

Hard science?

Wanna Have A Boy? Eat Cereals!

It's not unusual for the media to turn inflated claims of a weak paper into sensational headlines.

Jeremy Garwood recently came across such a case but, after closer scientific analysis, he finally burst the bubble.



In some parts of the world, the choice of baby sex is a rather messy affair, with unwanted female foetuses rejected by fair means, or foul. However, in England they have now found a rather more civilised way of influencing the gender of our offspring – breakfast cereal!!

I kid you not, dear readers! The popular English cereal breakfast has now been shown to be a determinant of sexual orientation! In a recent article in the *Proceedings of the Royal Society B* (vol. 275: 1661-8), Dr Fiona Mathews from the University of Exeter announces, “You are what your mother eats: evidence for maternal preconception influencing foetal sex in humans.” But how convincing is this latest claim? With all the ‘whodunit’ logic and style of a detective fiction to get to the bottom of Dr Mathews’ confident assertions, what emerges is a rather murky English tale combining forgettable food, a reserved attitude towards sex, and a wonderful arbitrary use of statistics to rehash old data.

Cereal mothers...

Although her paper notes that “little is known of natural mechanisms of sex allocation in humans,” Dr Mathews is confident: “Here, using data from 740 British women who were unaware of their foetus’s gender, we show that foetal sex is associated with maternal diet at conception. Fifty-six per cent of women in the highest third of pre-conceptional energy intake bore boys, compared with 45% in the lowest third.”

Primed by the associated upbeat tones of Exeter University’s Press Release, proclaiming this to be the very “first evidence that mother’s diet influences infant sex,” the world’s press has been trumpeting the result as an established confirmation of

what we knew all along: “What are little boys made of? Scientists pinpoint bananas” (from the UK’s Guardian newspaper), “Going bananas for boys” (The Guardian Weekly), “Diet before pregnancy can affect baby’s sex” (UK’s Telegraph), “Cereal Mothers: Babies’ Sex Linked to Moms’ Breakfast Calories” (Scientific American), “Start the day with cereal if you want a boy” (The Australian), “L’alimentation de la mère influencerait sur le sexe de l’enfant” (France’s Le Monde), “Muesli macht Männer: Was Mama isst, beeinflusst das Geschlecht des Babys” (Germany’s Süddeutsche Zeitung), not to mention all the associated radio and TV news reports worldwide. Breakfast cereal manufacturers are no doubt salivating at their dramatically improved commercial prospects in countries with a strong selective preference for boys, such as China and India (over two billion new potential cornflake consumers!). Whether Mathews has financial interests in Kellogg’s and co. is not clear but her message is: “If you’re looking for a boy, then eating breakfast cereal every day and within safe limits looks like a sensible option. It’s the converse of that if you’re hoping for a girl, but again, only within safe limits.” Furthermore, “Prior to pregnancy, breakfast cereal, but no other food item, was strongly associated with infant sex.” Indeed, she says, “Our findings are particularly interesting given the recent debates within the Human Fertilisation and Embryology Authority about whether to regulate ‘gender’ clinics that allow parents to select offspring sex, by manipulating sperm, for non-medical reasons. Here we have evidence of a ‘natural’ mechanism that means that women appear to be already controlling the sex of their offspring by their diet.”

... Serial mothers?

We are even assured that this finding is highly significant, since “over the last 40 years there has been a small but consistent decline, of about one per 1000 births annually, in the proportion of boys being born in industrialised countries.” Upon re-reading this sentence could be forgiven for wondering just how small is an *annual* decrease of one boy per 1000 births in 40 years, since

$1/1000 \times 40 = 4\%$! Undeterred, the BBC News site reprinted the claim online under “High-calorie diet linked to boys”.

What will happen to the future of English football? Already dismayed by the absence of our national team from this summer’s European Football Championship, I was horrified to learn there might be an ever-depleting pool of future male sportsmen to choose from. What can be done? Surveying the official birth statistics for the last 20 years soon reassured me – in England and Wales, contrary to Mathews’ claim, the sex ratio at birth is surprisingly stable. From 1988 to 2006, the sex ratio of boys to girls varied between 1.047 and 1.055, with a mean value of 1.051. In fact, a cursory glance at the literature shows that the measured human sex ratio at birth is consistently found to be 105 boys to 100 girls.

