

# Increases in perinatal mortality in prefectures contaminated by the Fukushima nuclear power plant accident in Japan

## A spatially stratified longitudinal study

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### Abstract

Descriptive observational studies showed upward jumps in secular European perinatal mortality trends after Chernobyl. The question arises whether the Fukushima nuclear power plant accident entailed similar phenomena in Japan. For 47 prefectures representing 15.2 million births from 2001 to 2014, the Japanese government provides monthly statistics on 69,171 cases of perinatal death of the fetus or the newborn after 22 weeks of pregnancy to 7 days after birth. Employing change-point methodology for detecting alterations in longitudinal data, we analyzed time trends in perinatal mortality in the Japanese prefectures stratified by exposure to estimate and test potential increases in perinatal death proportions after Fukushima possibly associated with the earthquake, the tsunami, or the estimated radiation exposure. Areas with moderate to high levels of radiation were compared with less exposed and unaffected areas, as were highly contaminated areas hit versus untroubled by the earthquake and the tsunami. Ten months after the earthquake and tsunami and the subsequent nuclear accident, perinatal mortality in 6 severely contaminated prefectures jumped up from January 2012 onward: jump odds ratio 1.156; 95% confidence interval (1.061, 1.259), *P*-value 0.0009. There were slight increases in areas with moderate levels of contamination and no increases in the rest of Japan. In severely contaminated areas, the increases of perinatal mortality 10 months after Fukushima were essentially independent of the numbers of dead and missing due to the earthquake and the tsunami. Perinatal mortality in areas contaminated with radioactive substances started to increase 10 months after the nuclear accident relative to the prevailing and stable secular downward trend. These results are consistent with findings in Europe after Chernobyl. Since observational studies as the one presented here may suggest but cannot prove causality because of unknown and uncontrolled factors or confounders, intensified research in various scientific disciplines is urgently needed to better qualify and quantify the association of natural and artificial environmental radiation with detrimental genetic health effects at the population level.

**Abbreviations:** CP = change-point, O = odds, OR = odds ratio, PD = perinatal death, SAS = Statistical Analysis System, software produced by SAS Institute Inc., TEPCO = Tokyo Electric Power Company.

**Keywords:** change-point analysis, detrimental pregnancy outcome, ionizing radiation, nuclear accident, radiation induced genetic effect, stillbirth

## 1. Introduction

After the Great East Japan Earthquake and Tsunami on March 11, 2011, the destroyed Tokyo Electric Power Company

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(TEPCO) Fukushima No.1 nuclear power plant released radioactive elements with an estimated total activity of 900 PBq (Peta-Becquerel) into the atmosphere.<sup>[1]</sup> The World Health Organization estimates that the rates of all solid cancers in male and female infants who were exposed to radiation at the age of one in Namie-Machi in the Fukushima prefecture, a highly contaminated area, would increase by 14% and 24% in 15 years, and that the rates of leukemia would increase by 83% and 57%, respectively.<sup>[2]</sup> Moreover, the World Health Organization estimates that the rates of thyroid cancer among those males and females would increase 7.4 and 9 times, respectively, and suggests increases in breast cancer as well.<sup>[2]</sup>

Disorders that may occur in irradiated fetuses include cancer and principal radiation injuries.<sup>[3]</sup> Due to the vulnerability of the embryo and the fetus, concerns have been raised that even the low dose energy transfer to developing tissue by the frequency magnetic field exposure during ultrasound examinations might entail some health risk.<sup>[4]</sup> As early as in 1958, UNSCEAR acknowledged that an increase in the frequency of radiation induced dominant mutations associated with visible effects would manifest itself to some unknown extent as an increase in the frequency of malformations and stillbirths.<sup>[5]</sup> In 10% of the miscarriages, a genetic defect may cause a baby to be stillborn or to die shortly after birth (perinatal

death [PD]), possibly since a vital organ has not developed properly. UNSCEAR emphasizes that increases in stillbirth and changes in the sex ratio are easily observable criteria (<http://www.unscear.org/unscear/en/publications/1958.html>). Lethal mutations in humans<sup>[5,6]</sup> may, therefore, be observed in several ways: increase in frequencies of miscarriages, perinatal mortality, stillbirths, reduction in fertility, sterility, and disturbance in the ratio of the sexes at birth. A variety of such detrimental reproductive effects, including early childhood cancers, after occupational, diagnostic, therapeutic, and environmental exposures, have been investigated and reported in the scientific literature:

- Atomic bombing of Japan<sup>[7–9]</sup>
- Windscale/Sellafield nuclear processing plant fire<sup>[10,11]</sup>
- Occupational exposure<sup>[12–16]</sup>
- Diagnostic and therapeutic exposure<sup>[17–20]</sup>
- Chernobyl nuclear power plant accident<sup>[21–33]</sup>
- Fukushima nuclear power plant accident<sup>[34,35]</sup>
- Background radiation<sup>[36–38]</sup>
- Living near nuclear facilities<sup>[9,39–42]</sup>

