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Human sex ratio at birth and residential proximity to nuclear facilities in France

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ABSTRACT

The possible detrimental genetic impact on humans living in the vicinity of nuclear facilities has been previously studied. We found evidence for an increase in the human secondary sex ratio (sex odds) within distances of up to 35 km from nuclear facilities in Germany and Switzerland. Here, we extend our pilot investigations using new comprehensive data from France. The French data (1968–2011) account for 36,565 municipalities with 16,968,701 male and 16,145,925 female births. The overall sex ratio was 1.0510. Using linear and nonlinear logistic regression models with dummy variables coding for appropriately grouped municipalities, operation time periods, and corresponding spatiotemporal interactions, we consider the association between annual municipality-level birth sex ratios and minimum distances of municipalities from nuclear facilities. Within 35 km from 28 nuclear sites in France, the sex ratio is increased relative to the rest of France with a sex odds ratio (SOR) of 1.0028, (95% CI: 1.0007, 1.0049). The detected association between municipalities' minimum distances from nuclear facilities and the sex ratio in France corroborates our findings for Germany and Switzerland.

1. Introduction

1.1. Abundance of nuclear facilities

Nuclear energy constituted 11% of global electricity production in 2011. Three countries obtain more than half their electricity from nuclear plants (France leads at 78%, followed by Slovakia and Belgium at 54% each), and ten additional countries, all but one in Europe, draw at least 25% from this source [1]. In France, 78% of the country's electricity is supplied by the 58 currently active nuclear reactors. France is also the largest exporter of nuclear electricity in the European Union and is second only to the United States in terms of total nuclear power production contributing 16 percent to the world's nuclear-derived electricity. While the environmental and human health risks posed by nuclear power plant accidents are well documented, modeling results by Lelieveld et al. [2] indicate that the occurrence of INES 7 major accidents and the risks of global radioactive contamination have been underestimated. Hence, human exposure risks exist around reactors in densely populated regions, notably in Central Europe and South Asia, where a major reactor accident could subject around 30 million people to radioactive contamination. The recent decision by Germany to phase out its nuclear reactors will reduce the national risk, though a risk by reactors in neighboring countries remains. Furthermore, many nuclear facilities are 30–50 years old, contributing to the potential for catastrophic failure.

1.2. Health risks

The possible health risks to populations living near nuclear facilities have prompted studies into the incidence of childhood cancer. For example, a *meta*-analysis of standardized incidence and mortality rates of childhood leukemia in proximity to nuclear facilities indicated elevated disease rates in the majority of the studies considered, although many findings were not statistically significant [3]. Case-control studies on juvenile cancer and leukemia were performed in Germany [4,5], Switzerland [6], Great Britain [7], and France [8]. Although these studies generally provided limited evidence (possible confounding, restricted statistical power), they nonetheless indicate an increased general human health risk in the vicinity of nuclear facilities.

1.3. Determinants of the sex ratio

According to Neel and Schull, the sex ratio, or technically the sex odds, is unique among the genetic indicators [9]. Its uniqueness

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arises from the fact that maternal exposure is expected to produce sex odds different from sex odds after paternal exposure.

This expectation is attributed to the hypothesis that if an X-linked recessive lethal gene is induced in a mother's germ cell line by ionizing radiation, it would have no effect on a heterozygous daughter, but would be lethal to a hemizygous male zygote. X-linked dominant lethal mutations in mothers would be equally lethal to both genders. X-linked dominant mutations induced in fathers would only suppress female offspring. Recessive X-linked lethal mutations in fathers would not influence the gender ratio as sons do not receive the paternal X chromosome and daughters carry (and are protected by) a second X chromosome from their mother [10]. In situations where mothers and fathers are nearly equally exposed on average (e.g. Chernobyl), it seems unlikely or unrealistic that the opposite maternal and paternal effects would precisely cancel each other out. That the paternal effect exceeds the maternal effect seems to be evident from increased overall sex ratios after large scale radiological incidents like the atomic bomb tests, the Windscale fire, and the Chernobyl accident [11–15].

Therefore, the odds of male to female offspring at birth may be a simple and non-invasive way to study and monitor the reproductive status or reproductive health of a population. Scholte and Sobels suggest that the observation of changes in the sex odds in the offspring of irradiated parents may be one of the few methods available for studying the genetic effects of ionizing radiation in humans [16]. Briefly, the survival probability of the female zygote is impacted by a number of lethal factors of varying degree of dominance located on the X chromosome. These factors may be impacted by radiation to either the mother or the father resulting in an impaired X chromosome, thus reducing the viability of female zygotes and changing the sex odds. In accordance with theoretical predictions, Cox found a reduced offspring sex ratio in irradiated women. James, on the other hand, states, "ionizing radiation is the only reproductive hazard, which causes (irradiated) men to sire an excess of sons" [17–19].

