Congenital Malformations and Perinatal Deaths among the Children of Atomic Bomb Survivors: A Reappraisal

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ABSTRACT
From 1948 to 1954, the Atomic Bomb Casualty Commission conducted a study of pregnancy outcomes of children of atomic bomb survivors who had received radiation doses from zero to near-lethal levels. Past reports (1956, 1981, and 1990) on the cohort did not identify significant associations of radiation exposure with untoward pregnancy outcomes such as major congenital malformations, stillbirths, or neonatal deaths, individually or in aggregate. We have re-examined the risk of major congenital malformations and perinatal deaths in the children of the atomic bomb survivors (N=71,603) using fully reconstructed data to minimize the potential for bias, with refined estimates of the gonadal dose from the Dosimetry System 2002 and refined analytical methods for characterizing dose-response relationships. The analyses show that parental exposure is associated with increased risk for major congenital malformations and perinatal deaths, but the estimates are imprecise for direct radiation effects and most are not statistically significant. Nonetheless, the uniformly positive estimates for untoward pregnancy outcomes among children of both maternal and paternal survivors are useful for risk assessment purposes, although extending them to circumstances other than atomic bomb survivors comes with uncertainty as to the generalizability of the Hiroshima and Nagasaki populations.
Keywords: children of atomic bomb survivors, congenital malformations, genetics, perinatal deaths, radiation effects, untoward pregnancy outcomes

Abbreviations: ABCC: the Atomic Bomb Casualty Commission, UPO: untoward pregnancy outcome, RERF: the Radiation Effects Research Foundation, ERR: excess relative risk, CI: confidence interval.

From 1948 to 1954, the Atomic Bomb Casualty Commission (ABCC) conducted a large-scale study of pregnancy outcomes of children of atomic bomb survivors who had received radiation doses ranging from zero to near-lethal levels (1). This research was motivated by already firm experimental findings showing that ionizing radiation causes genetic effects; consequently, examination of pregnancy outcomes in the children of radiation-exposed parents was considered imperative.

The first reported analyses of the data in 1956 considered a non-overlapping hierarchy of untoward pregnancy outcomes (UPOs) that included major congenital malformations, stillbirths of children without major malformations, and neonatal deaths of children without major malformations (1). Further analyses in 1981 (2) and 1990 (3) used individual parental dose estimates based on the revised tentative 1965 radiation dose estimation and the dosimetry system 1986, respectively, to assess the effects of total (conjoint) parental dose on the risk of UPOs as a group (Web Table 1).

While the past analyses generally showed a positive trend between the frequency of UPOs and total parental dose, the effects were not statistically significant (2-4).
Children born to atomic bomb survivors were further studied by researchers of the ABCC and its successor, the Radiation Effects Research Foundation (RERF), for other indicators of genetic effects: sex ratio (4), chromosome aberrations (4), electrophoretic variants of serum and erythrocyte proteins (4), and mutation rate at micro- and minisatellite loci (5). Non-specific outcomes investigated include mortality (6), and multifactorial diseases in adults (7). To date, these studies have not found associations of the various outcomes with parental radiation exposure.

More recently, RERF has reconstructed and refined the data from the original ABCC genetic study. This re-assessment showed that all previous analyses excluded around 700 induced terminations with birth weight less than 2,500 g and around 500 terminations with unknown birth weight, although the exclusion criteria differed among the various UPO analyses (Web Table 1) (8). Comparisons between the datasets for each previous analysis with the original data indicated that approximately 15% of the total malformations in the original data were not treated as malformations in the 1990 analysis, possibly in error (3). In addition, updated estimates of the gonadal dose from the dosimetry system 2002 (9) and refined analytical methods for characterizing dose-response relationships became available.

In view of limitations of the earlier analyses and recently increased concerns about heritable effects of parental exposure to radiation, particularly following the
2011 Fukushima accident in Japan (10), we have re-examined the risk of major congenital malformations and perinatal deaths in the offspring of the atomic bomb survivors.

