Binary data on radiation-related brain damage prenatally exposed and statistical threshold model

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Exposure to ionizing radiation has been testified to have harmful effects on the developing human brain, particularly in the highly vulnerable period of 8-15 weeks after ovulation as an increased frequency of severe mental retardation. However, the distribution of cases of severe mental retardation suggests a threshold in the low dose region. Data are composed of a binary (1, 0) for mentally retarded or normal individuals. The statistical approaches with a threshold are conceivable for a simple, odds, logistic and Gompertz regression models. Estimation of threshold and 100(1-α)% confidence limits are derived from the maximum likelihood technique based on a profile approach.

Keywords: mental retardation, threshold model, prenatal exposure, profile approach, atomic bombings

1. Introduction

Many epidemiological studies generate data in which the response measurement for each individual may take one of only two possible values. Such a response is called a binary response. In this study suitableness or reasonableness of several statistical models based on binary data would be clarified by the relationship of radiation exposure to the occurrence of severe mental retardation, and specifically, a statistical technique provides better or more reasonable estimates of the threshold of gestational groups with radiation sensitivity. The human brain is arguably the most complex of all organs of the body. It is known in radiobiology that actively dividing cells are more sensitive to ionizing radiation than cells that have completed division or differentiated cells that seldom undergo cell division. The effects of ionizing radiation are customarily viewed as either "stochastic" if the probability of their occurrence is a direct function of dose, or "deterministic

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(nonstochastic)" if it is the severity of the effect which is dose-dependent (ICRP 1986). It is of great interest to evaluate dose-response models with or without a threshold with regard to these data on severe mental retardation. This matter of threshold is central to radiation protection, however, and warrants more exhaustive study. Several models involve binomial types of an odds regression, a Gompertz regression, a logistic regression, a one-hit regression, and a simple regression. The likelihood of observing the entire data set in these models fitted is

$$L = \Pi (P)^y (1-P)^{1-y} = f(\beta_0, \beta_1, \beta_2, \ldots, \beta_k, T_1, T_2, \ldots, T_m)$$

in an individual binary-response array, where the likelihood is a function of $\beta_0, \beta_1, \beta_2, \ldots, \beta_k$ of an intercept and k observations with thresholds $T_1, T_2, \ldots, T_m$ ($k < m$) and y is 1 for abnormal cases and 0 for others.

2. Study Materials

2.1 Applied data

The clinical sample used here consists of 1565 prenatally exposed individuals born between 6 (Hiroshima) and 9 (Nagasaki) August 1945 and 31 May 1946. Thirty cases of severe mental retardation have been recognized among these 1565 survivors (Table 1), all were diagnosed before the age of 17 at the ABCC clinical facility (Otake et al. 1987, 1996). The diagnoses of severe mental retardation were based on clinical findings, not on IQ. A child was diagnosed as severely mentally retarded if he or she was "unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized" (Wood et al. 1967). Figure 1 shows the distribution of the 1565 individuals including the 30 mentally retarded cases by gestational weeks postovulation and DS86 uterine dose. Almost all of the mentally retarded cases occur among the individuals exposed in the 8th through the 25th week postovulation.

2.2 Gestational age of pregnancy

The most important single factor in determining the nature of the insult to the developing cranium and brain from exposure to ionizing radiation is developmental age expressed either in post-ovulatory weeks. Days of pregnancy are based upon the inferred first day of the last menstrual period, and have been calculated as

follows:

Days of pregnancy = 280 - (days between 6 or 9 August 1945 and the date of birth),

where the mean duration of pregnancy is taken to be 280 days. The dates of birth are based on the dates obtained in interviews with the subjects or their mothers and not on the birth reports found in the household registers (koseki). To obtain postovulatory age (weeks after ovulation) (G), 14 days were subtracted from the 'days of pregnancy age at time of bombings (ATB)' (Y), and in days was converted to age in weeks by dividing by seven, G = (Y - 14)/7, G was presumed to be zero if it was negative.

Table 1. Distribution of mentally retarded cases by gestational age and DS86 uterine dose.

