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DOWN SYNDROME, TEMPORAL VARIATION AND FALLOUT RADIATION REVISITED: STATISTICAL EVIDENCE

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Abstract: To revisit a study on the prevalence of Down Syndrome (DS) in the Fylde of Lancashire and ionizing radiation, using new birth data that allow better control for maternal age. Associations between ionizing radiation and DS prevalence have been controversial. Some studies link temporal variation in prevalence to ionizing radiation; others do not. Cases were ascertained in a prospective survey of major congenital malformations among residents in the Fylde of Lancashire between 1957 and 1991. New data on the birth maternal age distribution in the Fylde were obtained from the Office for National Statistics for most of the study period. Temporal clusters in prevalence rates were again detected using the Poisson log linear models used to measure the association between prevalence and ionizing radiation from atomic fallout. Significant effects of fallout radiation were found when maternal age was both controlled and not controlled for. Two DS prevalence peaks occurred during the study period. The first started in June

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1958 and lasted for five months. The second lasted longer, starting in October 1962 and ending in August 1964. Although these peaks corresponded to peaks in fallout radiation dosage, they were not significant.

Keywords: down syndrome; trisomy 21; temporal clustering; fallout radiation, Poisson regression; maternal age.
2010 AMS Subject Classification: 62J12, 62P10.

1. INTRODUCTION

A 1994 study conducted in the Fylde of Lancashire, UK, ascertained all cases of Down syndrome (DS) over a 35-year period from 1957 to 1991 and examined the sequence of cases for evidence of temporal clustering. An increase in the prevalence of cases in 1963 and 1964 was observed, and a smaller cluster was also found in 1958. In addition, a significant association between DS prevalence and radiation fallout was found. Full details on the study are provided in Bound et al. [1].

Bound et al. [1] used a relatively crude method of controlling for maternal age; they used only two coarse age groups (< 35 and 35+), maternal age being the only well-established risk factor for DS [2]. Once age was controlled for, the two temporal clusters failed to reach statistical significance, although, when the older age group was analyzed separately, a significant increase was still found for a four-month period in 1958. A significant association between DS conception prevalence rates and fallout radiation was detected both when maternal age was controlled for and when it was not. It is now widely recognized, however, that DS birth prevalence increases smoothly and non-linearly with maternal age from age 16 onwards, with the steepness of the curve increasing as age increases [3]. The two coarse age groups used by Bound et al. [1] are thus a poor approximation to this curve, and their work has been criticized for not controlling properly for maternal age. This study therefore reanalyzes the effect of maternal age in the detection of temporal clusters using new data on normal births obtained from the Office of National Statistics (ONS). A better controlling for age also enables a more accurate assessment of the association between DS prevalence and fallout radiation.

2. MATERIALS

Cases were ascertained as part of a prospective survey (described in detail else- where [4]) of babies with major congenital malformations born to Fylde residents from 1957 to 1991 (details on the data can be found in [1]). There were 167 cases of DS, including five stillbirths and eight terminations, out of 124,015 total births, giving a rate of 1.35 per 1,000 total births.

New information on the birth maternal age distribution in the Fylde was obtained for this study from the ONS for most of the study period. The information provided by ONS varied in quality but still represented a substantial improvement over the maternal age data used in [1]. For 1963 to 1974 and 1983 to 1991, seven age groups were available: <20, 20–24, 25–29, 30–34, 35–39, 40–44, and 45+. For 1975 to 1980 and for 1982, five age groups were available: <20, 20–24, 25–34, 35–44, and 45+. For years prior to 1963 and for 1981, no information was available despite extensive enquiries. We thus supplemented the ONS information with sources used in [1], as follows:

- The General Register Office (GRO) collected data on all births in Blackpool County Borough from 1957 to 1962, disaggregated into two age groups (< 35, 35+); Blackpool births accounted for around 50% of all births.
- For 1981, data were available from the Consultant Hospital Registers (CHR) for Blackpool Victoria hospital, disaggregated into two age groups (<35, 35+); mothers were admitted from all parts of the Fylde and made up approximately 75% of area births in 1981.