METHODS

Subjects

The genetic study of pregnancy outcomes occurring after 20 weeks of the pregnancy among atomic bomb survivors was initiated in 1948 (three years after the bombing) by the ABCC and continued until 1954 (1). In those post-war years, women at the fifth month of pregnancy in Hiroshima and Nagasaki were eligible for a food ration program upon pregnancy registration. Each mother received an oral explanation and a brief printed description of the study program at the time of pregnancy registration. Based on an agreement made with informed consent, they were asked personal identifying information, information on paternal exposure from the blasts, and other items. During the post-war era, most mothers gave birth at home and the majority of deliveries were attended by midwives and the rest by physicians. Soon after delivery of a baby, midwives and doctors collected information on the pregnancy and a total of 76,614 births were reported to the ABCC.

For each delivery, ABCC physicians and nurses visited the baby's home to conduct a further systemic examination. The examining physicians were required to
record all abnormalities including minor defects. At the examination, detailed information was collected for stillbirths, neonatal deaths, and children with malformations observed at birth and for a randomly selected subset of 10% of all births (8). When the final report on each delivery was coded, a decision was made as to the presence of a major malformation based on the list of major malformations ("Diagnoses of malformations" in the Web Appendix).

In selecting the study subjects, the exclusion and inclusion criteria differed somewhat from those used in previous studies (Web Appendix). The principal exclusions were for multiple births and induced terminations occurring prior to the 30th week and the detailed explanations of exclusion are provided in the Web Appendix. After exclusions, the total number of eligible births was 71,603.

The current reanalysis has been approved by the RERF institutional review board. Because RERF restricts the provision of personal data of atomic bomb survivors and their children to third parties, all data and documentation have been permanently archived at RERF.

Radiation dose

The current reanalysis used dose estimated with the dosimetry system 2002 (9) which provides individual gonadal doses for a larger number of parents than the
previous systems. For the fraction of neutrons, the radiation weighting factor of 10 was used to account for the greater biological effect (9). We used adjusted dose estimates intended to overcome the regression bias that can arise from random uncertainties in exposure estimation (9).

The current study analyzed the data separately for the maternal and paternal gonadal doses to account for any sex-dependent difference in transgenerational mutability reported in animals that might occur in humans (11). The biological rationale for that decision follows. In 1980, the Biological Effects of Ionizing Radiation (BEIR) III Committee noted that the reproductive cells of female mice were much less mutable than those of males (12). In addition, recent mouse studies have found that the frequency of radiation-induced germline mutations at a minisatellite locus differed comparing maternal and paternal exposures (13). Analyses were also carried out with the conjoint dose. Table 1 shows the distribution of parental gonadal doses in the current analysis. Maternal dose was available for 68,533, paternal dose for 69,433, and conjoint dose for 66,363 births. About 55% of mothers and 77% of fathers were not in Hiroshima or Nagasaki at the time of the bombings (referred to as the not in city subjects) and those were assigned a dose of zero. The means of maternal, paternal, and conjoint doses were 0.03, 0.02, and 0.05 Gy, respectively.
Malformation and perinatal death

In the current reanalysis, outcomes were major congenital malformations observed at birth and also perinatal deaths. Because of the diverse causes associated with each outcome (14, 15), these outcomes were treated separately in the main analyses. Additional analysis based on a hierarchy of outcomes (we treated major congenital malformation at first, then perinatal death without major congenital malformation) was also conducted. Although stillbirths (i.e., an infant showing no signs of life at birth) and neonatal deaths were treated separately in the first analyses reported in 1956 (Web Table 1), both were considered as perinatal deaths in the current analysis because of the difficulties in differentiating the two. Among the eligible births, there were 3,530 births classified as having one or more UPOs: 783 births with major malformation, 2,667 births with perinatal death within 7 days, 2,904 births with perinatal death within 14 days.

Although an autopsy was conducted for about 30% of perinatal deaths, the main analyses do not include major malformation cases identified only by autopsy, due to potential bias resulting from autopsy sampling with differential selection by dose and city (Web Table 2) and the uneven quality of the autopsies. As a sensitivity analysis, the risks of major malformation cases identified both at birth and at autopsy are provided in WebTable 3.
Statistical analysis

We used binomial regression models to analyze the radiation-associated risk for each of the three outcomes of interest (major malformation, perinatal death within 7 days, and perinatal death within 14 days). The primary models were relative risk models of the form  \( p(x,d) = \pi_0(x)\{1 + \text{ERR}(d)\} \).