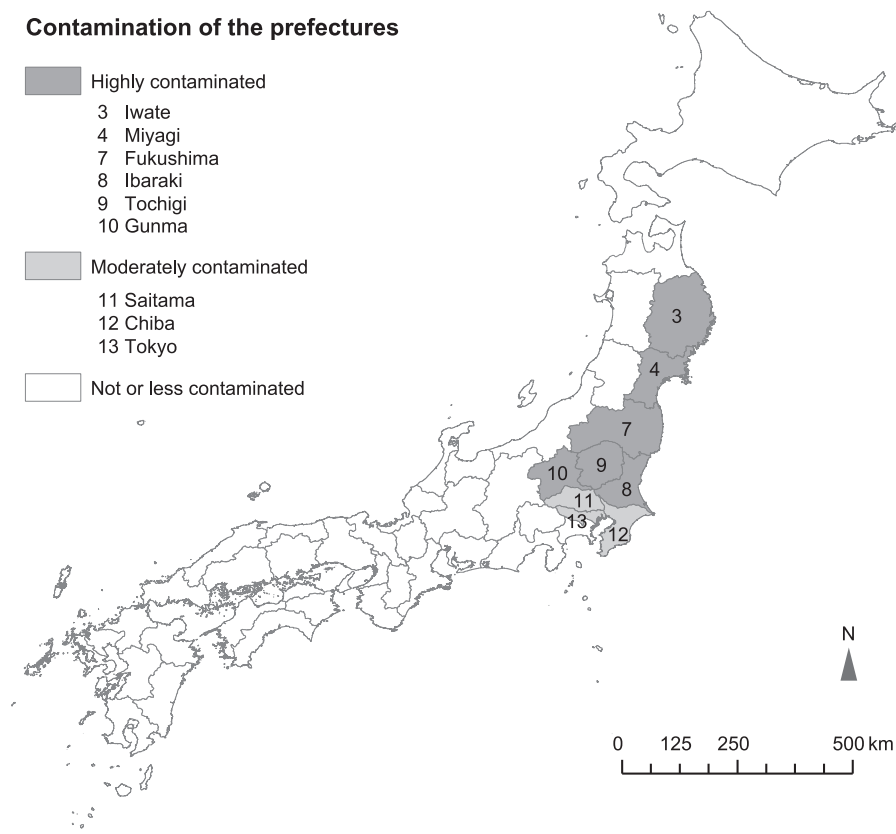
Tsuda et al<sup>[43]</sup> reported that there was an increase in thyroid cancer morbidity after the Fukushima No.1 nuclear power plant accident, which suggests an influence of radiation exposure. However, the findings by Tsuda et al have been criticized for presumably being artifacts of a screening effect.<sup>[44]</sup> Following the nuclear accident in Fukushima and based on data from 2002 to 2013, increases in the numbers of spontaneous fetal deaths,<sup>[34]</sup> as well as an increase in the number of infant deaths<sup>[35]</sup> were reported. However, to date there are no reports of increased PDs

in Japan, even though they have been reported in the case of the Chernobyl nuclear accident.<sup>[23,27]</sup>

Based on more comprehensive and more recent data from 2001 to 2014, we aim to examine whether or not there were increases in perinatal mortality in areas contaminated with radioactive substances in Fukushima prefecture following the nuclear accident. The Fukushima accident differs from the one at Chernobyl since people in Japan were additionally affected by the earthquake and the tsunami. Therefore, we also examine whether there are associations between the earthquake, the tsunami, radiation, and perinatal mortality overall and in moderately and highly contaminated prefectures.

## 2. Methods

The Japanese Statistics Bureau publishes demographic statistics including the monthly numbers of live births and PDs created by the Ministry of Health, Labour, and Welfare. Six prefectures – Iwate, Miyagi, Fukushima, Ibaraki, Tochigi, and Gunma – were classed as severely contaminated; they include wide areas in which the radiation dose in the air was higher than 0.25  $\mu\text{Sv/h}$  (micro-Sieverts per hour), according to a map documenting estimated radiation doses as of December 2011.<sup>[45]</sup> Chiba, Tokyo, and Saitama prefectures were designated as moderately contaminated areas that involve only few areas where the radiation dose in the air was higher than 0.25  $\mu\text{Sv/h}$ . The rest of Japan (38 prefectures) excluding severely and moderately contaminated areas was considered not or only slightly affected. Figure 1 is a map of Japan with the selected prefectures grouped



**Figure 1.** Map of Japan with prefectures classed according to wide areas in which the radiation dose in the air was lower or higher than 0.25  $\mu\text{Sv/h}$  (micro-Sieverts per hour) as of December 2011.

**Table 1**  
**LB, PD, and PDp in Japanese prefectures by contamination level after Fukushima.**

Year	Highly contaminated prefectures (n=6)			Moderately contaminated prefectures (n=3)			Rest of Japan (n=38)			Total (n=47)		
	PD	LB	PDp_6	PD	LB	PDp_3	PD	LB	PDp_38	PD	LB	PDp_47
2001	723	119,830	0.00600	1239	218,349	0.00564	4505	832,285	0.00538	6467	1,170,464	0.00549
2002	697	117,278	0.00591	1333	219,487	0.00604	4295	816,895	0.00523	6325	1,153,660	0.00545
2003	670	114,011	0.00584	1147	214,547	0.00532	4105	794,882	0.00514	5922	1,123,440	0.00524
2004	653	111,437	0.00583	1074	214,201	0.00499	3811	784,907	0.00483	5538	1,110,545	0.00496
2005	505	106,150	0.00473	995	206,861	0.00479	3645	749,349	0.00484	5145	1,062,360	0.00482
2006	522	107,639	0.00483	1033	214,637	0.00479	3539	770,222	0.00457	5094	1,092,498	0.00464
2007	533	106,134	0.00500	973	216,476	0.00447	3395	767,048	0.00441	4901	1,089,658	0.00448
2008	486	105,870	0.00457	932	218,841	0.00424	3294	766,272	0.00428	4712	1,090,983	0.00430
2009	455	102,741	0.00441	921	218,177	0.00420	3139	749,018	0.00417	4515	1,069,936	0.00420
2010	452	101,482	0.00443	889	219,205	0.00404	3167	750,492	0.00420	4508	1,071,179	0.00419
2011	398	97,213	0.00408	871	214,465	0.00404	3041	739,006	0.00410	4310	1,050,684	0.00409
2012	438	95,536	0.00456	865	213,225	0.00404	2825	728,403	0.00386	4128	1,037,164	0.00396
2013	418	95,404	0.00436	782	215,799	0.00361	2659	718,559	0.00369	3859	1,029,762	0.00373
2014	389	93,226	0.00416	811	213,143	0.00379	2547	697,105	0.00364	3747	1,003,474	0.00372
Total	7339	1,473,951	0.00495	13,865	3,017,413	0.00457	47,967	10,664,443	0.00448	69,171	15,155,807	0.00454

LB=live births, PD=perinatal death, PDp=perinatal death proportions.

according to the estimated radiation exposure. Table 1 lists the live births and the PD cases stratified by year and prefecture group according to the defined contamination levels. Note, the smaller moderately exposed area represents approximately twice the population of the much larger highly contaminated area.