Table 1 shows the complexity of the data available on maternal age groups. Data on the effective total dose equivalents to adults from atomic weapons fallout up to 1985 were obtained from a report of the National Radiological Protection Board [5], and figures for the testis up to 1979 came from an additional source [6]. Doses to the ovary are similar to those to the testis. Total adult dose in μSv shows two peaks, one in 1959 (82 μSv) and the second in 1963 (150 μSv), before declining to around 6 μSv by 1985. Dose to the testis shows a similar pattern, with the 1959 peak at 49 μSv and the 1963 peak at 89 μSv before declining to 6 μSv in 1979. A graph of the fallout data can be found in [1].

Table 1: Maternal age groups by period and data source

Data source	**GRO**	**ONS**	**ONS**	**CHR**	**ONS**	**ONS**
Period	1957–62	1963–74	1975–80	1981	1982	1983–91
Age group	< 35	< 20	< 20	< 35	< 20	< 20
	≥ 35	20–24	20–24	≥ 35	20–24	20–24
		25–29	25–34		25–34	25–29
		30–34	35–44		35–44	30–34
		35–39	≥ 45		≥ 45	35–39
		40–44				40–44
		≥ 45				≥ 45

3. Statistical Methods

The completeness of ascertainment for the 35-year period in the Fylde was assessed by comparing local age-specific birth prevalence rates to international rates [7]. Three time periods were examined: 1963–1974, 1975–1980, and 1983–1991, corresponding to the different aggregation levels for maternal age in the data supplied by the ONS. The international rates are given in maternal age intervals of one year. Aggregated rates for an age group were calculated by first estimating the number of total births (by dividing the number of DS cases by the prevalence rate for each age), which was summed over the relevant ages in the age group. Then, the number of DS cases in the age group was summed, and this was divided by the total number of births in the period. This procedure produced aggregated rates, which are slightly different from those presented in Dean et al. [8].

Table 2 below gives details on the birth prevalence rates for the Fylde and compares them to the international rates. A one-sample χ^2 test of the Fylde rates against the expected numbers (assuming the international rates are accurate) showed no significant differences between the Fylde rates and the international rates. The standardized morbidity ratio (SMR) for DS was slightly elevated in the 1963–1974 period and was lower in the latter two time periods.

Table 2: Down syndrome birth prevalence rates (number of cases) in the Fylde compared to international rates

Maternal age	**International rates**	**Fylde 1963–74**	**Fylde 1983–91**	**Maternal age**	**International rates**	**Fylde 1975–80**
<20	6.7	4.1(2)	9.8(3)	**<20**	6.7	12.1(2)
20–24	6.8	6.1(10)	3.1(3)	**20–24**	6.8	9.4(5)
25–29	8.3	8.2(12)	6.3(7)	**25–34**	10.3	10.6(10)
30–34	14.7	14.7(11)	11.5(7)	**35–44**	60.1	35.1(4)
35–39	40.1	61.5(22)	48.2(10)	**≥ 45**	430.4	0(0)
40–44	128.4	93.9(9)	162.2(6)			
≥ 45	430.4	441.2(3)	0(0)			
χ2 test		5.60	4.56			3.15
df		6	6			4
p-value		0.47	0.60			0.53
SMR		1.027	0.890			0.826

The analysis of the data followed the same three steps used in [1]. We first examined the consistency of the data on total births over time, then examined the data to see if rate spikes could be identified in the time series, and finally examined the association between the DS rates and ionizing radiation.

The first step was thus determining whether the ONS data on total births could be supplemented by the poorer-quality data for 1957 to 1962 and for 1981, which came from different sources. We used the rates for the proportion of births to mothers aged 35 and the rates over total births, the only age cutpoint that is common across the three series. We tested whether the proportions could be taken as one continuous series by using a technique similar to that used in [1]: fitting a statistical model where the expected proportion of births to women over 35 in the Fylde was a smooth unknown function of time f, and where the source of the data (a three-level factor) was included as an additional term, shifting the function up or down (see Figure 1). The model was fitted in R [9] using a natural cubic spline smoother for the unknown function f. The number of degrees of

freedom (df) was determined by fitting a sequence of models including the factor source with different smoothing degrees of freedom; the model with the smallest value of the Bayesian information criterion (BIC) was found to be at 4 df. The deviance of this model including the source factor was 31.44 on 28 df; excluding the source factor gave a deviance of 32.51 on 30 df. The effect of the dataset source was therefore small (1.07 on 2 df; p-value = 0.58), which indicated that no bias occurred due to the data source.