In model, \( \pi_0 \) is the baseline (zero dose) probability described as a log-linear function of baseline risk factors \( (x) \) (included risk factors are maternal and paternal ages at birth, parity, consanguinity, year of birth, gender, and city of registration). The excess relative risk (ERR) is relative risk minus one and \( \text{ERR}(d) \) is a function of parental doses, where children of parents exposed at dose \( d \) compared to those of unexposed parents. The ERRs per unit dose (1 Gy) were estimated for maternal, paternal, and conjoint doses. We calculated maximum likelihood estimates of the model parameters using the gnm package of R (16), based on hypothesis tests, confidence intervals (CIs) and two-sided \( P \)-values on likelihood ratio tests. In addition to 95% CIs, 90% CIs were also calculated when the \( P \)-value was < 0.1.

RESULTS

Table 1 provides the joint distribution of maternal and paternal gonadal doses
while Table 2 describes demographic characteristics by paternal and maternal gonadal doses. The mean number of children per parent during the study period was 1.3. About a quarter (26%) of the parents had no prior children. Mean maternal and paternal ages at the time of delivery were 28 and 33 years, respectively, and 23 and 28 years at the time of the bombings. The most common major malformations found in eligible births were cleft palate and cleft lip (N=97), single cleft palate (N=42), cleft lip (N=62), club foot/hand (N=93), polydactyly (N=67), syndactyly (N=35), and anencephaly (N=48).

Table 3 shows the adjusted rates per 100 births for major malformations and perinatal deaths by selected characteristics. Background prevalence estimates per 100 births, adjusted to reference categories of non-radiation factors, were 0.95 for major malformations, 3.72 for perinatal deaths within 7 days, and 3.95 for perinatal deaths within 14 days. High parity was associated with higher risk of major malformations. The risk of perinatal deaths was increased significantly for first pregnancies (parity=0). Children of closely related parents had a higher risk of adverse outcomes than children born to unrelated parents (about 60% higher for major malformations and 40% higher for perinatal deaths). Maternal age above 40 years was a risk factor for major malformations. Infants of younger fathers and older mothers were at higher risk of perinatal deaths. Major malformation risks increased
significantly ($P < 0.01$) over the study period of 1948 to 1952. While perinatal death rates varied with calendar period, a trend over time was not apparent. In 1948, the risk of perinatal deaths was about 30% higher and the risk of major malformations about 30% lower than in other years. Major malformation risks did not vary by sex, but risk for perinatal deaths tended to be higher for boys than girls ($P < 0.01$). In Hiroshima, relative to Nagasaki, the risk tended to be higher for major malformations ($P = 0.08$), but not for perinatal deaths.

Table 4 presents the radiation risk estimates for the various UPOs. Considering the effects of parental doses on malformations separately, the ERR per Gy for the maternal dose was $0.28$ (95% CI: -0.30, 0.86) and that for paternal dose was $0.40$ (95% CI: -0.30, 1.09). When the effects of conjoint doses were considered, ERR per Gy for malformations was $0.35$ (95% CI: -0.11, 0.81 and 90% CI: 0.02, 0.80). As for the risk for perinatal deaths within 7 days, ERR/Gy estimates were 0.22 (95% CI: -0.08, 0.52) for maternal dose, 0.11 (95% CI: -0.18, 0.41) for paternal dose, and 0.14 (95% CI: -0.07, 0.34) for conjoint dose. The corresponding figures for perinatal deaths within 14 days were 0.26 (95% CI: -0.04, 0.55 and 90% CIs; 0.01, 0.50) for maternal dose, and 0.21 (95% CI; -0.09, 0.51) for paternal dose. Using conjoint dose, the estimated ERR/Gy for perinatal deaths within 14 days was 0.21 (95% CI; 0.00, 0.42 and 90% CI; 0.05, 0.40), similar to the estimates for maternal and paternal doses.
separately. The analyses of perinatal deaths excluding major malformations based on a hierarchy of outcomes showed similar results.

The plots in Figure 1 present the fitted maternal and paternal dose-response curves for each of the three outcomes with ERR estimates for each dose-category. The categorical estimate for the paternal 0.5 - 1 Gy group was significantly \((P<0.05)\) increased for major malformations but not for perinatal death outcomes. For the maternal 0.5 - 1 Gy group the ERR was increased significantly for both of the perinatal death outcomes but not for major malformations. None of the categorical estimates for the over 1 Gy group were significantly increased.