Ionizing radiation may differ from other causes of sex ratio variation at birth, because the effect is mediated by direct genetic intervention. It has been hypothesized that other (known) causes of variation of the sex ratio at birth may change parental hormone levels around the time of conception, which affects the probability that fertilization will be by a male sperm, or that altered hormone levels (e.g. by endocrine disrupting chemicals) may be detrimental to the survival of the male embryo [20–23]. It has also been suggested that high androgen levels in fathers (hepatitis B carriers, prostatic cancer patients) may entail male biased offspring [24]. Catalano et al. established that exposure of pregnant women to many forms of stress increases the probability of miscarriage—especially of frail male fetuses [25].

In addition to lethal factors on the X chromosome, Scholte and Sobels allude to nondisjunction resulting in X0 genotypes, which are non-viable in humans and, thus, may also distort the birth sex odds [16]. Down syndrome is a well-known consequence of meiotic nondisjunction in man, and increased Down syndrome prevalence at birth serves to indicate increased nondisjunction across Europe after Chernobyl [26]. More generally, there seems to be an association between maternal radiation history and chromosomally abnormal fetuses, e.g., Klinefelter syndrome (47, XXY) [27]. From the sex determining mechanism in man, involving the X and the Y chromosomes (XX = female, XY = male), it is obvious that the birth sex ratio must necessarily depend on three factors:

- ratio of X- and Y-bearing sperm
- selection of sperm within the female reproductive tract
- differential implantation and survival rates of embryos

Investigations in the ratio of X- and Y-bearing sperm did not show significant differences in the X/Y sperm ratio, even in men with three or more same sex children [28]. Recently, Orzack et al. presented data that the sex ratio at birth is due to a higher prenatal female mortality, perhaps due to dysfunction of the paternal X [29]. If the sex ratio near or at conception is 1:1, as the extensive data by Orzack et al. indicate, but the birth sex ratio is male-biased 105:100, then female fetuses are the frailer sex (karyotype) during embryonal and fetal life, possibly mediated through their fathers' enhanced genetic vulnerability [30]. Findings after Hiroshima and Nagasaki indicate that the sex ratio increase in the offspring of irradiated fathers per unit dose is approximately twice the sex ratio decrease in the offspring of irradiated mothers [10].

In humans, the sex odds at birth is relatively constant at the secular population level, with approximately 105 boys born for every 100 girls [31]. However, considerable variability may be observed under a variety of specific circumstances, including selective abortion in some societies. Many determinants of the sex odds, e.g., race or season as well as methodology to study those determinants have been discussed in the literature [32]. Steiner [33] points out that proposed determinants often showed associations in small samples but could not be replicated in larger populations. This, of course, may be due to insufficient statistical power due to small effects and/or small study-populations.

Anthropogenic chemicals and ionizing radiation are determinants of the human secondary sex odds at birth. The effect of mutagenic chemicals or ionizing radiation on sex odds has been well established in animal experiments [34–36]. Stevenson and Bobrow [37] provide a detailed account of methodological issues relevant for the assessment of determinants of the sex odds in humans with special emphasis on the impact of male fetal mortality dynamics on the sex odds. Terrell et al. [38] reviewed approximately 100 publications on possible environmental and occupational determinants of the sex ratio. They concluded that, "limitations in study design and methodological issues make it difficult to draw firm conclusions from the existing sex ratio literature". This highlights the general difficulties in obtaining firm knowledge about the sex odds determinants in humans.

We previously studied the birth sex ratio near nuclear facilities in Germany and Switzerland, and we found evidence for increased gender proportions at birth within distances of up to 40 km from nuclear installations [13,39]. Since many anthropogenic chemicals are also mutagenic, it was natural to employ our spatial temporal methodology [40] to study the possible influence of chemical accidents on the sex odds in the vicinity of chemical plants. We specifically looked at the birth sex odds near Hoechst-Griesheim, the site of an accident in 1993 that spread tons of nitroarenes into the nearby environment [41]. We detected a decrease in the sex odds after the chemical accident [42]. Sociological influences such as stress have also been implicated in sex determination, for example following the earthquakes in Chile [43] and Italy [44]. In accordance with the Trivers-Willard hypothesis [45], these studies suggest a decrease in the human sex odds at birth under adverse living conditions. Lastly, while environmental influences play a significant role, the most dramatic determinant of human sex odds at birth seems to be man-made, namely sex selective abortion. Biased sex ratios pose a problem to societies for example in China and in India [46,47].

1.4. Objectives

Motivated by positive findings of radiation induced genetic effects after the atomic bombing of Japan [10,48], after Windscale/Sellafield [11,49], after the atmospheric nuclear weapon tests [12,13], after Chernobyl [26,50–52], and last but not least in the vicinity of nuclear facilities [39], we decided to study the