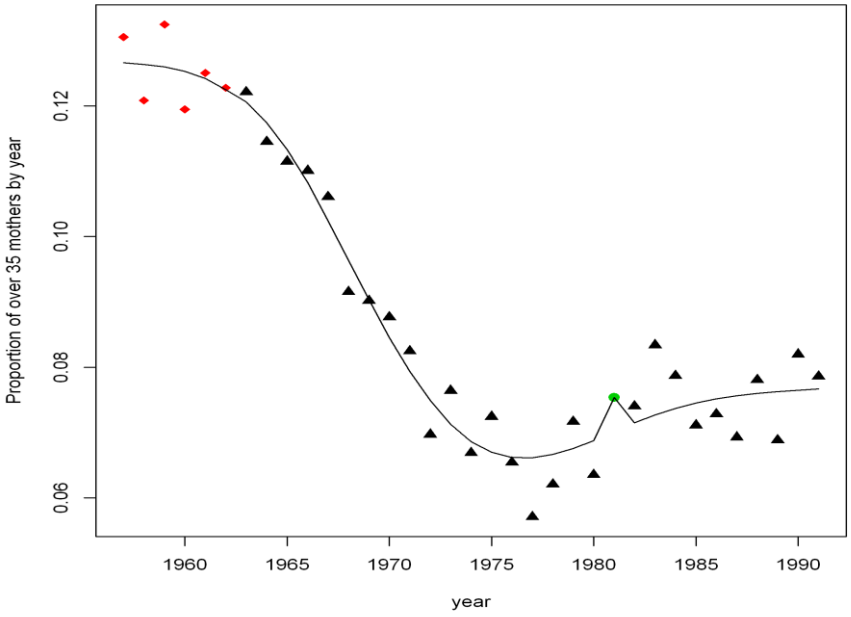

Figure 1: Observed and fitted proportions of births to over 35 mothers by year, showing information source (♦ GRO, ▲ ONS, • CHR). Fitted model is a cubic spline smoother with a "source of information" factor.

The next step was determining whether temporal clustering existed in the data series. Although several methods have been proposed to affect a temporal clustering of rate data [10,11,12,13,14,15], none is appropriate when there is a need to control for the effect of an important covariate that varies in detail over the period of the study. As before, we thus adopted an approach based on Poisson log-linear regression. Our approach considers that we wish to analyze the data according to the date of the last menstrual period (LMP) rather than the date of

birth, and also allows for the complication of differing age group categorizations.

We start the analysis by choosing those cases with LMP dates between January 1957 and December 1990 (inclusive), giving 408 months of data. Each LMP month i has an age group categorization g associated with it, which is defined as the level of aggregation of the total birth information available nine months into the future. This categorization g will have either j = 2 (g = 1), j = 5 (g = 2), or j = 7 (g = 3) levels. We control for the differential birth prevalence rates by including a separate parameter αjg for each categorization. Each month contributes to the estimation of a subset of these αjg. We also include a linear trend term to allow for possible long-term changes in overall prevalence rates. If we now define the number of DS cases in LMP month i for age group j as cij(g) and the total number of births nine months hence as bIj(g) with I = i + 9, we can write the Poisson log linear model[1] (assuming no temporal clustering) as follows:

$$\log\left(\mu_{ij(g)}\right) = \log\left(b_{Ij(g)}\right) + \beta_0 + \beta_1 i + [g \in 1]\alpha_{j1} + [g \in 2]\alpha_{j2} + [g \in 3]\alpha_{j3} \quad (1)$$

with $c_{ij(g)} \sim \text{Poisson}(\mu_{ij(g)})$. In this model, β_1 estimates the long-term trend.