Gestational age (weeks)	Item	Total	Radiation doses in gray				
			≤0.01	0.01–0.09	0.10–0.49	0.50–0.99	≥1.00
0–7	Subjects	288	205	42	33	6	2
	Retarded	1	1	0	0	0	0
	Percent(%)	0.35	0.49	0.0	0.0	0.0	0.0
8–15	Subjects	390	255	46	61	16	12
	Retarded	19	2	2	2	4	9
	Percent(%)	4.9	0.78	4.3	4.3	25.0	75.0
16–25	Subjects	452	309	60	59	16	8
	Retarded	6	2	1	0	0	3
	Percent(%)	1.3	0.65	1.7	0.0	0.0	37.5
≤26	Subjects	435	300	64	62	5	4
	Retarded	4	4	0	0	0	0
	Percent(%)	9.2	1.3	0.0	0.0	0.0	0.0
Total	Subjects	1565	1069	212	215	43	26
	Retarded	30	9	3	2	4	12
	Percent(%)	1.9	0.84	1.4	0.93	9.3	46.27

2.3 DS86 dose estimation

Maternal uterine absorbed doses, based on the DS86 dosimetry system (DS86), are used in the present study since fetal doses are not available. The DS86 dose estimates were newly computed and added in 1989 (Roesch 1987). When detailed shielding histories are available, the DS86 dose estimates are derived from a

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direct evaluation of the effects of body orientation, posture, and dispersion of energy occurring in the tissues or by structures between the burst point and the individual.
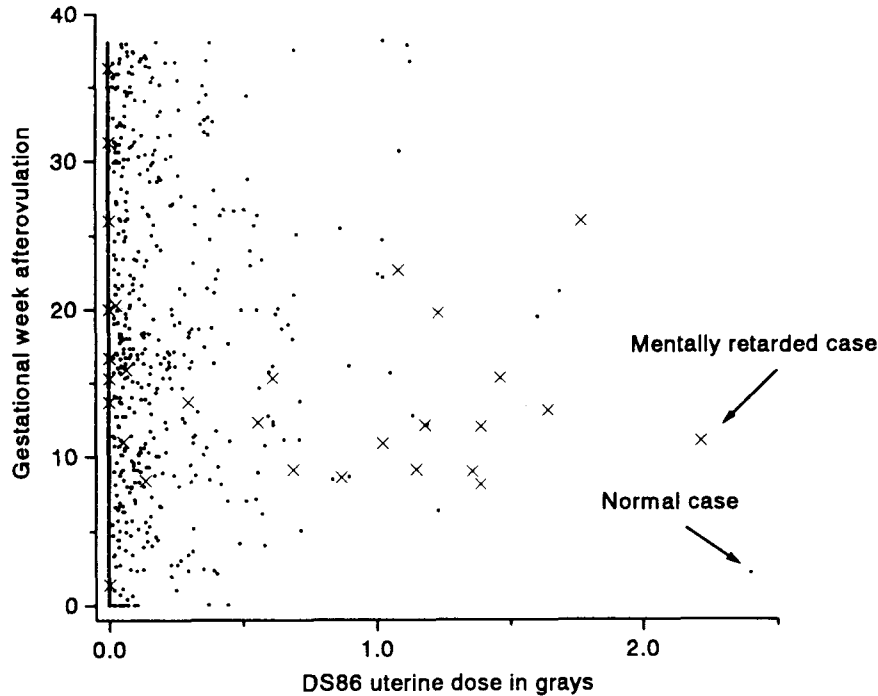

Fig. 1 Distribution of 1535 normal and 30 mentally retarded cases.
Note that two cases overlap with 31.3 gestational week and zero dose.

3. Development of the brain

Different functions of the human brain are localized in different structures and the differentiation of these takes place at different stages of development and over different periods of time. The embryonic stage is generally considered to be the period from fertilization through the first 56 days thereafter, i.e., up to and including the 8th week after ovulation. The fetal stage is the period after the 8th week. Most human organs have completed their initial development by the 8th week postovulation but histogenesis may continue much longer. This is particularly true of the brain where development progresses rapidly in the 8-15 week period after fertilization. To reflect the known phases in the normal development of the brain gestational ages in weeks are often grouped. Four age categories, measured from the presumed moment of fertilization, have been used: 0-7, 8-15, 16-25, and 26 weeks or more. These correspond to the following developmental events. In the first period, the precursors of the neurons and neuroglia, the two principal types of cells that make up the cerebrum, have emerged and are mitotically active. In the second period, a rapid increase in the number

of neurons occurs; they migrate to the cerebral cortex and lose their capacity to divide, becoming perennial cells (Rakic 1975). In the third period, differentiation in situ accelerates, synaptogenesis that began about the 8th week after fertilization increases, and the definitive cytoarchitecture of the brain unfolds. The fourth period is largely one of continued architectural and cellular differentiation and synaptogenesis; however, in this period a more rapid growth of the cerebellum occurs.