To examine the potential influences of the earthquake and the tsunami as well as the possible effects of radiation contamination, the 6 prefectures designated as severely contaminated were divided into group 1: Iwate (the number of deaths and missing due to the tsunami as of March 11, 2016: n=5797) and Miyagi (n=10,777), in which the numbers of the dead and missing were high; and group 2: Fukushima (n=1810), Ibaraki (n=25), Tochigi (n=4), and Gunma (n=1), in which the numbers of the dead and the missing were more than 20 times lower compared to the areas heavily hit, see Table 2.<sup>[46]</sup> Monthly perinatal mortalities for those 2 groups were calculated based on the available monthly numbers of births and PDs to analyze a possible association between tsunami intensity and PD.

Temporality and biologic gradient are 2 indispensable requisites for inferring causality. Temporality means that the presumable cause precedes the observed effect in time, and biologic gradient refers to the presence of an exposure-response association.<sup>[47,48]</sup> Consequently, we investigate whether there are changes in perinatal mortality trends after Fukushima and whether those changes, if any, are associated with the level of

contamination. To this end, we applied linear logistic regression allowing for jumps at certain time lags (in months) after the tsunami to model perinatal mortality trends and to test for trend changes possibly associated with contamination. We denote the number of PDs by  $n_t$ , the number of total birth by  $N_t$ , and the estimated PD proportion as  $p = n_t/N_t$ . Two central parameters in this context are the odds  $O = n_t/(N_t - n_t)$ , and the odds ratio  $OR = O_1/O_0 = n_1/(N_1 - n_1)/(n_0/(N_0 - n_0))$ , which is the ratio of the odds for 2 populations with  $O_1$  and  $O_0$  to be compared, for example, in exposed versus nonexposed strata. The dummy variable for the time window from T onward, for example, T=January 2012, is defined as  $d_T(t) = 0$  for  $t < T$  and  $d_T(t) = 1$  for  $t \geq T$ . The distributional assumption and the parsimonious logistic jump model for a trend in t and a jump in T are:

$$n_t \sim \text{Binomial}(N_t, \pi_t); \log \text{odds}(\pi_t) = \text{intercept} + a * t + \beta * d_T(t) \tag{1}$$

In formula (1), t denotes time (year and month),  $n_t$  the number of PD in t,  $N_t$  the number of total births in t, and  $\pi_t$  is the probability of PD in t. If time t is significant in a certain setting it may be considered a confounder as it is associated with the outcome variable “perinatal death” as well as with the exposure classed “before versus after Fukushima.” Note that the

**Table 2**  
**The numbers of dead and missing due to the earthquake and the tsunami in 6 highly contaminated prefectures<sup>[46]</sup> in relation to population size of the prefectures ([https://en.wikipedia.org/wiki/List\\_of\\_Japanese\\_prefectures\\_by\\_population](https://en.wikipedia.org/wiki/List_of_Japanese_prefectures_by_population)).**

Hit by tsunami	Prefecture	Population (2010)			Death + missing per 100,000
		in 1000	Death	Missing	
Strong	Iwate	1330	4673	1124	435.86
	Miyagi	2348	9541	1236	458.99
	total	3678	14,214	2360	450.63
Weak	Fukushima	2029	1613	197	89.21
	Ibaragi	2970	24	1	0.84
	Tochigi	2008	4	0	0.20
	Gunma	2008	1	0	0.05
	Total	9015	1642	198	20.41

assumption of a binomial distribution implies that the variances of the random variables are determined by the binomial parameter  $\pi$ . In practice, the estimated sample variances are smaller or larger than theory predicts (heterogeneity) for randomness or for unknown reasons, for example, unspecified or unknown covariables. Underdispersion may be due to correlated variables, over-fitting, or over-adjustment. Overdispersion may be a consequence of relevant variables missing in the corresponding model. Therefore, statistical models can be generalized by introducing a heterogeneity parameter, and, to be conservative in this respect, we will allow for this extension in the case of overdispersion but never in the case of underdispersion.<sup>[48]</sup> For example, the data and models in Figs. 3–5 involve only minor heterogeneity: deviance/(degree of freedom) 0.951, 1.124, and 0.998, respectively. In Statistical Analysis System, software produced by SAS Institute Inc. (SAS), for example, correction for overdispersion may be invoked by the option “. . ./scale=d” in the model statement of the “procedure logistic.” The basic model in formula (1) will be complemented by further variables, for example, confounders, including appropriate interactions to estimate or to account for the effects of interesting periods or seasonality, that is, the month-to-month variation, or the immediate or possible late effects of the tsunami. For the Japanese monthly PD trend functions, a change-point (CP) analysis<sup>[49,50]</sup> based on logistic regression and the minimum deviance criterion (goodness of fit) is carried out. The deviance for a logistic model is defined in equation (2).

$$deviance = 2 * \sum observed * \log(observed/expected) \quad (2)$$

The purpose of the CP method is to estimate an optimum point in time, if any exists, when the occurrence of PDs after Fukushima changes its trend. The data in this study were processed with Microsoft Excel 2010. For statistical analyses, we used MATHEMATICA 10.4 and SAS 9.4 (SAS Institute Inc.: SAS/STAT User’s Guide, Version 9.4, Cary NC: SAS Institute Inc., 2012). Ethical approval for this study was not necessary as only publicly available documents and data are being used.

