Sex Distribution of Offspring-Parents Obesity: Angel's Hypothesis Revisited

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Abstract This study, which is based on two cross sectional surveys' data, aims to establish any effect of parental obesity sex distribution of offspring and to replicate the results that led to the hypothesis that obesity may be associated with sex-linked recessive lethal gene. A representative sample of 4,064 couples living in Renfrew/Paisley, Scotland was surveyed 1972–1976. A total of 2,338 offspring from 1,477 of the couples screened in 1972–1976, living in Paisley, were surveyed in 1996. In this study, males represented 47.7% among the total offspring of the couples screened in 1972–1976. In the first survey there was a higher male proportion of offspring (53%, $p < 0.05$) from parents who were both obese, yet this was not significant after adjustment for age of parents. Also, there were no other significant differences in sex distribution of offspring according to body mass index, age, or social class of parents. The conditions of the original 1949 study of Angel (1949) (which proposed a sex-linked lethal recessive gene) were simulated by selecting couples with at least one obese daughter. In this subset, ($n = 409$), obesity in fathers and mothers was associated with 26% of offspring being male compared with 19% of offspring from a non-obese father and obese mother. Finally we conclude that families with an obese father have a higher proportion of male offspring. These results do not support the long-established hypotheses of a sex-linked recessive lethal gene in the etiology of obesity.

Perhaps the most striking suggestion of genetic determination in relation to nutrition of humans was made by Angel in 1949 (Angel 1949). Angel observed that in families with at least one obese daughter (whom he saw as patients), there were fewer males among the offspring of two "fat parents" than from other parental pairings. He also noted that this group had larger families (Table 1). This observation led Angel to suggest the explanation of a sex-linked recessive lethal

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Table 1. Percentage of Males and Family Size in Families with Different Parents Mating Group in Families Identified as Having at Least One Obese Daughter in the Original 1949 Angel Study and in the MIDSPAM Family Study

	Sex Ratio of Offspring				
Type of Mating	*No. Sons*	*No. Daughters*	*% Males*	*95% CI*	*Family Size*
Angel Study					
Average father & average mother	57	73	43.85%	35.1–52.5	4.33
Average father & obese mother	87	123	41.43%	34.6–48.2	5.00
Obese[a] father & average mother	32	38	45.71%	33.8–57.6	3.89
Obese father & obese mother	51	77	39.84%	31.2–48.5	4.92
MIDSPAM Family Study					
Families with at least one obese daughter					
Father <30 & mother <30	63	181	25.82%	20.2–31.4	3.29 (1.87)
Father <30 & mother ≥30	17	71	19.32%	10.9–27.7	3.95 (2.02)
Father ≥30 & mother <30	10	32	23.81%	10.6–37.0	3.74 (2.60)
Father ≥30 & mother ≥30	9	26	25.71%	10.9–40.5	3.54 (1.70)
Families with at least one non-obese daughter					
Father <30 & mother <30	282	872	24.44%	21.8–27.0	3.23 (1.36)
Father <30 & mother ≥30	38	147	20.54%	14.6–26.4	3.69 (1.60)
Father ≥30 & mother ≥30	28	90	23.73%	15.9–31.5	3.75 (2.14)
Father ≥30 & mother ≥30	8	14	36.36%	15.8–56.9	3.55 (1.47)

a. Angel used the word "fat" rather than "obese."

gene that might be contributing to obesity. Male offspring with this gene on the single X-chromosome would be more likely to undergo spontaneous abortion: if this gene contributed to obesity, more male birth loses would occur with obese parents. Angel's findings have never been replicated or challenged.

Angel's observation was based on the first 103 adult white female obese outpatients seen at the endocrine clinic of Jefferson Hospital between May 1944 and February 1948, and information about their parents was collected retrospectively. In the present study, we replicated the same analysis done by Angel that lead to the hypothesis of a sex-linked lethal recessive gene in the etiology of obesity based on sex-ratios of offspring of parental groups categorized according to their body mass index (BMI). The data of this study are based on parents and offspring who participated in the MIDSPAN family study.