As described in the Statistical analysis section of the Web Appendix, the dose-response models were fit using all of the data including births for which either the maternal or paternal dose was unknown. When we conducted sensitivity analyses limiting the data to births for which the dose to both parents was known, the dose-response parameter estimates, the significance test results and CIs were essentially unchanged.

DISCUSSION

Shortly after the ABCC was established, a surveillance system was implemented for the children born to the survivors in Hiroshima and Nagasaki and for children of
unexposed parents (1, 8). Given the unique nature of the exposed population and the
general recognition at the time from experimental studies that radiation causes
genetic damage, the ABCC’s founders considered that a study of pregnancy
outcomes was critical to quantify the extent of genetic injury. That surveillance, which
ended in 1954, was the data source used in this and prior analyses directed at the
associations of UPOs with parental radiation exposures.

This is the latest major report on UPOs among children born to the atomic bomb
survivors (Web Table 1). The present report uses an updated and corrected data set
with more refined estimates of the relevant dose. The first report in 1956 used a
distance-based measure of radiation exposure at the blast (1), while later reports
used radiation exposure estimated by increasingly sophisticated dosimetry systems
(2, 3) (Web Table 1). The present report uses estimated gonadal dose from the
dosimetry system 2002. The prior reports have been based in the original data
collected, but with somewhat different exclusion and inclusion criteria and different
approaches to exposure and dose calculation. Based on extensive review of the
original data, corrections have been made. The population for the present study was
selected so as to minimize the potential for bias. Additionally, over time, the analytical
methods for characterizing dose-response relationships have been refined. Overall,
the prior reports have not reported significant associations of radiation exposure or
dose with risk for UPOs. The most recent report in 1990 by Otake et al. found positive, albeit not statistically significant associations for UPO overall (3).

Given the substantial body of experimental evidence showing that radiation causes genetic changes (11), there has been a strong prior hypothesis that exposure to radiation from the blasts caused genetic changes with implications for the occurrence of UPOs (1-3). The genetic studies were implemented with the goal of quantifying the magnitude of the additional risk of genetic abnormalities from radiation. For that purpose, multivariate models were used that took into account these other factors; some were associated with the rate of UPO (Table 3).

The adjusted estimates of ERR were uniformly positive, although most estimates were not statistically significant at the 0.05 level (Table 4). Arguably, one-sided testing might be used based on the prior evidence on radiation and mutation, resulting in smaller p-values and narrower confidence intervals, but leaving the estimates unchanged. Following prior analyses, we used two-sided testing.

Beyond the precision of estimates, epidemiological findings need to be interpreted with the possibility that the results are affected by bias. A possible concern is information bias that might be related to differential ascertainment of the occurrence of a UPO based on exposure status. Consequently, the outcomes identified only by autopsy were excluded from the analyses, except for sensitivity analyses. Another
concern is measurement error. Although error in assessment of exposure would affect exposure estimates, the dosimetry system 2002 estimated “true” dose assuming a 35% error in the individual dose estimates and made adjustment for this error (9). Such adjustment increases risk estimates compared with unadjusted estimates (9).

Confounding is another concern, particularly given variation in several determinants of outcome (e.g., parity) by exposure (Table 2). Diverse maternal and paternal factors affect risk for UPOs (Table 3); to the extent possible, these factors were considered in the analyses to date, as there was awareness of the potential for confounding when the study was designed (1).

Regarding phenotypes in human studies such as malformation, stillbirth, and neonatal death, the contribution of non-genetic factors is substantial. According to Brent, genetic causes account for 15-25% of congenital malformations observed during the first year of life (15). Aminu et al. reported that the most frequent causes of stillbirths are problems on the maternal side, which are also related to socioeconomic status such as poverty and lack of education (14). Therefore, harsh living conditions and the limited socioeconomic resources after the war among heavily exposed atomic bomb survivors might lead to an overestimate of genetic effects by radiation. Kato reported that the exposed parents had less education than the non-exposed parents.
among atomic bomb survivors (17). Poverty after the war due to social and human damages by atomic bombings was closely associated with the distance from the hypocenters, a surrogate for radiation dose (18). But information was not available on the full suite of determinants of pregnancy outcome and their consequences for post-war births in the unique circumstances of Hiroshima and Nagasaki.