We now account for temporal clustering by defining a "spike" of raised or lowered prevalence starting at month m and lasting l months. We limit the spike length to a three-month minimum and 36-month maximum duration. We thus examine the series for short-term spikes or raised or lowered prevalence rates once age is controlled for. For fixed m and l, the spike can be defined as a dummy variable and be included in the model, which now becomes

$$\log\left(\mu_{ij(g)}\right) = \log\left(b_{Ij(g)}\right) + \beta_0 + \beta_1 i + [g \in 1]\alpha_{j1} + [g \in 2]\alpha_{j2} + [g \in 3]\alpha_{j3} + \beta_2 \,\text{SPIKE}(m, l) \quad (2)$$

We estimate m, *l*, and the other model parameters through a grid search over the range m = 1...408 and *l* = 3...36. For fixed m and *l*, the model can be fitted and the deviance of the resulting fit calculated. The maximum likelihood estimates of m and l are those values producing the largest reduction in scaled deviance between models (1) and (2). Note that exp(β_2) denotes the prevalence

[1] For a more information on Poisson regression modeling, see, e.g., [36,37,38,39].

rate ratio of DS in the spike period.

Once the best spike has been found, the process can be repeated by searching for a second spike. The first spike is included in the model specification, and a new grid search estimates the position of a second spike in the model, now calculating differences in deviance between the model with two spikes and the model with one. We continue with this procedure until the deviance differences are small.

The significance of the spikes detecting temporal clustering was again assessed by simulation. We simulated 99 sets of Poisson counts from model (1), which assumed only a linear trend and had no temporal clustering. We then fitted a spike model to each of the datasets and calculated the maximum deviance difference for each. These deviance differences provide a distribution of the deviance changes under the null hypothesis of no temporal clustering. Examining the position of the "spike" deviance differences on the observed data with the ranked order of simulated deviance differences provides a p-value [16].

Finally, the effect of ionizing radiation (measured by either the estimated total dose equivalent or the estimated dose to the testis) is assessed through a set of separate log-linear models, this time examining the yearly number of DS counts cij and total births bij in a specific LMP year i and age group j, then including ionizing radiation as an explanatory variable in the log linear models:

$$\log(\mu_i) = \log(b_j) + \beta_0 + \beta_1 \mathrm{RADIATION_i}$$

for the analysis uncontrolled for age and

$$\log(\mu_{ij(g)}) = \log(b_{Ij(g)}) + [g \in 1]\alpha_{j1} + [g \in 2]\alpha_{j2} + [g \in 3]\alpha_{j3} + \beta_1 \mathrm{RADIATION_i}$$

for the data disaggregated by age group. To assess significance, the deviance differences from the models including and excluding ionizing radiation are then calculated and compared to a chi-squared distribution on one degree of freedom.

4. RESULTS

Table 3 reports the detected peaks and troughs. Two troughs and two peaks appear over the study period. The table shows the following. The first spike found was a trough (model 2), which detected a lower DS rate from April 1976 to February 1978. This gave a deviance change of 15.79 (p-value = 0.10). The next spike found was a peak (Model 3); the next was a trough (Model 4).

We now focus on the peaks. The first peak started in June 1958 and lasted for five months until October 1958. The prevalence rate ratio gives the multiplicative increase of the prevalence rate. For the first peak, this is estimated at 5.212, indicating a risk increase of more than five times in this period over the baseline rate for each age group. The deviance difference is 14.28, which is not significant. The second peak was smaller and lasted longer, from October 1962 to August 1964. The prevalence rate ratio was estimated at 2.489, giving a raised prevalence of nearly two and a half times in this period over the baseline.

Table 3: Peaks and troughs detected in prevalence of Down syndrome

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
No of Peaks / Thtroughs	**0**	**1**	**2**	**3**	**4**
Prevalence rate ratios exp (β_2): **Trough 1** **Peak 1** **Trough 2** **Peak 2**			 **5.212**		 **2.489**
Location of Trough 1 **Location of Peak 1** **Location of Trough 2** **Location of Peak 2**		Apr 1976 for 23 m	 Jun 58 for 5 m	 Jan 84 for 18 m	 Oct 62 for 23 m
Deviance	798.74	782.95	768.66	755.98	744.76
Change in deviance		15.79	14.28	12.69	11.21
p-value		0.10	0.20	0.41	0.68

Table 4 shows the results of fitting the radiation log linear models. The effect of the total adult dose is found to be significant for both the analysis that did not control for age (p-value = 0.0035) and that which did (p-value = 0.0172). The radiation dose to testis is significant in both analyses.