### 3. Results

For the monthly PD trend function in the 6 severely contaminated prefectures, a CP analysis based on logistic regression and the minimum deviance criterion (goodness of fit) is carried out in Fig. 2.<sup>[49,50]</sup> The deviance (2) of a model of type (1) with parallel trends and a possible downward or upward jump in a given month between January 2008 and December 2014 is plotted against that month in Fig. 2. This CP analysis discloses a unique and significant upward jump of the perinatal mortality in January 2012 with minimum deviance among all other months from the beginning of 2008 to the end of 2014. For comparison, we included in Fig. 2 the deviance curve for the 3 moderately contaminated prefectures. No single distinct CP can be identified for those less affected parts of Japan. The deviance analyses are most informative for approximately balanced time periods before or after the assumed “event.” Therefore, the analysis of the period prior to 2008 is of minor interest in the context of our paper that puts emphasis on the year 2011 of the Fukushima accident. The CP analysis in Fig. 2 is so to speak a comprehensive sensitivity analysis as it allows for a wide range of potential jump dates and emphasizes the optimum one, which is, here, the optimum time lag of 10 months between the effect and the foregoing event, that is, the

Deviance of the CP models for the contaminated prefectures

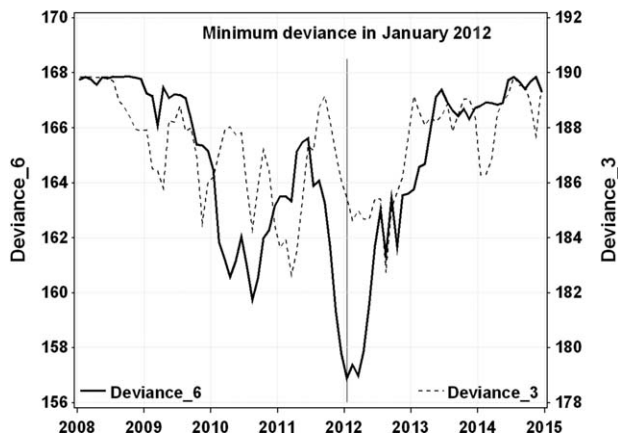


Figure 2. Change-point analysis based on the minimum deviance criterion for the perinatal mortality trend in the 6 severely contaminated prefectures Fukushima, Gunma, Ibaraki, Iwate, Miyagi, and Tochigi; optimum jump in January 2012, minimum deviance 156.89 with 165° of freedom: solid curve; and corresponding analysis for the 3 moderately contaminated prefectures Chiba, Saitama, and Tokyo: broken curve.

Fukushima accident followed by an upward jump in perinatal mortality.

Figure 3 presents monthly perinatal mortality in the 6 severely contaminated prefectures: Fukushima, Gunma, Ibaraki, Iwate, Miyagi, and Tochigi. The annual perinatal mortality proportions are subject to a rather uniform decrease from 2001 to 2014. Perinatal mortality proportions decline with an OR per year of 0.960; (0.952, 0.968). However, estimating a jump 10 months after the Fukushima accident (see Fig. 2) yields the upward jump OR 1.156; (1.061, 1.259). To concretize this effect, the jump in the perinatal mortality proportion from January 2012 to December 2014 may be translated into 165 (66, 278) excess PD cases. Adjusting the parsimonious basic model (1) for seasonality by including independent dummy variables for the months February to December yields practically the same estimates: trend  $OR_{adjusted} = 0.961$ ; (0.953, 0.968); jump  $OR_{adjusted} = 1.150$ ; (1.055, 1.253). To estimate the presumable immediate effect of the earthquake and the tsunami in the 6 contaminated prefectures in March and April 2011 we include in model (1) the independent

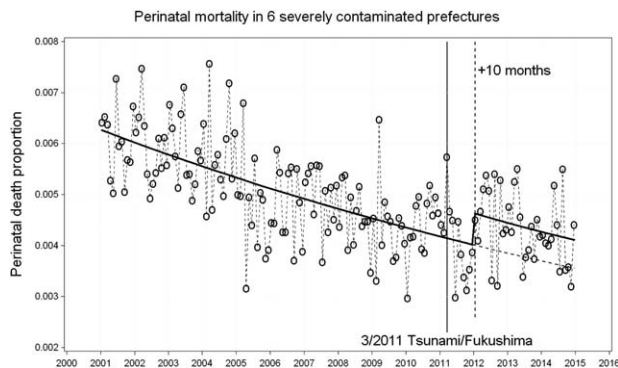
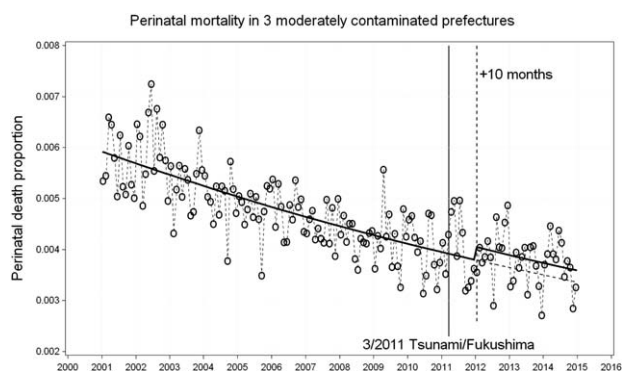
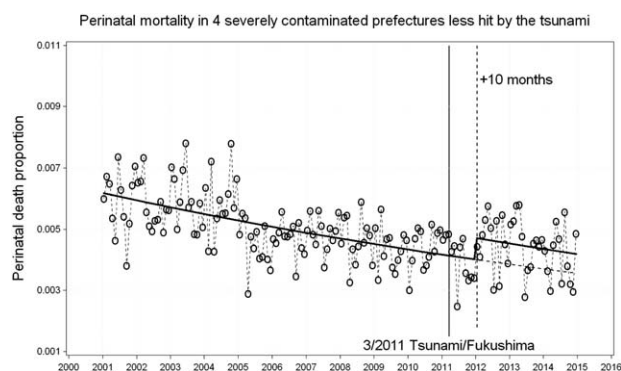


Figure 3. Monthly perinatal mortality in 6 severely contaminated prefectures Fukushima, Gunma, Ibaraki, Iwate, Miyagi, and Tochigi; jump in January 2012, jump odds ratio 1.156 (1.061, 1.259).