4. Statistical models

Suppose that on each individual we have an observation that takes one of two possible forms. The data are composed of binary elements which take on the value 1 for mentally retarded and 0 normal cases. The statistical methods used involve the fitting of an odds regression model, a Gompertz regression model, a logistic regression model, a one-hit regression model and a simple regression model, assuming a binomial distribution. The goodness of fit of a particular model is determined by the deviance of the expected values (based on that model) from the observed ones. The likelihood of observing the entire data set in the fitted models is $L = \Pi(P)^y(1-P)^{1-y} = f(\alpha_H, \alpha_N, \beta_{sd}, T_s, \beta_{td}, T_t)$ for a linear dose–response relationship or

$L = \Pi(P)^y(1-P)^{1-y} = f(\alpha_H, \alpha_N, \beta_{sd}, \beta_{sd^2}, T_s, \beta_{td}, \beta_{td^2}, T_t)$ for a linear–quadratic dose–response

relationship in an individual binary–response array, where $\alpha_H, \alpha_N, \beta_{sd}, T_s, \beta_{td}, T_t$ or $\alpha_H, \alpha_N, \beta_{sd}, \beta_{sd^2}$,

$T_s, \beta_{td}, \beta_{td^2}, T_t$ are a constant term of all cases, α_H in Hiroshima and α_N in Nagasaki, the linear dose effect of the 8–15 week period β_{sd} (suffix: s), and linear dose effect of the 16–25 week period β_{td} (t), respectively. D_s and T_s and D_t and T_t are DS86 doses and thresholds of the 8–15 week and the 16–25 week periods, respectively, and the $100(1-\alpha)\%$ confidence limits were obtained by the step likelihood method. The threshold models fitted here can be expressed as follows:

Odds ratio regression (model I) : $P/(1-P) = \ln(\alpha_H + \alpha_N + \beta_{sd}(D_s - T_s) + \beta_{td}(D_t - T_t))$

Gompertz regression (model II) : $\ln(-\ln(P)) = \alpha_H + \alpha_N + \beta_{sd}(D_s - T_s) + \beta_{td}(D_t - T_t)$

Logit regression (model III) : $\ln\{P/(1-P)\} = \alpha_H + \alpha_N + \beta_{sd}(D_s - T_s) + \beta_{td}(D_t - T_t)$

One-hit regression (model IV) : $P = 1 - exp - [\alpha_H + \alpha_N + \beta_{sd}(D_s - T_s) + \beta_{td}(D_t - T_t)]$

Simple regression (model V) : $P = \alpha_H + \alpha_N + \beta_{sd}(D_s - T_s) + \beta_{td}(D_t - T_t)$

where $\beta_{sd}(D_s-T_s)$ for a linear–response relationship in 8–15 week period and $\beta_{td}(D_t-T_t)$ in 16–25 week

period is zero when $D_s<T_s$ or $D_t<T_t$. Instead of a linear–response function Models I to V become a linear–

quadratic response relationship with $\beta_{sd}(D_s-T_s)+\beta_{sd^2}(D_s-T_s)^2$ in the former or $\beta_{td}(D_t-T_t)+\beta_{td^2}(D_t-T_t)^2$

in the latter. The maximum likelihood estimates (MLE) of parameters based on the binomial regression models

are readily obtained by the Newton–Raphson iterative method,

that is,

$$[\beta_l(r+1)] = [\beta_l(r)] - \left[\frac{\partial^2 \log L}{\partial \beta_l \partial \beta_v}\bigg|_{(r)}\right]^{-1}\left[\frac{\partial \log L}{\partial \beta_l}\bigg|_{(r)}\right] \quad for \quad r = 0, 1, \ldots, \omega,$$

where $l, v = 1, \ldots, \tau$ and $\dfrac{\partial^2 \log L}{\partial \beta_l^2}\bigg|_{(r)} = 0$ for $l = v$, and $\dfrac{\partial^2 \log L}{\partial \beta_l \partial \beta_v}\bigg|_{(r)} = 0$ for $l \neq v$.

The iterative procedure is made by the Newton–Raphson method with step halving with a criterion:

$$|Deviance(r+1) - Deviance(r)| < 0.0001.$$

The largest likelihood value was selected from a number of deviances obtained by assigning successive

incremental values of T_s or T_t, where T_s was taken to be 0, 0.05, 0.10, ..., 1.5 Gy under T_t = a given value such

as 0, 0.5, 1.0, 1.5, etc. The deviance statistic is $\chi^2 = -2log(L_c/L_f)$, where L_c is the likelihood in the current

model and L_f the likelihood in the full model, which does not depend upon the estimates of the parameters

considered. The criterion of 95% confidence limits based on deviance values is used as $\chi^2 = 3.841$ with one

degree of freedom. The 100(1 − α)% confidence limits were determined from the χ^2 statistic, i.e.

$$\chi^2 = -2\log\left[\frac{L(X|T^*)/L_f}{L(X|T)/L_f}\right]$$

which is known as the log likelihood statistic. Hence, we have

$$-2\log L(X|T^*)/L_f = -2\log L(X|T)/L_f + \chi^2,$$

where $-2\log L(X|T^*)/L_f$ is a deviance of 100(1-α) lower or upper bound and $-2\log L(X|T)/L_f$

is the smallest deviance. The goodness of fit (deviance) of the different models has been compared to

determine which model is most appropriate for the estimation of the threshold. To examine the goodness

of fit, the deviances of three models were plotted by step threshold in gray (Figure 2).

