14 318	51.5	1.01 (0.98–1.03)	51.3	1.00 (0.97–1.02)
20–24	205 284	51.4	1.00 (0.99–1.01)	51.2	0.99 (0.98–1.01)
25–29	328 158	51.4	1.00[b]	51.4	1.00[b]
30–34	187 338	51.3	1.00 (0.99–1.01)	51.4	1.00 (0.99–1.02)
⩾35	67 215	51.2	0.99 (0.98–1.01)	51.5	1.00 (0.98–1.02)
NA	77				
Trend[c]		$P = 0.35$		$P = 0.36$	
Maternal birth order					
1	371 595	51.4	1.00[b]	51.4	1.00[b]
2	301 841	51.4	1.00 (0.99–1.01)	51.5	1.01 (0.99–1.02)
3	106 961	51.1	0.99 (0.98–1.00)	51.2	0.99 (0.98–1.01)
4	26 004	51.0	0.99 (0.97–1.02)	51.3	1.00 (0.97–1.03)
5	6325	51.2	1.01 (0.95–1.06)	51.7	1.01 (0.96–1.07)
6	1928	52.0	0.99 (0.91–1.09)	51.4	1.00 (0.91–1.10)
⩾7	1159	50.5	0.98 (0.87–1.11)	51.1	0.99 (0.88–1.12)
NA	78				
Trend[c]		$P = 0.29$		$P = 0.72$	

[a]Adjusted for one another.
[b]Reference value.
[c]Test for linear trend over categories.
NA = not available.

versus 52.8). Following two boys the sex ratio was 50.6, and 51.4 following two girls. The sex ratio for families with three, two, one or no previous boys among three previous children resulted respectively in sex ratios of 52.0, 50.7, 50.1 and 52.8.

Discussion

In this study, based on the entire Danish population in a 14 year period and covering more than 800 000 births, the sex ratio decreased with increasing number of children per plural birth and with increasing paternal age. Maternal age, maternal parity and sexes of previous children in the family had no significant effect on the sex ratio.

Multiple born children

The overall lower sex ratio for multiple born children compared with singletons is in accordance with previous findings (Pollard, 1969) and illustrates the importance of considering explicitly multiple births in sex ratio analysis, i.e. by exclusion of multiple born children from the analysis or by identification of multiple births as a separate group. Zygocity information was not available and the expected sex ratios for multiple born children in relation to zygocity could not be directly calculated. Therefore the direct comparison with the sex ratio of singletons probably underestimates the difference between multiple born children and singletons. For example, same sexed dizygous twins have an expected probability of 0.237 (0.487×0.487) for a girl–girl combination and 0.263 (0.513×0.513) for a boy–boy combination, with a resulting sex ratio of 52.6, whereas monozygotic twins have an expected sex ratio of 51.3. Thus, for twins the sex ratio is expected to be between 51.3 and 52.6, suggesting that the lower sex ratio observed in the present study is even more significant. The same calculations could be performed for same sexed dizygous triplets and quadruplets resulting in an expected sex ratio value in the range 51.3–53.9 for triplets and 51.3–55.2 for quadruplets, further suggesting a higher significance of the present results. The observed decrease in sex ratio with increase in number of children per plural birth is most likely due to an increased prenatal mortality of the male fetus in multiple births (Zahálková, 1978; Rydström, 1990).

Parental ages and birth order

Contradictory results are found in the literature for the effects of paternal age, maternal age and birth order, ranging from no effect at all to significant effects of one, two or all three factors. It has been suggested (James and Rostron, 1985) that the paternal age effect is stronger than the maternal effect, and illustrated that the observation of no effect of maternal age in a study could be due to a low sample size. If this suggestion is right, this could explain why no effect of maternal age was found in the present study, whereas the stronger effect of paternal age was correctly identified. Indeed, all studies of relatively low numbers of births ($<2\times10^6$) have failed to identify the effect of maternal age (Table I), whereas larger

Table IV. Sex ratio in and adjusted odds ratios for having a boy by sex of the immediately preceding sibling

Birth order and sex of preceding sibling	No. of children	Adjusted sex ratio[a]	Adjusted odds ratio[a] (95% CI)	P-value
2nd births				
Boy	105 597	51.6	1.00[b]	
Girl	99 218	51.3	0.99 (0.98–1.01)	0.42
3rd births				
Boy	21 089	51.1	1.00[b]	
Girl	19 344	51.7	1.02 (0.98–1.06)	0.24
4th births				
Boy	2696	50.9	1.00[b]	
Girl	2583	51.2	1.01 (0.91–1.13)	0.82
All birth orders				
Boy	129 382	51.5	1.00[b]	
Girl	111 148	51.4	1.00 (0.98–1.01)	0.82

[a]Adjusted for paternal age.
[b]Reference value.