**Figure 4.** Monthly perinatal mortality in 3 moderately contaminated prefectures Chiba, Saitama, and Tokyo; jump in January 2012, jump odds ratio 1.068 (1.001, 1.139).



**Figure 6.** Monthly perinatal mortality in the 4 less tsunami-impacted but severely radioactively exposed prefectures Fukushima, Gunma, Ibaraki, and Tochigi; jump in January 2012, jump odds ratio 1.175 (1.062, 1.301).

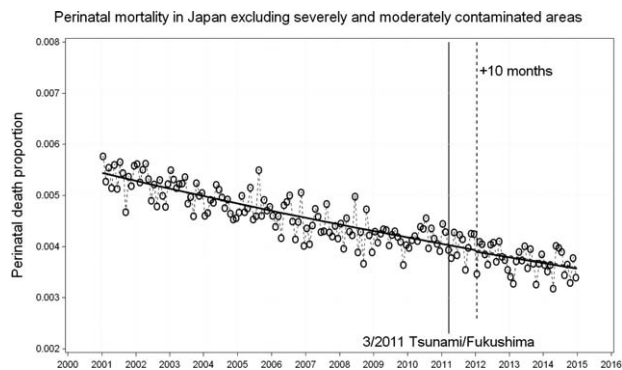
dummies for February to December and the interaction of those dummies for March and April (for any year) with the dummy variable for the year 2011. It appears that the perinatal mortality in the 6 contaminated prefectures in March and April 2011 is increased by approximately 20% compared to March and April of the remaining years: OR 1.202; (0.959, 1.506). This may be anticipated from Fig. 3 by inspection of the somewhat elevated perinatal mortality in March 2011.

Figure 4 presents monthly perinatal mortality in the 3 moderately contaminated prefectures: Chiba, Saitama, and Tokyo. The overall trend is similar to the one in Fig. 3. In Fig. 4, perinatal mortality proportions decline with an OR per year of 0.960 (0.954, 0.966). The estimated jump 10 months after the Fukushima accident yields an OR of 1.068 (1.001, 1.139). This effect translates into 153 (10, 309) excess PD cases. The effect estimate is nearly half the value in the highly contaminated prefectures. Combining the data from Figs. 3 and 4 yields an overall and more accurate estimate of the presumable total excess PDs in Japan from January 2012 to December 2014 of 318 cases with 95%-confidence limits of (136, 519). Interestingly, the downward trends in perinatal mortality in the contaminated prefectures continue after Fukushima, however, at somewhat elevated levels.

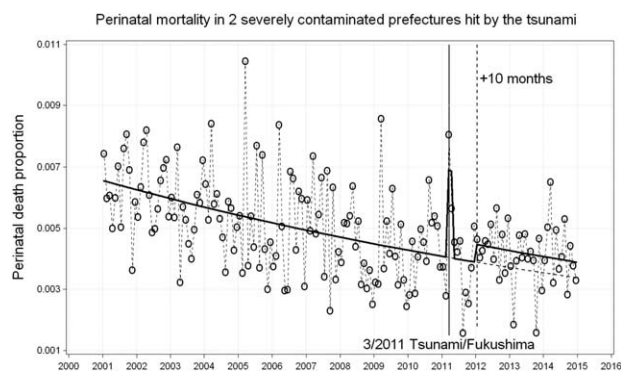
The monthly perinatal mortality in the rest of Japan, that is, Japan excluding the 6 severely and 3 moderately affected

prefectures dealt with above, is shown in Fig. 5. The overall trend is again similar to the ones in Figs. 3 and 4. In the unaffected Japan, the perinatal mortality declines with an OR per year of 0.971 (968, 0.974), and in contrast to the 9 contaminated prefectures, there is no discernible jump 10 months after Fukushima: OR 0.991 (0.958, 1.024).

Figures 6 and 7 present the perinatal mortality trends in the 6 severely contaminated prefectures stratified by the impact of the earthquake and the tsunami according to Table 2. In the 4 less tsunami-impacted prefectures Fukushima, Gunma, Ibaraki, and Tochigi, the secular downward trend is consistent with the overall trends in the 6 severely and 3 moderately contaminated prefectures with an OR of 0.961 (0.952, 0.970). The jump OR 1.175 (1.062, 1.301) in Fig. 6 is also consistent with the one based on the 6 severely contaminated prefectures in Fig. 3. In Fig. 7, representing the perinatal mortality in the 2 severely contaminated prefectures strongly impacted by the tsunami, we can see a similar downward trend and jump from January 2012 onward compared to the situation in Fig. 6. Additionally, in Fig. 7 we observe an uptick of the perinatal mortality already in March and April 2011 that can be attributed to the immediate impact of the earthquake and the tsunami. The OR of this peak in the seasonally adjusted trend model is 1.479 (1.013, 2.161) and the jump OR is 1.132 (0.960, 1.3334), which is consistent with



**Figure 5.** Monthly perinatal mortality in Japan excluding the 6 severely and 3 moderately affected prefectures (see Figs. 3 and 4); insignificant jump in January 2012, jump odds ratio 0.991 (0.958, 1.024).