5. Results

Logit regression model III was stable for parameter solution, but gave the poorest fitting to the model used. Models I, II and IV gave good fits and were also stable for an iterative solution of parameters. The deviance values of Gompertz model II and one-hit model IV fit better than those of odds ratio model I, and the threshold value of models II and IV seem more reasonable than that of odds ratio model I in the low dose area. The deviances of one-hit model IV were exactly the same as those of Gompertz model II. Deviances for data of 1565 individuals were also plotted for models I to IV. Figure 2 shows how the estimates of the threshold and its 95% confidence limits were obtained from the same estimates based on Gompertz model II and one-hit model IV. Simple regression model V gave an unstable solution to the individual data for parameter estimation using an iterative method, and failed in this. The ML estimates of the model V may not exist for this parameterization.
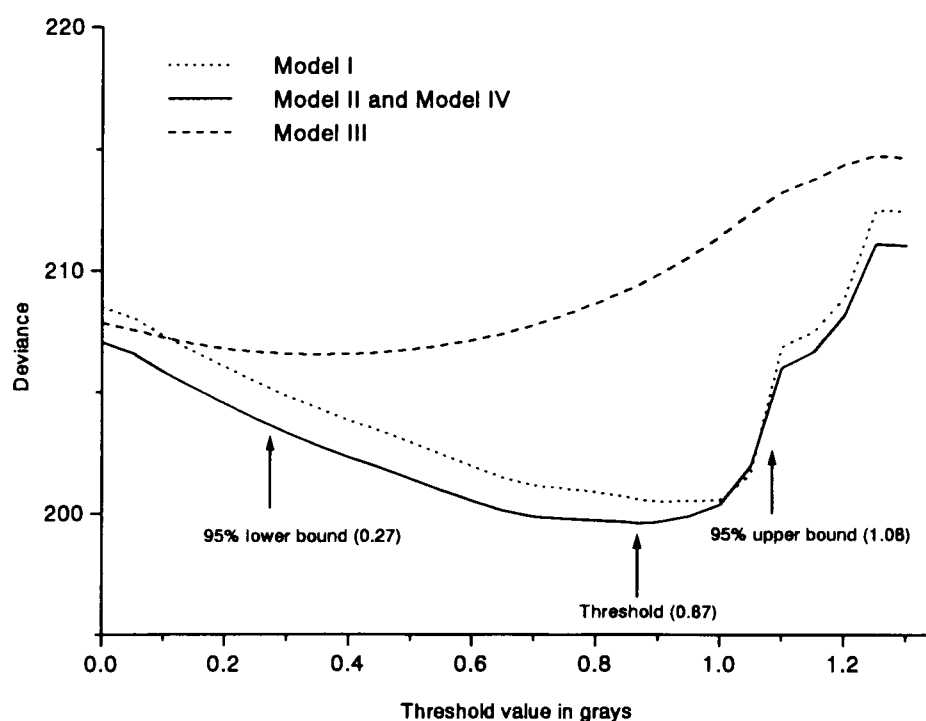

Fig. 2 Goodness of fits (deviances) to individual binary data depending upon each threshold.

The solution was not obtained even when several different starting values were tried. In this paper, we employed one-hit regression model IV so that these estimates may compare with the previous results of

the 1987 and 1996 studies.