My curiosity about the whole question of baby sex had been aroused, so I skipped lunch and did something that most journalists rarely seem to do; I actually went to look in more detail at the original data used by Dr Mathews when staking her claim.

Mathews based her conclusions on the statistical analysis of nutritional data obtained from less than a thousand first-time pregnant women registered at “a district general hospital in the south of England”. The women were not asked about their dietary habits until their first clinical visit around 14 weeks into pregnancy.

“Full details are...

Subsequently, 740 women kept a food diary, noting their daily food intake during one week of ‘early pregnancy’ (around the 16th week). 721 of these women also filled out “a retrospective report of their usual diet in the year prior to conception (‘pre-conception’ data)”. Finally, around 28 weeks into their pregnancy, some 661 of the ladies “reported their usual diet during pregnancy”. It seems the two “retrospective reports” were obtained using “food frequency questionnaires”.

Obviously, Mathews’ conclusions about food intake and sex selection came from the “pre-conception” data but when looking in the ‘Materials and Methods’ for more in-

formation about exactly what kind of questions the mothers-to-be were asked in their food questionnaires or how they filled out their food diaries, I came across the standard phrase: “Full details of the study methods have been reported elsewhere (Mathews, F., 1999).”

In her 1999 paper, (“Influence of maternal nutrition on outcome of pregnancy: prospective cohort study.” (*Brit. Med. J.* 319, 339–343) Mathews presents nutrition data from 739 pregnant women at “St. Mary’s Hospital, Portsmouth (a coastal town in South England), between May 1994 and February 1996” but in this report she only looked at two points in time: ‘Early pregnancy’, when they first met the women and asked them to complete a seven-day “semi-quantitative” food diary, listing their diet for seven whole days, and ‘Late pregnancy’, at 28 weeks, when the women were asked to fill out a ‘food frequency questionnaire’ to give an idea of their “usual diet during pregnancy”. However, there was absolutely no mention of any ‘pre-conception’ data nor of the questions asked. Instead, we are once again told: “Full details of the survey

methods are reported elsewhere (Mathews and Neil, 1998)”

This 1998 paper (“Nutrient intakes during pregnancy in a cohort of nulliparous women” *J. Human Nutrition and Dietetics* 11: 151-61) is also about the pregnant Portsmouth women, however, this time it only gives us the early pregnancy data from their seven-day food diaries “which were converted into nutrient values using the COMP-EAT 4 nutritional system.”

... reported elsewhere”

Frustrated by the absence of the promised methodological details, I brewed a large pot of tea and proceeded to look up Mathews’ bibliography on PubMed. It turns out that, prior to the 2008 paper, she had worked at Oxford University where she published at least seven other papers on the nutrition of pregnant women with her faithful senior author, Andrew Neil. Wading through these, I finally found some ‘pre-conception’ data in a second 1998 paper: “Folates in the periconceptual period: are women getting enough?” (*Brit. J. Obstetrics and Gynaecology* 105(9), 954-59). This

study, again looking at the feeding habits of her pregnant Portsmouth women, concentrated on their folic acid supplementation “prior to conception” and during early pregnancy. Alas, despite more references to a food questionnaire “administered at approximately 16 weeks gestation”, no real details were given of it in this study either.

Nevertheless, leafing through Mathews’ papers, I was surprised at how the results for all these pregnant women seemed to be strangely alike. In the medical journals, authors are often obliged to provide dates and places for clinical data and, sure enough, between May 1994 and February 1996 it was the same pregnant women from a Portsmouth hospital who gave their data (and, for papers published in 2004 and 2005, their blood). In the 2008 paper, Mathews coyly mentions a general hospital in Southern England but in the acknowledgements, it’s clear we’re in Portsmouth and that the same two nurses “Mrs L. Willis and Mrs L. McRoberts” collected the data. But, you may say, does it really matter that Mathews and Neil have used this same data in at least eight publications

over a 12-year period? Well, to some extent, that depends on whether the original data collected for one set of experiments (in this case looking at whether baby health suffers from poor maternal nutrition or smoking) is still appropriate many years later for answering completely new questions, for example, does food intake affect the selection of the baby's sex?