Method

Populations. In 1972–1976, 15,406 residents of Paisley and Renfrew, comprising 78% of the general population aged 45–64, completed a questionnaire and attended a cardiorespiratory examination. Of this group, 4,064 were married couples. In 1996, 5,016 offspring aged 30–59 yrs were identified from 2,365 couples with children: 3,202 offspring from 1,767 families lived locally and formed the eligible population to participate in a similar survey. Participating in the study were 1,477 families and their offspring, which included 1,040 males

and 1,298 females. Response rate for families was 84% and individuals 73%. Details of the study have been described previously (Upton et al. 2000).

Statistical Analysis. Statistical analysis used SPSS (version 15). First, paternal and maternal BMI were categorized using WHO criteria (World Health Organization 1998) (BMI < 25, 25–29.9, ≥ 30 kg/m^2), resulting in a categorization of families in nine mating groups, including four mating groups of particular interest (obese BMI ≥ 30, non-obese BMI ≤ 30 kg/m^2). To be able to compare the results of this study with Angel's study, the obese category (BMI $>$ 30) was used to be compared with the "fat" category as referred to by Angel.

The proportion of males for each mating group was calculated by dividing the number of males by the total number of offspring in each of the four mating groups. Further, for the sake of comparison with Angel's results, the mean family size was calculated for each group.

Analyses was initially conducted for the entire study population of Renfrew and Paisley 1972–1976, based on total offspring reported (i.e., not just those who participated in the Renfrew/Paisley offspring study because there was no restriction on the offspring obesity status).

To be able to test the hypothesis of Angel in a sample selected similar to Angel's original 1949 study, the analysis was then calculated for families with at least one obese adult daughter. Another selection criteria was to follow where families with at least one non-obese daughter were selected (which Angel could not do). This selection was done to test whether Angel's results were biased by the selection criteria used.

Results

The 4,064 married couples screened in 1972–1976 had 5,016 offspring; of these, 2,338 offspring from 1,477 couples participated in the follow-up survey in 1996. There were 211 families with at least one obese daughter from the follow-up sample, selected to mimic the characteristics of Angel's 1949 study.

Families with at Least One Obese Daughter. For families with at least one obese daughter (selected to mimic the conditions of Angel's original study), the percentage of male offspring was 24.2%. A lower male proportion (more daughters) was found in families with a non-obese father (BMI < 30) and an obese mother (BMI ≥ 30), which was 19.3%. The offspring in families with both parents obese and both parents non-obese had similar male proportions (Table 1).

The smallest family size was observed in families with two non-obese parents (3.29 ± 1.87) and the largest in families with an obese mother and non-obese father (3.95 ± 2.02). In general, family size was similar in the different mating groups ($p = 0.096$).

Families with at Least One Non-Obese Daughter. The lowest male proportion was found in families with an obese mother and a non-obese father, similar to

Table 2. Percentage of Males and Family Size (SD) in Families with Different Parents Mating Group (non-obese = BMI < 30, obese = obese ≥ 30), in the Entire Offspring of MIDSPAN 1972 Sample

	Sex Ratio of Offspring				
Type of Mating	*No. Sons*	*No. Daughters*	*% Males*	*95% CI*	*Family Size*
Father < 30 & mother < 30	1896	1929	49.57%	33.4–65.8	3.04 (1.65)
Father < 30 & mother ≥ 30	294	323	47.65%	43.6–51.7	3.46 (2.00)
Father ≥ 30 & mother < 30	195	214	47.68%	42.7–52.6	3.41 (2.00)
Father ≥ 30 & mother ≥ 30	79	70	53.02%	44.8–61.2	3.45 (1.69)

results in families with at least one obese daughter. On the other hand, a higher male percentage was found in offspring of parents who were both obese (Table 1).

Family size was lowest in families with non-obese parents, and this was statistically different from those families with non-obese father and obese mother ($p = 0.001$) and families with obese father and non-obese mother ($p = 0.002$) but not different from families with both parents obese ($p = 0.405$).