Among the 1565 individuals, 30 were cases of severe mental retardation diagnosed before the age of 17 at the ABCC clinical facility. The distribution of the 1565 subjects by DS86 uterine absorbed dose is shown in Table 1 for four postovulational periods. Significant effects on the developing brain of exposure to ionizing radiation are seen only among those individuals exposed in the 8-15 week and 16-25 week periods; however, the DS86 dosimetry system reveals the risk of severe mental retardation from radiation damage to be highest 8-15 weeks after ovulation. Eighty percent of the 17 children with radiation-related mental retardation were exposed to more than 0.005 gray (Gy) in this period (see Figure 3). The other two groups of the 0-7 week and ≥26 week periods have no risk of radiation-related mental retardation. When the data of these two vulnerable gestational periods are distributed by DS86 uterine absorbed dose, there seems to be a threshold in the low-dose region.
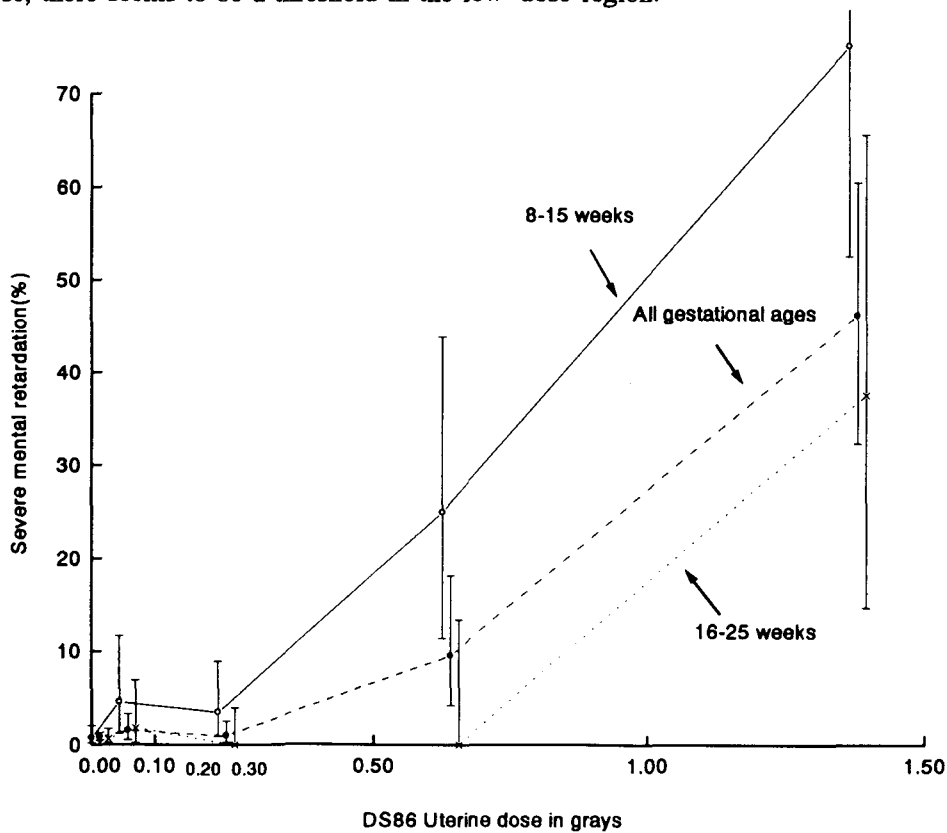

Fig. 3 Proportion of mentally retarded cases and 90% confidence limits

Table 2 shows the results of estimation based on a one-hit model when five probable nonradiation-related cases with mental retardation were included and excluded. The 95% lower bound of this threshold in the 8-15 week period after ovulation appears to be at 0.04 Gy and the 0.46 Gy estimate

of threshold is statistically demonstrable. When the two cases of Down's syndrome (0.29 and 0.56 Gy) probably unrelated to radiation exposure were excluded from the 19 children with severe mental retardation in the 8–15 week period, the threshold changed to 0.55 Gy and the 95% lower limit of the threshold was 0.31 Gy. For exposure in the 16–25 week period after ovulation, the 95% lower limit of the threshold of 0.87 Gy was 0.27 Gy with and without inclusion of the two cases of mental retardation considered to be non–radiation related, one a case of Japanese B encephalities at age 4 (0.03 Gy) and the other a case with a retarded sibling (0 Gy). The remaining one case (0 Gy) is a case of Down's syndrome and belongs to the ≥26 week period.

6. Discussion

It is important heuristically and for regulatory purposes to know whether a threshold exists for the radiation effects on the developing brain that we have described. Although no clear threshold is yet available for the prenatally exposed atomic bomb survivors, the efforts to reveal a threshold, if one exists, will now be described. The 1987 paper by Otake et al. showed that there is some evidence of a threshold with the DS86 dosimetry. The 95% lower bound of the threshold included zero and thus the existence of a threshold in the 8–15 weeks postovulation group was not statistically demonstrable based on the simple linear model, but a 0.15 Gy threshold were demonstrable in the 1987 paper for individuals of each period group based on the one–hit model IV. When the 2 cases of Down's syndrome presumably unrelated to radiation are excluded from the 19 cases of severe mental retardation, with 18 small heads and one normal head, exposed 8–15 weeks after ovulation, the period of maximum radiosensitivity, and a linear threshold model is fitted to the data, the 95% lower bounded of the estimated threshold based on simultaneously here with all cases ranges from 0.06 to 0.31 Gy with , which suggests the presence of a threshold (Otake et al. 1996). As for the 16–25 week group, the 95% lower bound of the estimated threshold is 0.28 Gy, irrespective of whether the two cases of mental retardation presumably unrelated to radiation are or are not included. These results based on the present and 1996 one–hit model were almost the same. The ML estimate of the threshold varies substantially with the model fitted. In the 1987 report, we obtained the estimates of the threshold values by a least square method when an iterative procedure did not converge or give a ML estimation. In the present paper, the 95% lower limit changed slightly from 0.06 Gy in 1996 to 0.04 Gy. We chose the best of the five models evaluated from the standpoints of the smallest deviance or the best goodness of fit. The results of the present paper with two constant terms were almost the same