Table 4: Effect of radiation on prevalence of Down syndrome

Model	β_1	exp (β_1)	Change in deviance and df	p-value
Not controlling for maternal				
Age				
Adult total dose equivalent	0.0059 (0.0019)	1.060	8.52 on 1 df	0.0035
Adult dose to testis	0.01002 (0.0033)	1.105	8.65 on 1 df	0.0033
Controlling for maternal				
Age				
Adult total dose equivalent	0.0052 (0.0021)	1.053	5.67 on 1 df	0.0172
Adult dose to testis	0.0087 (0.0037)	1.091	5.31 on 1 df	0.0212

The prevalence rate ratio associated with an increase in radiation of 10 microsieverts (μSv) is estimated by $\exp(10\beta_1)$. For the age-controlled analysis, this amounts to an increase of 10 μSv in total adult dose associated with a DS prevalence of about 5%. Similarly, an increase of 10 μSv in testis dose is associated with an increase in DS prevalence of around 9%.

5. Discussion and Conclusion

The effect of radiation on DS risk is controversial. Much evidence has accumulated since our original study. A case-control study [17] found no association between parental occupational exposure to low-level ionizing radiation and DS risk, and an investigation of the impact of Chernobyl on the prevalence of congenital anomalies in 16 regions of Europe [18] concluded that the increasing prevalence of DS in the 1980s was probably unrelated to Chernobyl. However, two studies in Germany showed a significant increase in DS prevalence in January 1987, which the authors related causally to the Chernobyl reactor accident [19,20]. In addition, a study in Belarus [21] showed a very significant DS cluster months after the Chernobyl accident, which suggested that exposure at conception to substantially increased irradiation dose rates is related to a doubling

of DS prevalence at birth. A more recent study [22] conducted in seven European countries investigated the association between DS prevalence and Chernobyl fallout, finding that the observed DS increase after the accident was likely causally related.

Table 5 shows the number of atmospheric tests carried out by the US, the former USSR, the UK, France, and China [23] These countries conducted 368 tests between 1956 and 1963. Between 1956 and 1958, 184 atmospheric tests occurred, with most occurring in 1962 (117). The peaks in the tests shown in this table in 1958 and 1962 occurred one year before the peaks in effective total dose equivalents from fallout in the UK used in our analysis.

The US, USSR, and the UK stopped atmospheric tests after 1963. However, atmospheric testing continued in France and China, neither of which signed the Limited Test Ban Treaty (LTBT) until 1974 and 1980 respectively [24].

Table 5: Number of atmospheric nuclear tests for five nuclear countries

Year	US	USSR	UK	France	China	Total
1956	18	9	6	0	0	**33**
1957	27	16	7	0	0	**50**
1958	62	34	5	0	0	**101**
1959	0	0	0	0	0	**0**
1960	0	0	0	3	0	**3**
1961	0	58	0	1	0	**59**
1962	39	78	0	0	0	**117**
1963	4	0	0	0	0	**4**
1964	0	0	0	0	1	**1**
Total	**150**	**195**	**18**	**4**	**1**	**368**

Our study has several limitations. The first is its failure to control for parity. However, its effect on DS risk is debatable, with most studies showing a marginal effect at most. Schimmel et al. [25] suggested that increased parity was an independent risk factor for DS. However, this work has been criticized; first, because age was not completely controlled [26], second, because it provided

no evidence of a parity effect on incidence [27]. Support for the parity effect came from a Swedish study that found a statistically significant risk decrease for primiparas and a significant risk increase for grand multiparas (5+) [28]. This suggested that the effect of maternal age was marginal. However, many studies have shown that the association with parity was only a reflection of the effect of age [29,30,31] and that the parity effect disappeared once the maternal age effect was taken into account.