Other studies have addressed the consequences of preconception radiation exposure to mothers and fathers and pregnancy outcomes. Studies of the children born to cancer survivors who underwent radiation therapy are an important source of information on parental radiation exposure and the risk of UPOs (19, 20). Largely null results have been obtained on risk for UPOs in the systematic reviews on studies comparing offspring of cancer, leukemia, and lymphoma survivors with those of cancer-free controls (including siblings) (19-21). Although only a limited number of studies assessed exact doses to the target organ (20), a statistically significant excess of congenital malformations was not detected even among children born to parents with high gonadal dose (22, 23), and dose-response relationships were not suggested (22, 23). Studies of preconceptional radiation exposure and pregnancy outcomes in various occupationally- and environmentally- exposed groups had limited power due to the small sample size, low gonadal dose, lack of dosimetry information, or inadequate comparison groups (19). Although some of the individual
malformations showed a positive association with radiation exposure such as an increased risk of neural tube defects among Hanford male workers (24), the findings may reflect type 1 error (24, 25). There was no evidence of an increased risk when congenital malformations in aggregate were analyzed (24-27).

In the US Childhood Cancer Survival Study, adverse effects of radiotherapy on stillbirths and neonatal deaths were reported for maternal exposure before menarche, but not for maternal exposure after menarche or for paternal exposure (28). This result was interpreted as reflecting uterine damage induced by high-dose pelvic irradiation prior to puberty (28). Parker et al. reported an excess risk of stillbirths among children of male workers at the Sellafield nuclear facilities (29). Abrahamson and Tawn examined the findings from the report of Parker and colleagues and found them to be too high when considered in the context of the foundation of evidence on radiation and mutations. They suggested that inadequate control of background maternal risk factors for adverse outcomes may have led to the findings of Parker et al. (30). A larger study involving workers in the British nuclear industry found no increase in stillbirths among newborns of the males (27). While the same study reported that the number of stillbirths increased among children of female workers, this result was considered equivocal due to the small number of female workers (27).

A case-control study in Denmark of children born to childhood and adolescent cancer
survivors showed no significant association between risk for UPOs (congenital malformation and perinatal death combined) and parental gonad doses, median dose, .10 Gy; mean dose, 1.16 Gy; max, 40 Gy for ovarian dose, .10 Gy; 2.30 Gy; 100 Gy for uterine dose, and .039 Gy; .41 Gy; 8 Gy for testicular dose (31). Overall, other studies on radiation exposure of parents prior to conception provide mixed evidence on UPOs.

This report is written based on a study that was implemented more than 70 years ago; the population is unique and represents the most extensive data set on parental radiation and subsequent birth outcomes. The findings show that radiation is associated with increased risk for UPO, but the estimates are imprecise for direct radiation effects and most are not statistically significant. Nonetheless, the estimates are useful for risk assessment purposes, although extending them to current circumstances comes with uncertainty as to the generalizability of the experience in Hiroshima and Nagasaki. With this report, an effort begun shortly after the bombings comes to a close. We suggest that additional insights on radiation and reproduction may be gained by using contemporary genomic methods to make comparisons of the DNA of parents radiated by the bombings with that of their children.
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Table 1. Paternal and maternal gonadal dose distribution in eligible births.

| Paternal dose (Gy) | Maternal dose (Gy) | 0 | <0.05 | 0.05-0.49 | ≥1 | Unknown | not in city | Total |
|-------------------|-------------------|---|-------|-----------|----|---------|------------|-------|
| 0                 |                   | 2,565 | 1,226 | 265 | 47 | 25 | 244 | 1,936 | 6,308 |
| <0.05             |                   | 871 | 2,222 | 320 | 52 | 36 | 304 | 1,911 | 5,716 |
| 0.05-0.49         |                   | 166 | 351 | 425 | 31 | 14 | 62 | 537 | 1,586 |
| 0.5-0.99          |                   | 58 | 55 | 47 | 49 | 10 | 15 | 158 | 392 |
| ≥1                |                   | 58 | 98 | 32 | 11 | 16 | 19 | 144 | 378 |
| Unknown           |                   | 376 | 830 | 136 | 31 | 19 | 0 | 778 | 2,170 |
| not in city       |                   | 7,569 | 8,045 | 2,161 | 584 | 315 | 2,426 | 33,953 | 55,053 |
| Total             |                   | 11,663 | 12,827 | 3,386 | 805 | 435 | 3,070 | 39,417 | 71,603 |
Table 2. Demographic characteristics by paternal and maternal gonadal dose.