The male percentages in offspring of the four obese/non-obese mating groups (parental BMI ≥ 30 or < 30) were not different between families with at least one obese daughter, or families with at least one non-obese daughter, as well as in all families among the general population.

General Population. To test the hypothesis for a general population, all offspring identified for the 4,064 married couples living in Renfrew and Paisley were used in this analysis. Amongst the 5,016 offspring of the 4,064 married couples, there were 2,464 (49.1%) males. The lowest male proportions were in families with either an obese father or an obese mother, 47.7% and 47.7% respectively and a significantly higher proportion of males with both parents obese, at 53% ($p = 0.048$). However this difference disappeared with age-adjustment. In the nine possible mating groups defined by WHO BMI criteria (<25, 25–30, >30 kg/m^2) there were no significant differences in sex ratio of offspring.

Families with two non-obese parents had the smallest family size (3.0 ± 1.65) compared with other parental groups (Table 2). There were no significant differences in family size amongst families defined by WHO body mass index classes of parents (Table 3) although smaller family sizes were found in groups with normal weight mothers (BMI < 25 kg/m^2) before and after age adjustment.

Smallest family size was noted in families with both parents non-obese. Family sizes were not statistically different in the other mating groups either obese or non-obese according to WHO BMI groups (Table 2 and Table 3).

Discussion

There is current interest in genetic factors, which might have a role in obesity (Bouchard 2007). About 253 quantitative trait loci for obesity-related

Table 3. Percentage of Males and Family Size (SD) in Different Parent Mating Groups Using the WHO Criteria (BMI < 25, 25–29.9, ≥ 30 kg/m^2), in the Entire Offspring of MIDSPAN 1972 Sample

Matting Group	*No. Males*	*% Males*	*Family Size*
Mother < 25 and father < 25	505	50.9%	2.84 (1.87)
Mother < 25 and father 25–29.9	560	50.7%	2.67 (1.67)
Mother < 25 and father ≥ 30	92	52.2%	2.66 (2.2)
Mother 25–29.9 and father < 25	334	48.8%	2.64 (1.54)
Mother 25–29.9 and father 25–29.9	497	47.6%	2.91 (1.99)
Mother 25–29.9 and father ≥ 30	106	45.5%	3.16 (2.45)
Mother ≥ 30 and father < 25	106	47.9%	3.32 (2.58)
Mother ≥ 30 and father 25–29.9	188	40.2%	3.2 (2.11)
Mother ≥ 30 and father ≥ 30	78	53.0	3.25 (1.81)

phenotypes from 61 genome-wide scans (Perusse et al. 2005; Rankinen et al. 2006). Genetic theories of obesity are not new. This interest started a long time ago, when Angel, in 1949, suggested the presence of a sex-linked recessive lethal gene associated with obesity etiology based on observation of families with at least one obese daughter (Angel 1949). It is interesting to note that Angel's article was cited more than sixty times without really testing the proposed hypothesis.

In this study, we tested the hypothesis that a sex-linked recessive lethal gene promoted obesity in women in the whole population of the Renfrew and Paisley study. Taken as a whole, the study suggests that obese fathers are marginally more likely to have more male offspring than non-obese fathers, but only if the mother is also obese. However, this effect was explained by the greater age of obese parents. Restricting the analysis to families with at least one obese daughter, the lowest male proportion was found in families with an obese mother and a non-obese father. These results allow us to reject Angel's hypotheses of a sex-linked recessive lethal gene promoting obesity.

Angel looked at male-to-female ratios in adult offspring, but his study design was different from ours. His study was limited to the first 103 adult white female obese outpatients seen at the endocrine clinic of Jefferson Hospital between May 1944 and February 1948. The sample was drawn from a Pennsylvania and New Jersey urban environment, the average age being just under 40 years, and almost 60% of whom were overweight. His sample was not random.

Angel reported that families with an obese mother and non-obese father had larger family size (5.0) than families with an obese father and non-obese mother. In our study, obese mothers have larger families. At the same time families with non-obese parents have the smallest family size, in both the general population and families with at least one obese daughter. This observation was confounded by couples' age, and there were no differences in family size in the different mating groups.