**Figure 7.** Monthly perinatal mortality in the 2 severely tsunami and Fukushima impacted prefectures Iwate and Miyagi; jump in January 2012, jump odds ratio 1.151 (0.977, 1.355); March/April 2011 peak odds ratio 1.709 (1.186, 2.463); trend model not adjusted for seasonality.

the jumps in January 2012 in Figs. 3 and 6. It is interesting to note that the perinatal mortality decreased after this uptick in March/April 2011 and increased again 10 months after those natural and technical disasters in January 2012. In conclusion, the tsunami does not confound the association of PD with the presumed radiation exposure.

#### 4. Discussion

We investigated monthly perinatal mortality in Japan for the years 2001 to 2014 with emphasis on detrimental pregnancy outcome possibly caused by the earthquake, the tsunami, or the subsequent Fukushima nuclear disaster in March 2011. In the 2 severely contaminated prefectures Iwate and Miyagi that were also heavily hit by the tsunami, there was a more than 50% increase in perinatal mortality in March and April 2011, and there was essentially no increase in the remainder of the year 2011. By contrast, looking at the 4 other severely radioactively affected prefectures (Fukushima, Ibaraki, Tochigi, and Gunma), which remained nearly untroubled after the natural disasters, we see essentially no increase in the occurrence of PDs in March and April 2011, and this applies to the rest of that year as well. In addition to the short-term effects in March and April 2011 in all those 6 severely radioactively contaminated prefectures, however, we observed distinct long-term increases in perinatal mortality of approximately 15% from January 2012 onward. Furthermore, in the 3 moderately exposed prefectures Chiba, Saitama, and Tokyo there is a long-term relative 6.8% increase in perinatal mortality after January 2012, and there is apparently no impact on perinatal mortality in Japan excluding the severely and moderately affected prefectures, neither by the earthquake and the tsunami nor by the Fukushima accident.

Although the present study is of an ecological type based on highly aggregated data that cannot prove causality in principle, it nevertheless provides some evidence of causality according to the well-known Bradford-Hill criteria: temporality and biologic gradient. The observed effects occur 10 months after the possible cause (ionizing radiation). This suggests impact primarily on ovum and sperm and less on the embryo or the fetus. Moreover, the PD increases show a certain dose–response association with the presumable exposure: unaffected as well as moderately and severely impacted prefectures are associated with no, medium, and maximum effects, respectively. The observed optimum overall time-lag of 10 months between the radiological event and the jump in the PD proportion may be explained by the superposition of the periods necessary for the dispersal of the radioactivity (several weeks) and the pregnancy length. Note that the duration of pregnancies at elevated risk of adverse perinatal outcome may be considerably shorter than the usual 9 months.

Similar spatiotemporal associations between a nuclear accident and subsequent detrimental reproductive effects have been previously found in Europe after Chernobyl. A time trend analysis of German perinatal mortality (1980–1993) disclosed a 4.8% increase in 1987, that may be linked to the Chernobyl accident in 1986.<sup>[23]</sup> Higher contaminated parts of Germany, Bavaria and the former German Democratic Republic, showed perinatal mortality increases of 8.5% and 8.2%, respectively.<sup>[27]</sup> Significant ecological relative risks in the range of 1.005 to 1.020 per kBq/m<sup>2</sup>. <sup>137</sup>Cs (kilo-Becquerel per square meter [kBq/m], Cesium [Cs]) for stillbirths and congenital malformations in Germany and Finland as well as relatively increased stillbirth proportions across Europe were also seen after Chernobyl.<sup>[26,31,51]</sup>

A major limitation of this study is the highly aggregated nature of the data considered impeding causal inference in principle. The only potential confounding variables controlled for were time (secular trend), seasonality (month-to-month variation), and the tsunami itself. Otherwise, we are not aware of any monthly statistics on a prefecture-by-prefecture basis that reflects possible confounding variables like stresses to pregnant women and any other risk factors for PD that could be linked to the PD occurrence in Japan before and after Fukushima. Ideally, population based data on perinatal risk factors will be generated to complement future investigations. Another problem is whether the displacement of the population during the Tsunami and the nuclear accident might have confounded our results and conclusions. We are again not aware of any data concerning this issue. However, if young parents have been exposed and put at a higher risk for untoward pregnancy outcome prior to displacement, this could have biased our effect estimates downward, as corresponding PDs would have been counted in the “unexposed” prefectures (exposure misclassification).

In view of the detrimental reproductive effects in Europe after Chernobyl, and acknowledging the observed tentative spatio-temporal ecological dose–response association between radiation exposure and perinatal mortality 10 months after Fukushima, we conjecture that the increases of PDs in the radioactively contaminated prefectures in Japan may possibly be due to radioactive releases by the Fukushima nuclear power plant accident. It will be interesting to more precisely monitor the future temporal development of the various reproductive outcome measures in Japan stratified by radiological exposure to weaken or to corroborate our findings and conclusions.