as those of the 1996 paper based on one-hit model with a constant term.

Table 2 Estimation of linear dose–response relationship and threshold of severe mental retardation

Item	Included non–radiated five cases	Excluded non–radiated five cases
$\hat{\alpha}_H$	0.830	0.498
$\hat{S}\alpha_H$	0.262	0.203
$\hat{\alpha}_N$	1.269	1.268
$\hat{S}\alpha_N$	0.635	0.634
$\hat{\beta}_{sd}$	1.602	1.958
$\hat{S}_{\beta_{sd}}$	0.476	0.618
t (probability)	3.368 (<0.001)	3.170 (0.002)
Threshold (T_s Gy)	0.46	0.55
(95% lower, 95% upper)	(0.04, 0.57)	(0.31, 0.62)
$\hat{\beta}_{td}$	1.096	1.104
$\hat{S}_{\beta_{td}}$	0.681	0.681
t (probability)	1.610 (0.107)	1.621 (0.105)
Threshold (T_t Gy)	0.87	0.87
(95% lower, 95% upper)	(0.27, 1.08)	(0.27, 1.08)

$\hat{\alpha}_H$ and $\hat{\alpha}_N$ are the estimated intercepts of cases of mental retardation (per 100 individuals) in the 0 Gy group. $\hat{\beta}_{sd}$ or $\hat{\beta}_{td}$ is the increase in the frequency of severe mental retardation with dose (D) expressed in grays and $\hat{S}_{\beta_{sd}}$ or $\hat{S}_{\beta_{td}}$ its standard error. Threshold and its 95%lower (L) and upper (U) bounds are expressed in grays.

Figure 4 showed the deviances between the present and 1996 models. The present model is slightly better

than the previous models with a constant term in 1996. Furthermore, a linear–quadratic dose–response model gave poorer goodness of fit than that of linear dose–response one. The linear–quadratic dose–response model did not converge for iteration of appropriate initial value. The ML estimates of these models may not exist for the parameterization.
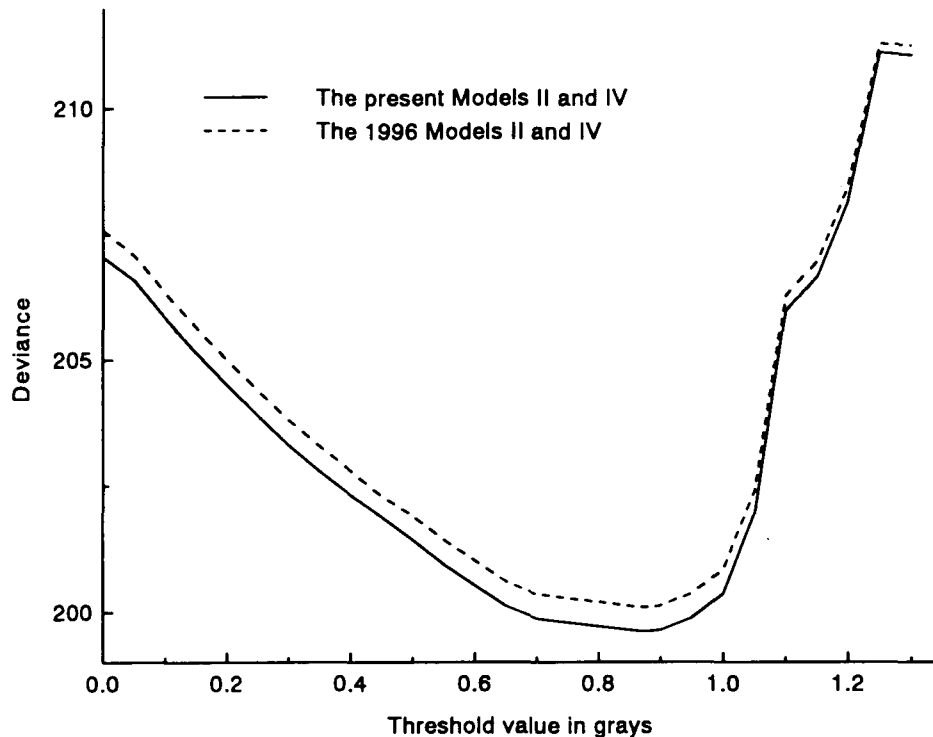