Other risk factors could be controlled for, but, again, the evidence base is not strong. A recent review article on DS risk factors identified both habitual and epidemiological risk factors [32], including the use of contraceptive pills, maternal smoking, and periconceptional alcohol use. None of these was collected in our study and thus cannot be controlled for.

Our earlier paper discussed other sources of radiation that may need to be considered. No evidence was found in that paper of an increase in medical radiation in the main hospital serving the Fylde region. Discharges from the nuclear reprocessing plant at Sellafield showed a peak, not in the 1950s or 1960s, but in the 1970s [33]. Background radon radiation is very low in the Fylde area [34], with less than 1% of homes at or above the action level of 200 becquerels per cubic meter, which is unlikely to change over time or by locality.

This study found an association between DS prevalence and fallout radiation, which remains when maternal age is controlled for. Moreover, the peaks in fallout radiation coincide with the two nonsignificant peaks found in the temporal analysis of monthly DS rates, one in 1958 and the other in 1962/63. These peaks were associated with irradiation nuclear testing fallout even after maternal age was controlled for. It is important to continue monitoring the effects of radiation and their association with DS. Data from the Fukushima area in Japan following the 2011 tsunami will be important in this regard. As a future work, one can extend this study to include multiple countries, especially after the spread of the COVID-19 pandemic [35].

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

REFERENCES

[1] J.P. Bound, B.J. Francis, P.W. Harvey, Down's syndrome: prevalence and ionising radiation in an area of north west England 1957-91. J. Epid. Community Health, 49 (1995), 164-170.

[2] E.B. Hook, Epidemiology of down syndrome; in S.M. Peuschel, J. Rynders (eds): Down Syndrome: Advances in Biomedicine and the Behavioural Sciences. Cambridge, Ware Press, 1982, pp 11–88.

[3] I. Bray, D.E. Wright, C. Davies, E.B. Hook. Joint estimation of down syndrome risk and ascertainment rates: A meta-analysis of nine published data sets. Prenat. Diagn. 18 (1998), 9-20.

[4] J.P. Bound, P.W. Harvey, B.J. Francis. Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J. Epid. Community Health, 43 (1989), 330-342.

[5] J. Dionian, S.L. Wan, A.D. Wrixon. Radiation doses to members of the public around AWRE, Aldermaston, ROF, Burghfield and AERE, Harwell. London: HMSO49 (1987), (NRPB-R202).

[6] S.C. Darby, J.H. Olsen, R. Doll, et al. Trends in childhood leukaemia in the Nordic countries in relation to fallout from atmospheric nuclear weapons testing. Br. Med. J. 304 (1992), 1005-1009.

[7] H.S. Cuckle, N.J. Wald, S.G. Thompson. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. BJOG: Int. J. Obst. Gynaecol. 94 (1987), 387-402.

[8] G. Dean, N.C. Nevin, M. Mikkelsen, et al. Investigation of a cluster of children with Down's syndrome born to mothers who had attended a school in Dundalk, Ireland, Occup. Environ. Med. 57 (2000), 793–804.

[9] R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; (2012) www.R-project.org.

[10] T. Tango, The detection of disease clustering in time. Biometrics, 40 (1984), 15- 26.

[11] D.J. Best, J.C. Rayner, Disease clustering in time. Biometrics, 47(1991), 589-593.

[12] F. Edere, M. Myers, N. Mantel, A statistical problem in space and time: Do leukemia cases come in clusters? Biometrics, 20 (1964), 626-638.

[13] J. Naus, The distribution of the size of the maximum number of points on a line. J. Amer. Stat. Assoc. 60 (1965), 532-538.

[14] G. Knox, The detection of space-time interactions. J. R. Stat. Soc. Ser. C (Appl. Stat.), 13 (1964), 25-230.

[15] P. Boberson, Controlling for time-varying population distributions in disease clustering studies. Amer J. Epidemiol. 132 (1990), 131-135.

[16] A.C. Hope, A simplified Monte Carlo significance test procedure. J. R. Stat. Soc. Ser. B (Methodol.), 30 (1968), 582-598.

[17] L.E. Sever, E.S. Gilbert, N.A. Hessol, et al., A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. Amer. J. Epidemiol. 127 (1988), 226-242.