| Characteristic | 0 | <0.05 | 0.05-0.49 | 0.5-0.99 | ≥1 | Unknown | not in city | Total |
|---------------|---|------|-----------|----------|----|---------|------------|-------|
| Dose, Gy      | Mean | %   | Mean | %   | Mean | %   | Mean | %   | Mean | %   | Mean | %   | Mean | %   | Mean | %   | Mean | %   |
| **Paternal**  |     |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| Total No.*    | 6,308 | 5,716 | 1,586 | 392 | 378 | 2,170 | 5,053 | 71,603 |
| No. of major malformations* | 76 | 61 | 17 | 11 | 5 | 21 | 592 | 783 |
| No. of perinatal deaths* | <7days | 207 | 231 | 70 | 13 | 17 | 95 | 2,034 | 2,667 |
|                       | ≤14days | 227 | 251 | 78 | 14 | 21 | 100 | 2,213 | 2,904 |
| Parity*         |     |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 0              | 17.8 | 18.3 | 20.2 | 19.9 | 24.1 | 22.1 | 27.5 | 25.5 |
| 1-3            | 55.6 | 55.6 | 58.3 | 60.2 | 60.6 | 61.8 | 60.5 | 59.6 |
| ≥4             | 26.6 | 26.1 | 21.4 | 19.9 | 16.3 | 16.1 | 12.1 | 14.9 |
| Relative (1st cousin) | 4.3 | 3.6 | 2.5 | 3.6 | 2.6 | 3.8 | 4.2 | 4.1 |
| Paternal age   | 35.2 | 35.7 | 35.6 | 35.1 | 34.6 | 33.6 | 32.4 | 33.1 |
| Maternal age   | 29.8 | 30.0 | 29.5 | 29.1 | 28.9 | 28.4 | 27.7 | 28.1 |
| Year of birth* | 1950.4 | 1950.4 | 1950.3 | 1950.6 | 1950.8 | 1950.5 | 1950.6 | 1950.6 |
| Sex (Boy)      | 51.0 | 51.3 | 50.1 | 53.1 | 53.4 | 51.7 | 51.9 | 51.8 |
| Hiroshima*     | 43.2 | 41.3 | 78.6 | 49.7 | 51.3 | 39.0 | 50.2 | 49.1 |
| Distance*      | 5270.5 | 2918.1 | 1633.2 | 1312.3 | 1125.1 | 1670.8 | 3522.0 | |
| <1.5km         | 0.0 | 0.0 | 24.7 | 88.5 | 100.0 | 32.3 | 2.6 | |
| <2.5km         | 0.0 | 25.5 | 100.0 | 100.0 | 63.9 | 7.3 | |
| **Maternal**   |     |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| Total No.*     | 11,663 | 12,827 | 3,386 | 805 | 435 | 3,070 | 39,417 | 71,603 |
| No. of major malformations* | 122 | 127 | 26 | 10 | 8 | 37 | 453 | 783 |
| No. of perinatal deaths* | <7day | 435 | 483 | 124 | 44 | 18 | 126 | 1,437 | 2,667 |
|                       | ≤14days | 470 | 533 | 158 | 47 | 21 | 137 | 1,557 | 2,904 |
| Parity*         |     |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 0              | 21.8 | 22.7 | 22.9 | 24.3 | 26.0 | 30.9 | 27.3 | 25.5 |
| 1-3            | 56.8 | 60.1 | 61.0 | 63.2 | 58.6 | 59.8 | 60.1 | 59.6 |
| ≥4             | 21.4 | 17.1 | 16.1 | 12.4 | 15.4 | 9.3 | 12.6 | 14.9 |
| Relative (1st cousin) | 4.5 | 3.9 | 2.2 | 2.9 | 2.1 | 3.0 | 4.5 | 4.1 |
| Paternal age   | 33.5 | 33.3 | 33.8 | 32.6 | 32.5 | 31.5 | 32.9 | 33.1 |
| Maternal age   | 28.8 | 28.6 | 28.4 | 27.5 | 27.6 | 27.0 | 27.9 | 28.1 |
| Year of birth* | 1950.4 | 1950.5 | 1950.6 | 1950.6 | 1950.6 | 1950.6 | 1950.6 | 1950.6 |
| Sex (Boy)      | 51.4 | 51.9 | 50.4 | 48.1 | 51.3 | 51.6 | 52.0 | 51.8 |
| Hiroshima*     | 36.2 | 43.0 | 77.3 | 56.0 | 56.3 | 52.1 | 52.1 | 49.1 |
| Distance*      | 5205.8 | 2822.6 | 1506.9 | 1255.5 | 1079.3 | 1705.2 | 3432.1 | |
| <1.5km         | 0.0 | 0.0 | 32.5 | 98.1 | 100.0 | 35.0 | 4.8 | |
| <2.5km         | 0.0 | 28.3 | 100.0 | 100.0 | 77.9 | 15.0 | | |