Fig. 4 Comparison of deviances between the present and 1996 models

The observations conceivably may compromise these assertions. First, some of these individuals have health problems, presumably nonradiation related, which could account for their mental retardation; second, there is the difference which appears to obtain between Hiroshima and Nagasaki in the frequency of radiation–related mental retardation. However, the difference was not observed

between two estimates of Hiroshima and Nagasaki constant terms from Table 2. Insofar as the first of these matters are concerned, three of these children are known to have, or have had Down's syndrome (0.56 Gy, 0.26 Gy and 0 Gy) and a fourth, a case of Japanese encephalitis in infancy at age 4 (0.03 Gy), and a fifth, a case with a retarded sibling (0 Gy). It is conceivable that in these instances the mental retardation was merely a part of the former syndrome or secondary to the infection, but in either event not radiation related. Exclusion of these children does not alter the findings appreciably for a dose–response relationship, but moved the 95% lower bound of the threshold estimate slightly to a high exposure area.

Generally, the embryonic stage in human is considered to be the period up to the 8th week after fertilization, and the fetal stage the period from the beginning of the 9th week after fertilization. Most organogenesis in humans is over by 8 weeks after fertilization, but development of the telencephalon (e.g., the cerebral hemispheres) proceeds rapidly during the 8-15 week period after fertilization. Indeed, Dobbing and Sands (1973) suggest that the adult neuronal cell number in man may largely be achieved by 16 weeks after fertilization. The consequence of loss of a single cell doubles with each intervening cell division. It is interesting to note in this connection that four of the in utero exposed have come to autopsy; of these four, two had been found to be mentally retarded and two not. Brain weights in the former two instances were conspicuously low, namely, 840g (at age 16) and 1,000g (at age 20); whereas in the latter two, brain weights were 1,440g (at age 9) and 1,450g (at age 29). One of the retarded individuals, a male, was exposed in Nagasaki in the 12th week of gestation and the other, a female, in Hiroshima at 31 weeks of gestation. In the retarded male, exposed to less than 0.005 Gy, the brain though small, was histologically normal. In 1991, Schull et al. reported that the magnetic resonance images of brain of the first in a series to be examined of sociologically better adapted five mentally retarded individuals exposed at 8-15 weeks disclose substantial, abnormal circumventricular areas of gray matter suggesting an impairment of migration. In two cases exposed at 8th and 9th week postovulation in this period, large areas of ectopic gray matter are seen, strong evidence of a failure of the neurons to migrate to their proper functional sites. Other investigators (Dunn et al., 1986) have shown that nonradiation-related mental retardation is frequently associated with areas of ectopic gray matter. Experimental observations on the effects of low doses of ionizing radiation (0.05 to 0.10 Gy) on the developing brain of rats exposed prenatally further support the belief that abnormal migration may be an important mechanism through which damage occurs. These studies reveal marked dysplasia of the cingulum, the band of association fibers in the medial portion of the centrum ovale of each hemisphere, at doses as low as 0.05 Gy (Reyners et al., 1986). Notwithstanding these observations, is an exponential linear dose-response relationship with a threshold such as the data from 8-15 weeks biologically plausible? An implicit premise in this relationship is that cells lost because of the loss of neuroblasts are not replaced by augmented division of the survivors. Experimental evidence shows the latter premise to be incorrect insofar as retinal neuroblasts are concerned, but need this be true for cerebral neuroblasts? An awesome implication of the linear model is a doubling dose for mental retardation of about 0.02 Gy. But if replacement does not occur, there exists the possibility of a true dose threshold for cerebral damage. The proportion of risk due to grouping cut of the 8-15 week period appears to be within error variation of the

control level of <0.005 Gy, and seems to show an existence of a threshold in the low dose area.