Despite trawling through Mathews' bibliography, the precise nature of the food questionnaire, which is so critical to the future growth of breakfast cereal sales, still remained unclear to me. Over a simple supper of beans-on-toast and jelly, I scoured the 2008 paper (leaving a few coloured stains) and successfully discovered two passing details in the 'Results' section. Firstly there was a total of 133 food items analysed in the food frequency questionnaire, although breakfast cereal was the only one to be "strongly associated with infant sex." The second was a hint as to the kind of questions Mathews was asking. In Figure 1, where the percentage of males is displayed as a function of cereal consumption, we are told: "For breakfast cereal, the bars represent less than one bowl per week, two to six bowls per week and one or more bowls per day." Were the ladies ticking just one of these three quantities in their questionnaire? Now just how do *six bowls a week* differ from *one bowl a day*? Mathews says that women consuming two to six bowls of cereal per week during 'pre-conception' had 45% boys while those on one bowl or more a day jumped to 59%. All power to shares in breakfast cereal companies!

Meanwhile, down at the local pub, the landlord agreed with Mathews' conclusion, "Well, it does sound fairly convincing, doesn't it?" I sat in a quiet corner near the dartboard with my pint of bitter and looked at the data, yet again. After a second pint, my closer analysis of the tabulated data from the food questionnaires and food diaries revealed some striking discrepancies that cast doubt upon the accuracy of Mathews' measurements. I celebrated my insight with a game of darts.

The good-food diaries.

By Mathews' own admission in her 1999 paper: "Food diaries, as used in this project, are considered a 'gold standard' method of dietary assessment." After all, in these "semi-quantitative" diaries, the women regularly noted down everything they ate, day-by-day, over a week. There might be some guesswork about the size of one industrial bread-slice compared to another, or the

fat and water content of processed meats but it is only "semi"-quantitative. So this is the best data Mathews presents in her paper. Unfortunately, this method was only used to collect data for seven days when the women were already 16 weeks' pregnant.

Food questionnaires – the routine or forgettable?

How accurately can you remember what you ate last week? Or even over the last month? Let alone how many times you went to the pub? The bulk of Mathews' 2008 data analysis relies on similar digestive souvenirs, as reflected in two retrospective food questionnaires. In the second of these, the 28 week pregnant women, who had already kept a food diary at 16 weeks, were no doubt more conscious of the inter-



est being taken in their daily diet when recalling what they had eaten in the three-month intervening period – that's to say, a 12-week recall of 133 food items.

But what of the critical "pre-conception" data? Here, our newly pregnant Portsmouth women, who had never given birth before and were being asked to fill out questionnaires covering an entire year of routine eating (minus the culinary highlights), recalled the first four months after that magical moment of conception – assuming they were not unduly distracted by the emotional turmoil of being pregnant.

Error bars?

Mathews is clearly undeterred by possible doubts about the accuracy of her data – besides, she's already happily used it in several other publications. So, how does she analyse her data this time? First, she divides

her three data sets (pre-conception, early and late pregnancy) to show the results for the male-bearing (MB) versus the female-bearing (FB) pregnant women. Then looking at 18 statistically processed summary items (fat, protein, carbohydrate, etc.), she uses 'p-values' to indicate significant differences between MBs and FBs. For 'early pregnancy', the lowest p-value for the 18 items was 0.119 – basically there was no difference between the diets of MBs and FBs when using the more precise data from food diaries. Meanwhile, in 'late pregnancy', only one in 18 had a p-value below 0.05 – fairly insignificant differences between MBs and FBs 'appeared' in data from this food questionnaire. However, for the 'pre-conception' data, fully half the items had p-values less than 0.05! Mathews chirpily notes that "inspection of the within-time period factor score pattern showed that the diet difference was greatest for the preconception diet, whereas there was not a significant difference for either early or later pregnancy."

As I sipped my bedtime cocoa, it occurred to me, it might be equally well argued that the large variation in the 'pre-conception' data instead reflects the highly inaccurate nature of human dietary recall stretched back over 16 months.

Mathews, though, is convinced: "Having established the existence of relationships between preconceptional nutritional patterns and foetal sex, we went on to examine individual nutrients in more detail."

Let's take a closer look at some of these figures. For each data set we are presented with overall daily energy intake in kilocalories, fat, protein and carbohydrate consumption in grams; then there are surprisingly precise estimates for metal ions and vitamins C and E, (in milligrams!), followed by beta-carotene, retinol, vitamin B12, and folate intake (in micrograms!!). Perhaps such precise daily figures could be obtained from the 'semi quantitative' food diaries, but who can trust microgram estimates based on retrospective food questionnaires going back 16 months?