As the Japanese Government plans to let inhabitants return to areas prospectively exposed to radiation by less than 20 mSv/a (milli-Sieverts per year), our findings are relevant for the resettlement of people formerly evacuated from the highly contaminated zone, see <http://www.pref.fukushima.lg.jp/site/portal-english/rev-plan-3.html>. The “Ottawa Charter of Health Promotion”<sup>[52]</sup> emphasizes that political responsibility is needed and that global and environmental factors play an important role in the care for public health. To take political responsibility requires full and continuous access to information, learning opportunities in the various environmental health research disciplines, as well as adequate funding support for ecological, environmental, and medical investigations.<sup>[53]</sup>

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#### References

- [1] The National Diet of Japan Fukushima Nuclear Accident Independent Investigation Commission. 4–1. Overview of damage from the nuclear power plant accident and 4–2. Problems with evacuation orders from the residents’ perspective. Chapter 4. Overview of the damage and how it spread. The official report of The Fukushima Nuclear Accident Independent Investigation Commission. 2012; 1–38. Available at: [http://warp.da.ndl.go.jp/info:ndljp/pid/3856371/naic.go.jp/wp-content/uploads/2012/08/NAIC\\_Eng\\_Chapter4\\_web.pdf](http://warp.da.ndl.go.jp/info:ndljp/pid/3856371/naic.go.jp/wp-content/uploads/2012/08/NAIC_Eng_Chapter4_web.pdf). [Accessed April 16, 2016].
- [2] World Health Organization. 5. Risk characterization. Health Risk, Assessment from the Nuclear Accident after the 2011 Great East Japan,