* Values are expressed as No.

Parity: distribution of parity for mother
\(^c\)Year of birth: year of birth for baby
\(^d\)Hiroshima: present in Hiroshima at the time of bombing including outside Hiroshima city
\(^e\)Distance: distance from the hypocenter for father by paternal dose and that for mother by maternal dose
\(^f\)Distance of unknown dose subjects: missing for 652 fathers (30.1%) and 454 mothers (14.8%)
Table 3. Adjusted rate per 100 births for major malformations and perinatal deaths (≤ 7 days or ≤14 days) by selected characteristics.

| Characteristic                                | Major malformations | Perinatal deaths |          |          |          |          |
|-----------------------------------------------|---------------------|------------------|----------|----------|----------|----------|
|                                               | Cases               | Adjusted<sup>a</sup> | Cases    | Adjusted<sup>a</sup> | Cases    | Adjusted<sup>a</sup> |
| **Parity**                                    |                     |                   |          |          |          |          |
| 0<sup>b</sup>                                 | 18,255              | 0.95              | 837      | 3.72     | 900      | 3.95     |
| 1                                             | 20,111              | 1.16              | 635      | 2.66     | 704      | 2.93     |
| 2-3                                           | 22,593              | 1.03              | 753      | 2.82     | 819      | 3.07     |
| 4-5                                           | 7,567               | 1.50              | 280      | 2.91     | 303      | 3.18     |
| ≥6                                            | 3,077               | 1.21              | 162      | 3.67     | 178      | 4.09     |
| **P**<sub>heterogeneity</sub>                  | 0.02                | <0.01             | <0.01    |          |          |          |
| **P**<sub>trend</sub>                         | 0.16                | 0.32              | 0.60     |          |          |          |
| **Parental consanguinity**                    |                     |                   |          |          |          |          |
| Unrelated<sup>b</sup>                         | 66,511              | 0.95              | 2,439    | 3.72     | 2,649    | 3.95     |
| First cousin                                  | 2,943               | 1.53              | 145      | 5.07     | 164      | 6.62     |
| Other relative                                | 2,149               | 0.90              | 83       | 3.99     | 91       | 4.27     |
| **P**<sub>heterogeneity</sub>                  | 0.01                | <0.01             | <0.01    |          |          |          |
| **P**<sub>trend</sub>                         | 0.42                | 0.01              | 0.03     |          |          |          |
| **Maternal age at birth**                     |                     |                   |          |          |          |          |
| 14-24                                         | 5,864               | 1.04              | 269      | 5.01     | 294      | 5.28     |
| 25-29                                         | 20,599              | 0.74              | 833      | 4.62     | 906      | 4.86     |
| 30-34<sup>b</sup>                             | 20,357              | 0.95              | 634      | 3.72     | 693      | 3.95     |
| 35-39                                         | 14,046              | 0.78              | 492      | 3.98     | 532      | 4.21     |
| ≥40                                           | 10,737              | 0.90              | 439      | 3.92     | 479      | 4.21     |
| **P**<sub>heterogeneity</sub>                  | 0.03                | <0.01             | <0.01    |          |          |          |
| **P**<sub>trend</sub>                         | 0.42                | 0.01              | 0.03     |          |          |          |
| **Year of birth**                             |                     |                   |          |          |          |          |
| 1948                                          | 4,602               | 0.66              | 220      | 4.97     | 240      | 5.30     |
| 1949                                          | 18,829              | 0.74              | 583      | 3.62     | 640      | 3.90     |
| 1950<sup>b</sup>                              | 14,644              | 0.95              | 514      | 3.72     | 557      | 3.95     |
| 1951                                          | 19,272              | 1.03              | 491      | 3.92     | 533      | 4.14     |
| 1952                                          | 12,015              | 1.10              | 475      | 4.24     | 513      | 4.50     |
| 1953                                          | 10,241              | 0.94              | 384      | 4.03     | 420      | 4.34     |
| **P**<sub>heterogeneity</sub>                  | <0.01               | <0.01             | <0.01    |          |          |          |
| **P**<sub>trend</sub>                         | 0.21                | <0.01             |          |          |          |          |
| **Sex**                                       |                     |                   |          |          |          |          |
| Boy<sup>b</sup>                               | 37,064              | 0.95              | 1,461    | 3.72     | 1,593    | 3.95     |
| Girl                                          | 34,539              | 1.00              | 1,206    | 3.30     | 1,311    | 3.49     |
| **P**<sub>heterogeneity</sub>                  | 0.50                | <0.01             | <0.01    |          |          |          |
| **City of Registration**                      |                     |                   |          |          |          |          |
| Hiroshima<sup>b</sup>                         | 35,181              | 0.95              | 1,309    | 3.72     | 1,433    | 3.95     |
| Nagasaki                                      | 36,422              | 0.84              | 1,358    | 3.76     | 1,471    | 3.95     |
| **P**<sub>heterogeneity</sub>                  | 0.08                | 0.77              | 0.98     |          |          |          |