Table V. Sex ratio in third to fourth order births and odds ratio for having a boy, by sex of the preceding siblings

Birth order and sex of preceding sibling	No. of children	Adjusted sex ratio[a]	Adjusted odds ratio[a] (95% CI)	P-value
Boy-boy	11 876	50.6	1.00[b]	
Boy-girl	9337	51.8	1.05 (1.00–1.11)	0.07
Girl-boy	9258	51.6	1.04 (0.99–1.10)	0.15
Girl-girl	10 007	51.4	1.03 (0.98–1.09)	0.24
Boy-boy-boy	842	52.0	1.00[b]	
Boy-boy-girl	619	51.2	0.97 (0.79–1.19)	0.76
Boy-girl-boy	622	51.9	1.00 (0.81–1.23)	0.97
Boy-girl-girl	598	49.6	0.91 (0.74–1.12)	0.37
Girl-boy-boy	628	49.0	0.89 (0.72–1.09)	0.26
Girl-boy-girl	604	50.6	0.95 (0.77–1.17)	0.61
Girl-girl-boy	604	50.0	0.92 (0.75–1.14)	0.46
Girl-girl-girl	762	52.8	1.03 (0.85–1.26)	0.75

[a]Adjusted for paternal age.
[b]Reference value.

studies seem to identify the effect. The results from studies examining all three factors (Table I) suggest that the number of factors identified increases with study size, such that the paternal effect is identified by most studies, birth order is the next most frequently identified and maternal age is identified only in very large studies. However, it should be noted that the results from the three studies that found an effect of maternal age (Takahashi, 1954; Pollard, 1969; James and Rostron, 1985) differed. Sex ratio has variously been reported to decrease (Pollard, 1969; James and Rostron, 1985) or increase (Takahashi, 1954) with maternal age. A possible explanation for this difference in results could be false registration of children by elderly women in Japan (James, 1972) or perhaps the lack of adjustment for birth order and paternal age in Takahashi's analysis. Recently, the sex ratio among children of grand-grand-multiparous women was examined in relation to maternal age (Juntunen *et al.*, 1997). A significantly lower sex ratio with age was found among grand-grand-multiparous women in Finland, supporting previous findings (James and Rostron, 1985), whereas no such association was found in a study (Almagor *et al.*, 1998) on Jewish Orthodox and Muslim women in Israel. This supports the idea that cultural, ethnic and environmental variables may be of importance in relation to the effect of maternal age (James, 1972; Almagor *et al.*, 1998).

Suggestions have been made of underlying biological effects leading to a decrease in sex ratio with increasing paternal age, including decline in male androgen concentrations with age (James, 1987). This suggestion seems to be supported by the observation that the *HLA* gene can affect androgen levels and thus the sex ratio (review in James, 1992, 1996). Such a hormone-induced effect could imply a skewed ratio of Y- and X-bearing spermatozoa, a reduced probability of fertilization by a Y-bearing spermatozoon or differential mortality of XX and XY fetuses with increasing paternal age. Analysis of the primary sex ratio measured as the ratio of X- and Y-bearing spermatozoa in semen samples showed no significant effect of age (Martin and Rademaker, 1992; Martin *et al.*, 1995). However, no alteration was found in the normal X:Y sperm ratio (Bowman *et al.*, 1998) but a significantly higher number of in-vitro fertilized male (n = 20) than female (n = 8) cleavage-stage embryos, when doing preimplantation analysis, indicating that the binding of Y-bearing or X-bearing spermatozoa to the oocyte has an effect on the primary sex ratio. Another line of speculation is that the decrease in the sex ratio with paternal age is due to less frequent sexual intercourse with increase in paternal age (James, 1975; Hilsenrath *et al.*, 1997), thus decreasing the probability for male offspring, since the probability of males is suggested to be lower near ovulation (James, 1980b). However, a recent study found no relationship between timing of insemination and day of ovulation on the secondary sex ratio (Gray *et al.*, 1998). This discrepancy in results is difficult to explain, but factors such as effects on precise reporting of intercourse, measurement errors and small scale studies with little power for detecting differences have been suggested (Gray *et al.*, 1998). One line of speculation is that precise reporting of intercourse could be influenced by the wish of couples in some cultural groups to indicate higher coital rates than in reality.

Sexes of preceding siblings

The suggestion that some individuals or some couples have a natural tendency towards having children of one or the other sex (James, 1975) is not supported by the present study. Indeed, no association was seen with the sex of the previous born child ('Markovian dependency') and no significant predisposition was found of couples or individuals to have children of a particular sex ('Lexis association'). It has been suggested (James, 1975) that if the sex ratio after one firstborn boy is lower than after two firstborn boys, this indicates Lexis association. In the present study this was not the case as the sex ratio was 1% lower after two firstborn boys than after one firstborn boy. Using the same argument for girls, but with the opposite expectation for the trend of the sex ratio, our analysis also failed to indicate Lexis association as the sex ratios following one firstborn girl and two firstborn girls were the same.

Taking into account the large number of births analysed in the present study and the lack of association found with previously born children and the sex ratio, we conclude that no strong relationship is present between sexes of adjacent sibs in Danish sibships in the period analysed. The lack of statistically significant correlation does not mean that some couples cannot have a higher probability of having children of a particular sex, just that such couples are a small fraction of the Danish population. One may see an indication of Lexis association in the observation of excesses of large sibships of only one sex when regarding all children born after the same-sex combination. However, the conditional probability of a particular sex of the immediately next born child, following a given sex combination of previous born children, would not be influenced by sex preference. For example, in Denmark, a preference for having children of both sexes in families has been found with increasing fertility rates in families with only children of one sex (Jacobsen *et al.*, 1999). This effect increased fertility rates following same-sexed children, for example for the fourthborn children. However, the higher number of fourthborn children could not influence conditional probability for a particular sex among these children. The analysis of incomplete families of decreasing family size, when compared to previous studies based on larger and completed families, may be contributing to the discrepancy between this study and some previous studies (Edwards, 1966; James, 1975).

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