- Earthquake and Tsunami Based on a Preliminary Dose Estimation. Geneva: WHO Press; 2013.
- [3] Centers for Disease Control and Prevention (CDC). CDC FACT SHEET Radiation and Pregnancy: A Fact Sheet for the Clinicians; <http://emergency.cdc.gov/radiation/prenatalphysician.asp>. [Accessed April 16, 2016].
  - [4] Park JS, Kim DW, Chung JW, et al. Safety of exposure from extremely low frequency magnetic fields during prenatal ultrasound examinations in clinicians and pregnant women. *Medicine (Baltimore)* 2015;94:e1194.
  - [5] UNSCEAR. UNSCEAR 2001 Report, Hereditary Effects of Radiation, United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR 2001 Report to the General Assembly, with Scientific Annex; [http://www.unscear.org/docs/reports/2001/2001Annex\\_pages%208-160.pdf](http://www.unscear.org/docs/reports/2001/2001Annex_pages%208-160.pdf). [Accessed April 16, 2016].
  - [6] Vogel F, Motulsky AG. *Human Genetics*. Berlin Heidelberg New York Tokyo:Springer; 1986.
  - [7] Neel JV, Schull WJ. The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki. In: Council NAOsNR, editor, *The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki*. Vol Publ. No. 461. Washington (DC) 1956.
  - [8] Schull WJ, Neel JV. Radiation and the sex ratio in man. *Science* 1958;128:343–8.
  - [9] Scherb H, Voigt K, Kusmierz R. Ionizing radiation and the human gender proportion at birth – a concise review of the literature and complementary analyses of historical and recent data. *Early Hum Dev* 2015;91:841–50.
  - [10] Grech V. Births and male:female birth ratio in Scandinavia and the United Kingdom after the Windscale fire of October 1957. *Int J Risk Saf Med* 2014;26:45–53.
  - [11] Scherb H, Kusmierz R, Voigt K. Letter to the editor. *Int J Risk Saf Med* 2014;26:173–4.
  - [12] Sever LE, Gilbert ES, Hessol NA, et al. A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. *Am J Epidemiol* 1988;127:226–42.
  - [13] Parker L, Pearce MS, Dickinson HO, et al. Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant. *Lancet* 1999;354:1407–14.
  - [14] Dickinson HO, Parker L, Binks K, et al. The sex ratio of children in relation to paternal pre-conceptual radiation dose: a study in Cumbria, northern England. *J Epidemiol Community Health* 1996;50:645–52.
  - [15] Shirangi A, Fritschi L, Holman CD. Maternal occupational exposures and risk of spontaneous abortion in veterinary practice. *Occup Environ Med* 2008;65:719–25.
  - [16] Wiesel A, Spix C, Mergenthaler A, et al. Maternal occupational exposure to ionizing radiation and birth defects. *Radiat Environ Biophys* 2011;50:325–8.
  - [17] Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. *Lancet* 1970;1:1185–8.
  - [18] Cox DW. An investigation of possible genetic damage in the offspring of women receiving multiple diagnostic pelvic X rays. *Am J Hum Genet* 1964;16:214–30.
  - [19] Goldberg MS, Mayo NE, Levy AR, et al. Adverse reproductive outcomes among women exposed to low levels of ionizing radiation from diagnostic radiography for adolescent idiopathic scoliosis. *Epidemiology* 1998;9:271–8.
  - [20] Winther JF, Boice JD Jr, Thomsen BL, et al. Sex ratio among offspring of childhood cancer survivors treated with radiotherapy. *Br J Cancer* 2003;88:382–7.
  - [21] Lazjuk GI, Nikolaev DL, Novikova IV. Changes in registered congenital anomalies in the Republic of Belarus after the Chernobyl accident. *Stem Cells* 1997;15(Suppl 2):255–60.
  - [22] Ziegler V, Hemprich A. Facial cleft birth rate in former East Germany before and after the reactor accident in Chernobyl. *Mund Kiefer Gesichtschir* 1999;3:195–9.
  - [23] Koerblein A, Kuchenhoff H. Perinatal mortality in Germany following the Chernobyl accident. *Radiat Environ Biophys* 1997;36:3–7.
  - [24] Luning G, Scheer J, Schmidt M, et al. Early infant mortality in West Germany before and after Chernobyl. *Lancet* 1989;2:1081–3.
  - [25] Scherb H, Voigt K. The human sex odds at birth after the atmospheric atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities. *Environ Sci Pollut Res Int* 2011;18:697–707.
  - [26] Scherb H, Weigelt E, Brüske-Hohlfeld I. European stillbirth proportions before and after the Chernobyl accident. *Int J Epidemiol* 1999;28:932–40.
  - [27] Scherb H, Weigelt E, Brüske-Hohlfeld I. Regression analysis of time trends in perinatal mortality in Germany, 1980–1993. *Environ Health Perspect* 2000;108:159–65.
  - [28] Sperling K, Neitzel H, Scherb H. Evidence for an increase in trisomy 21 (Down syndrome) in Europe after the Chernobyl reactor accident. *Genet Epidemiol* 2012;36:48–55.
  - [29] Wertenlecker W. Malformations in a Chernobyl-impacted region. *Pediatrics* 2010;125:836–43.
  - [30] Scherb H, Voigt K. Fehlbildungsrate in Bayern vor und nach dem Unfall von Tschernobyl. *Strahlentelex* 2014, 652–653. [http://www.strahlentelex.de/Stx\\_14\\_652-653\\_S01-05.pdf](http://www.strahlentelex.de/Stx_14_652-653_S01-05.pdf). [Accessed April 16, 2016].
  - [31] Scherb H, Weigelt E. Congenital malformation and stillbirth in Germany and Europe before and after the Chernobyl nuclear power plant accident. *Environ Sci Pollut Res*, Special Issue 2003;1:117–25.
  - [32] Scherb H, Kusmierz R, Voigt K. Increased sex ratio in Russia and Cuba after Chernobyl: a radiological hypothesis. *Environ Health* 2013; 12:63.
  - [33] Grosche B, Irl C, Schoetzau A, et al. Perinatal mortality in Bavaria, Germany, after the Chernobyl reactor accident. *Radiat Environ Biophys* 1997;36:129–36.
  - [34] Fukumoto M, Voigt K, Kusmierz R, Scherb H. Folgen von Fukushima: Totgeburten und Säuglingssterblichkeit in Japan. *Strahlentelex*. 2014, 650–651. [http://www.strahlentelex.de/Stx\\_14\\_650-651\\_S03-06.pdf](http://www.strahlentelex.de/Stx_14_650-651_S03-06.pdf). [Accessed April 16, 2016].
  - [35] Körblein A. InfantmortalityafterFukushima. *Strahlentelex*. 2014, 668–669. [http://www.strahlentelex.de/Koerblein\\_Fukushima-update\\_engl.pdf](http://www.strahlentelex.de/Koerblein_Fukushima-update_engl.pdf). [Accessed April 16, 2016].
  - [36] Koya PK, Jaikrishan G, Sudheer KR, et al. Sex ratio at birth: scenario from normal- and high-level natural radiation areas of Kerala coast in south-west India. *Radiat Environ Biophys* 2015;54:453–63.
  - [37] Scherb H, Grech V, Kusmierz R, et al. Letter to the Editor “Radiation and Environmental Biophysics”: Comment on “Sex ratio at birth: scenario from normal- and high-level natural radiation areas of Kerala coast in south-west India” by Koya PK, Jaikrishan G, Sudheer KR, Andrews VJ, Madhusoodhanan M, Jagadeesan CK, Das B. *Radiat Environ Biophys*. 2016 Mar;55 (1):3-4. doi: 10.1007/s00411-015-0627-0. Epub 2015 Dec 28.
  - [38] Spycher BD, Lupatsch JE, Zwahlen M, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. *Environ Health Perspect* 2015;123:622–8.
  - [39] Sermage-Faure C, Laurier D, Goujon-Bellec S, et al. Childhood leukemia around French nuclear power plants – the Geocap study, 2002–2007. *Int J Cancer* 2012;131:E769–80.
  - [40] Spix C, Schmiedel S, Kaatsch P, et al. Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980–2003. *Eur J Cancer* 2008;44:275–84.
  - [41] Scherb H, Kusmierz R, Voigt K. Human sex ratio at birth and residential proximity to nuclear facilities in France. *Reprod Toxicol* 2016;60: 104–11.
  - [42] Scherb H, Kusmierz R, Sigler M, et al. Modeling human genetic radiation risks around nuclear facilities in Germany and five neighboring countries: A sex ratio study. *Environ Model Software* 2016;79:343–53.
  - [43] Tsuda T, Tokinobu A, Yamamoto E, et al. Thyroid cancer detection by ultrasound among residents ages 18 years and younger in Fukushima, Japan: 2011 to 2014. *Epidemiology* 2016;27:316–22.
  - [44] Suzuki S. Re: thyroid cancer among young people in Fukushima. *Epidemiology* 2016;27:e19.
  - [45] Hayakawa Y. Radiation contour map of the Fukushima Daiichi accident. Kipuka.blog70.fc2.com By Yukio Hayakawa, Gunma University. 2011, <http://www.hayakawayukio.jp/pub/2011/0911gmap06.jpg>. [Accessed April 16, 2016].
  - [46] Anonymus. Great East Japan Earthquake and evacuation information and support information site (Japanese). 2016, <http://hinansyameibo.seesaa.net/category/10331937-1.html>. [Accessed April 16, 2016].
  - [47] Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.
  - [48] Scherb H, Voigt K. Analytical ecological epidemiology: exposure-response relations in spatially stratified time series. *Environmetrics* 2009;20:596–606.
  - [49] Carlstein E, Müller HG, Siegmund D. *Change-Point Problems*. Bethesda: Institute of Mathematical Statistics; 1994.
  - [50] Scherb H. Letter to the editor. *Int J Risk Saf Med* 2015;27:107–10.
  - [51] Auvinen A, Vahteristo M, Arvela H, et al. Chernobyl fallout and outcome of pregnancy in Finland. *Environ Health Perspect* 2001;109: 179–85.
  - [52] World Health Organisation. Ottawa Charter for Health Promotion. 1986. [www.euro.who.int/de/publications/policy-documents/ottawa-charter-for-health-promotion,-1986](http://www.euro.who.int/de/publications/policy-documents/ottawa-charter-for-health-promotion,-1986). [Accessed August 12, 2016].
  - [53] Leischik R, Dworak B, Strauss M, et al. Plasticity of health. *Ger J Med* 2016;1:1–7.