Models I to IV used here give a stable solution for the iterative procedure, but one-hit regression model IV was the best fitting of the four models investigated. In addition, a suggestive effect with or without mentally retarded cases was weakly observed at the probability level of p=0.107 or p=0.105 for the 16-25 week period based on one-hit model IV. The 95% lower bound of the threshold for exposure in the 8-15 week period after ovulation from one-hit model IV is 0.04 Gy. Excluding the two probable nonradiation-related cases of Down's syndrome from the 19 mentally retarded cases exposed 8-15 weeks postovulation, the 95% lower bound of the threshold changed to 0.31 Gy. For exposure in the 16-25 week period, the 95% lower bound of the threshold changed only from 0.25 Gy of the 1987 paper or 0.28 Gy of the 1996 paper to a 0.27 Gy both with and without inclusion of the two probable nonradiation-related cases. The deviance values for the linear model with a threshold, using the DS86 uterine absorbed doses in gray, were almost the same as those using DS86 uterine dose equivalents in sievert based on an assumed neutron of 10.

Data on seizures also suggest the presence of a threshold only in the 8-15 week group, but the 95% lower bound of the estimated threshold includes zero, so that the presence of a threshold is statistically doubtful (Dunn et al. 1990). The mean IQ scores (Schull et al. 1988) and school performance scores (Otake et al. 1988) are similar to the scores of the control group in the low dose range of ≤0.10 Gy, and no excess risk is observed. On the other hand, a significant effect of radiation is seen on head size in the first and second trimesters of pregnancy and in the 0-7 week and 8-15 week postovulation groups. No increase in risk of small head size was observed in the group exposed in the third trimester or in the group exposed 16 or more weeks after ovulation. The estimated threshold obtained from the dose-response relationship for small head size is zero or thereabouts (Otake and Schull 1993). Thus, the apparent lack of a threshold for small head size and the presence of some difference in the period in which fetuses are susceptible to damage suggest that there is an embryological difference in the occurrence of small head size and the occurrence of mental retardation. However, it is still unclear to what extent small head size is a finding independent of mental retardation and by what mechanism radiation-related damage is caused.

According to the report of Otake and Schull (1993) on radiation-related small head sizes, 26 of the 30 cases with severe mental retardation described elsewhere (Otake et al., 1987) are included among these subjects. Of these 26 severely mentally retarded cases, 15 (58%) had a small head size. Most (86%) of the individuals with a small head size were exposed in the first trimester (55%) or second trimester (31%) of pregnancy. A variety of dose-response relationships, with and without a threshold, have been fitted to

the data grouped by trimester or postovulatory age (weeks after ovulation) at which exposure occurred. A significant effect of radiation on the frequency of individuals with an atypically small head was noted only in the first and second trimesters, and for the intervals after ovulation of 0-7 weeks and 8-15 weeks. No increase in risk is observed for severe mental retardation in the 0-7 week period. When exposure occurred in the first trimester or during the 0-15 week period, the risk of an atypically small head suggests a possible linear-quadratic dose response relationship. The linear term is significant and the quadratic term suggestive. No excess risk of a small head size is seen in the third trimester or among individuals exposed at 16 weeks or more after ovulation. The estimated threshold, based either on a linear or a linear-quadratic dose-response relationship, is zero or thereabouts. This apparent absence of a threshold and the somewhat different periods of developmental vulnerability suggest an embryological difference in the events culminating in both a small head and severe mental retardation.

The morphological features and developmental processes in the histogenesis of the human cerebral cortex are basically the same as in other mammals. It is interesting, therefore, that the period of high susceptibility of the cerebral cortex to developmental damage noted in epidemiological studies of individuals exposed to the A-bomb while in-utero is consistent with the findings obtained from the exposure experiments in mice (Hoshino and Kameyama, 1988). Further systematic studies including animal experiments on the relationship of gestational age to impaired formation of the cranial bones, the areas of the brain involved and the nature of damage could be useful in determining the threshold of the production of radiation effects on the developing central nervous system.

The foregoing estimates of risks and the thresholds are associated with a number of uncertainties. Data are limited, and the heavily exposed survivors are few. Factors other than radiation can damage the central nervous system of the embryo and fetus such as malnutrition (*Winick, 1979*), genetic variation, and bacterial and viral infections during pregnancy, and the cerebrum and its adnexa have been suggested to be especially sensitive to oxygen deficiency (*Mole, 1982*). However, even if these factors had actually existed, it is doubtful whether they would have had dose dependent effects. Nonetheless, it probably would be best for the determination of the dose response relationship to assume that the risk of damage to the nervous system due to these several uncertainties is additive and not dependent on radiation dose. There are other uncertainties associated with these estimates of risk. Errors in the estimation of the tissue-absorbed dose and the prenatal age at exposure could have occurred; and the contributions of other confounding factors in the post-bomb period, including nutrition and disease, are difficult to assess. Epidemiological studies alone will not be able to address these uncertainties rigorously, but it may be

possible to assess their importance through experimental studies aimed at elucidating the underlying biological process.

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