"Hoist by (her) own petard" (to misquote Shakespeare)

One of the most damning critiques of the retrospective food questionnaire data and its reliability comes, surprisingly enough, from Mathews herself. In her 1999 paper, Mathews' vigorously dismissed a rival group's study of pregnant women in Southampton (approx. 40 km to the west

of Portsmouth), which found that poor maternal nutrition in early pregnancy affected birth weight, contradicting Mathews' claim of no effect. She argued that the Southampton group's data was flawed because it had been collected using food frequency questionnaires that were much "less accurate" than her own more precise food diary data. In particular, Mathews pointed at their overestimation of energy and carbohydrate consumption – in the 1999 paper, Mathews' women consumed 2044kcal at 'early pregnancy' (exactly the same as in 2008 if the MB and FB data is pooled), while the rival Southampton study gave a figure of 2346kcal, i.e. 15% higher. Similarly, daily carbohydrate intake was 256g for the Portsmouth ladies but 303g for those from Southampton, some 18% higher.

Nutritional stress?

In the 2008 sex selection paper, Mathews reports no difference in the daily median energy consumption between MB and FB women at "early pregnancy" (2033 kcal and 2061 kcal, respectively, based on the food diaries). By 'later pregnancy', i.e. with food questionnaire data stretching back over three months, to the day after the 'early pregnancy' data stopped, both MBs and FBs had increased energy consumptions (+9%, and +5%, respectively).

Before studying the data for 'pre-conception', let us recall the conclusion from Mathews second 1998 paper: "The dietary intake of the pregnant women in this study appears to be very similar to that of non-pregnant women in the Dietary and Nutritional Survey of British Adults." Well, ten years later, the 'pre-conception' data for these women was uniformly higher than at four months' pregnancy: energy consumption for MB women was +19%, and for FB, +11%. Similarly, carbohydrate consumption at 'early pregnancy' was 257g for MB and 255g for FB, considerably smaller than pre-conception when MB women "ate" +33% more, and FB +27%, or in later pregnancy: +25% for MB, +20% for FB. Should we be surprised to discover that this effect becomes even more distorted when looking at milligram and microgram estimates? The food questionnaires reveal 40% higher vitamin C consumption compared to the food diaries; 95% more vitamin B12; up to 85% more beta-carotene; 60% higher consumption of potassium, etc.!

Why are the large discrepancies in food intake found by Mathews between male-bearing and female-bearing women at 'pre-conception' no longer evident at 16 weeks'

pregnancy? Mathews has the answer: "The lack of dietary differences between mothers of sons and daughters during pregnancy itself is consistent with well-established observations that the very slow growth rate of the human foetus generates a lower incremental nutritional stress than in any other mammal: additional energy requirements are met via metabolic and behavioural energy-sparing mechanisms rather than increased intakes." Come again?

Evolution and other spurious conclusions

Mathews' conviction that greater breakfast cereal consumption implies a higher birth rate of boys appears to have gone to her head. Among her flights of fancy, she indulges in the evolutionary perspective: "The results fit into evolutionary frameworks developed with other species, where, as in humans, males have greater potential lifetime reproductive success and are also more costly to produce." She even proposes a biochemical mechanism for her discovery: "A pathway has been proposed that could explain our associations of foetal sex with energy intake and breakfast cereal consumption around conception. In vitro, glucose enhances the growth and development of male conceptuses while inhibiting that of females. Skipping breakfast extends the normal period of nocturnal fasting, depresses circulating glucose levels and may be interpreted by the body as indicative of poor environmental conditions." Furthermore, "This research may help to explain why in developed countries, where many young women choose to have low calorie diets, the proportion of boys born is falling."

Having waded through the eating habits of less than a thousand pregnant Portsmouth ladies collected over 12 years' ago and stretched out over at least 8 published papers, may I tentatively suggest that in a prospective future Dr Mathews might consider conducting some new experiments. In one she could look at the nutrition of the fathers in the period building up to their more traditionally recognised sex-determining role at conception. In the other, somewhat less ethical experiment, she might envisage controlling for all variables by using one man's sperm to inseminate 700 chosen women, half of whom will have been exclusively nourished on breakfast cereals at the 'pre-conception' stage. With their extra 'boy-selective' revenues, the cereal companies will no doubt have a bit of extra cash to invest in more cereal-intensive research.