[18] H. Dolk, R. Nichols, Evaluation of the impact of Chernobyl on the prevalence of congenital anomalies in 16 regions of Europe. EUROCAT working group. Int. J. Epidemiol. 28 (1999), 941-948.

[19] K. Sperling, J. Pelz, R.D. Wegner, et al., Frequency of trisomy 21 in Germany before and after the Chernobyl accident. Biomed. Pharmacother. 45 (1991), 255-262.

[20] K. Sperling, J. Pelz, R. Wegner, et al., Significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident: temporal correlation or causal relation? BMJ. 309 (1994), 158-161.

[21] I.A. Zatsepin, P.B. Verger, E.C. Robert-Gnansia, et al., Down syndrome time-clustering in January 1987 in Belarus: Link with the Chernobyl accident? Reprod. Toxicol. 24 (2007), 289–295.

[22] K. Sperling, H. Neitzel, H. Scherb, Evidence for an increase in Trisomy 21 (Down Syndrome) in Europe after the Chernobyl reactor. Genet. Epidemiol. 36 (2012), 48-55.

[23] Natural Resources Defense Council. Table of known nuclear tests worldwide: 1945-69 1970-96. (2013) www.nrdc.org/nuclear/nudb/datab15.asp.

[24] W. Burr, H.L. Montford, editors. The Making of the Limited Test Ban Treaty, 1958-1963. National Security Archive; (2003) https://nsarchive2.gwu.edu/NSAEBB/NSAEBB94/#2.

[25] M.S. Schimmel, A.L. Eidelman, C. Hammerman, et al., Increased parity and risk of trisomy 21: Review of 37110

live births. BMJ. 314 (1997), 720-721.

[26] R.J. Lilford, Commentary: Down's syndrome and parity, BMJ. 314 (1997), 721–721.

[27] P.O.D. Pharoah. Increased parity and risk of trisomy 21. BMJ. 314 (1997), 314-1760.

[28] K. Källén, Parity and Down syndrome. Amer. J. Med. Genet. 70 (1997), 196-201.

[29] E.E. Castilla, J.E. Paz, Parity and Down's syndrome. Lancet. 344 (1994), 1645-1646.

[30] J.E. Haddow, G.E. Palomaki. Multiparity and Down's syndrome. Lancet. 344 (1994), 956.

[31] A. Chan, K.A. McCaul, R.J. Keane, et al. Effect of parity, gravidity, previous miscarriage, and age on risk of Down's syndrome: Population based study. BMJ. 317 (1998), 923-924.

[32] S. Ghosh, S.K. Dey, Risk factors for Down Syndrome birth: Understanding the causes from genetics and epidemiology. In: Dey SK, editor. Down Syndrome. InTech (2013), 149-172.

[33] D. Black, Investigation of the possible increased incidence of cancer in West Cumbria. Report of the Independent Advisory Group. London: HMSO (1984), 47-53.

[34] Public Health England. UK maps of radon. (2019) https://www.ukradon.org/information/ukmaps.

[35] F.A. Awwad, M.A. Mohamoud, M.R. Abonazel, Estimating COVID-19 cases in Makkah region of Saudi Arabia: Space-time ARIMA modeling. PLoS ONE 16(2021), e0250149.

[36] E.A. Rady, M.R. Abonazel, I. M. Taha, A new biased estimator for zero-inflated count regression models, J. Mod. Appl. Stat. Meth. In press.

[37] A.F. Lukman, B. Aladeitan, K. Ayinde, M.R. Abonazel, Modified ridge-type for the Poisson regression model: simulation and application, J. Appl. Stat. (2021), https://doi.org/10.1080/02664763.2021.1889998.

[38] M.R. Abonazel, O.M. Saber, A comparative study of robust estimators for Poisson regression model with outliers. J. Stat. Appl. Probab. 9 (2020), 279-286.

[39] M.R. Abonazel, S.M. El-Sayed, O.M. Saber, Performance of robust count regression estimators in the case of overdispersion, zero inflated, and outliers: simulation study and application to German health data. Commun. Math. Biol. Neurosci. In press.