<sup>a</sup>Background rate per 100 births estimated from the individual dose model ((1) and (1)-1) described in the Statistical analysis section in the Web Appendix.

<sup>b</sup>Reference categories.
Table 4. Adjusted excess relative risk per Gy for major malformations and perinatal deaths.

| Outcome                        | Estimate | 95% CI     | P   |
|--------------------------------|----------|------------|-----|
| **Major malformations**        |          |            |     |
| Maternal dose                  | 0.28     | -0.30, 0.86| 0.28|
| Paternal dose                  | 0.40     | -0.30, 1.09| 0.24|
| Conjoint dose                  | 0.35     | -0.11, 0.81| 0.08|
| **Perinatal deaths ≤ 7 days**  |          |            |     |
| Maternal dose                  | 0.22     | -0.08, 0.52| 0.15|
| Paternal dose                  | 0.11     | -0.18, 0.41| 0.42|
| Conjoint dose                  | 0.14     | -0.07, 0.34| 0.18|
| **Perinatal deaths ≤ 14 days** |          |            |     |
| Maternal dose                  | 0.26     | -0.04, 0.55| 0.08|
| Paternal dose                  | 0.21     | -0.09, 0.51| 0.12|
| Conjoint dose                  | 0.21     | 0.00, 0.42  | 0.03|

Abbreviations: CI, confidence interval; ERR, excess relative risk; P, probability value.

*To estimate excess relative risk, we adjusted maternal and paternal ages at birth, parity, consanguinity, year of birth, sex, and city of registration as covariates.*
Figure legend

Figure 1. Excess relative risk estimated for major malformations, perinatal deaths within 7 days, and perinatal deaths within 14 days. Lines represent the fitted linear dose response (see Table 4) with dose-category-specific excess relative risk and 95% confidence interval for <0.05, 0.05 - 0.49, 0.5 - 0.99, and ≥1 Gy. A) Major malformations by paternal dose; B) Major malformations by maternal dose; C) Perinatal deaths within 7 days by paternal dose; D) Perinatal deaths within 7 days by maternal dose; E) Perinatal deaths within 14 days by paternal dose; F) Perinatal deaths within 14 days by maternal dose.