Both Angel's and our study have the same limitation, in that parents' weights were measured some time after marriage or after the birth of children. The BMI profiles of parents may reflect shared environment in addition to assortative mating. It is not possible to assess any different impact of cognitive weight control in either parental or offspring generations. In keeping with national data there was more overweight and obesity at the time of the second Renfrew/Paisley survey.

The clinical hypothesis of Angel has not previously been tested, although Weijin and Olsen reported the relation between offspring sex ratio and maternal body mass index, age, parity, and low fecundity (Weijin and Olsen 1996). This study followed Danish women between 1984 and 1987. The participants delivered 5,137 boys and 4,905 girls (sex ratio 0.51). This study found no association between maternal body mass index and the sex ratio.

As well as obesity, body fat distribution has been associated with differing offspring sex ratios. Women with high WHR (which implies a large waist) tend to have more sons than daughters (Sing and Zambarano 1997). This may be explained by the hormonal profiles associated with android body fat distribution. More males are expected with high androgen and estrogen concentrations at the time of conception, whereas higher levels of gonadotropins would favor a preponderance of females (James 1996). Because of an excessive expression of aromatase in expanded adipose tissue, and lower sex hormone binding globulin in obesity, one might have expected a greater proportion of males in the offspring of obese mothers. The work of Manning on 102 women aged from 35–55 years showed that women's waist circumference was the strongest predictor of the proportion of sons (Manning et al. 1996). Our data also suggest a small contribution from obesity in fathers, which could presumably be mediated by selective effects on sperm motility or potency. There were not enough underweight parents (BMI < 18.5 kg/m^2) to examine effects on the sex distribution of offspring, or on fecundity. On the other hand, Tovee et al. argued back that WHR does not predict child gender (Tovee et al. 2001). In the Tovee study, they took WHR measures from 458 women who intended to become pregnant and then correlated this with the genders of their subsequent children. No significant correlation was established.

Maternal nutritional status has been associated with variation in male-to-female ratio. Animal studies suggest that offspring sex ratio varies in response to environmental conditions associated with nutritional stress (Clutton-Brock and Iason 1986). In red deer hinds in the Isle of Rhum, for example, the proportion of males born declined each year with increasing population density and with winter rainfall (Kruuk et al. 1999). Similar results were reported in the Fallow deer, where a lower sex ratio was found in deer having low energy diet (Enright et al. 2001). Similar examples exist in birds, where females bird in better condition produce more male offspring (Nager et al. 1999), and an excess of females are produced when mothers are in poor condition (Pike 2005) selective survival of females under conditions of maternal nutritional stress.

Other factors that might affect offspring sex include maternal age, birth order, socioeconomic status, and dominant female personality (Rostron and James 1977). A variety of cultural factors affect family size, with education and higher economic status generally associated with smaller family size. In recent years these factors have also tended to relate to lower BMIs, but that was less evident in the 1970s (Knight 1984).

We also examined family size. Obesity is associated with infertility in men and women (Bray 1997; Diamanti-Kandarakis and Bergliele 2001). Men who have no children in our study had a higher BMI than those who have children, while women's BMI was not different in the two groups. In the case of the former, this can in part be explained by the fact that obese infertile men have low level of serum steroid hormone binding globulin, total testosterone, and testosterone/estradiol ratio (Jarow et al. 1993).

In many cultures it is considered desirable to have sons, and couples who initially have daughters may have larger families, with the youngest sibling being a son (Osman and Yamashita 1987). It is not known whether the reverse also applies equally with couples seeking daughters. We examined the structures of families with two or more daughters and then a youngest son (compared with families with two or more sons and a youngest daughter) and found no differences in terms of family size, parental age, and BMI of parents.

Conclusion. The present study provides limited evidence to link obesity and fecundity, with obese parents more likely to have more male offspring unless one partner is non-obese, in which case there are fewer male offspring. The results do not support the hypothesis of a sex-linked recessive lethal gene coding for obesity in women.

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