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Radiation-related small head sizes among prenatally exposed A-bomb survivors

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Abstract. Of 1566 individuals prenatally exposed to the atomic bombings of Hiroshima and Nagasaki, 1473 had the circumference of their head measured at least once between ages 9 and 19. Among these 1473 individuals, 62 had small heads—the circumference of the heads was two standard deviations or more below the observed specific-age-at measurement mean. Of 26 cases with severe mental retardation, 15 (58%) had small heads. Most (86%) of the individuals with small heads were exposed in the first trimester (about <12 weeks postovulation) or second trimester (about 12–24 weeks postovulation)—55% in the former period and 31% in the latter. Various dose-response relationships, with and without a threshold, have been fitted to the data grouped by the trimester or postovulatory age (weeks after ovulation) at which exposure occurred. A significant effect of radiation on the frequency of individuals with atypically small heads is observed only in the first and second trimesters and for the intervals postovulation of 0–7 weels amd 8–15 weeks. Although the risk of a small head at 0–7 weeks postovulation increases significantly with increasing dose, no increase in risk for severe mental retardation is noted in this period. No excess risk of a small head was seen in the third trimester (about ≥25 weeks postovulation) or among individuals exposed at 16 weeks or more postovulation. The mean IQ values of mentally retarded cases with and without small heads were 63·8 and 68·9, respectively. No significant difference exists between these two IQ means, but both were significantly smaller than 96·4, the IQ value for individuals with small heads without severe mental retardation and 107·8, the value for the overall sample.

1. Introduction

Various lines of evidence, epidemiological and experimental, attest to the harmful effects of exposure to ionizing radiation on the developing embryo and fetus. The latter has generally been considered to be more sensitive than the adult to the detrimental effects of radiation exposure (ICRP 1986, UNSCEAR 1986). Recent re-evaluations of the epidemiological data available on survivors exposed prenatally to the atomic bombings of Hiroshima and Nagasaki suggest that there may be greater sensitivity than heretofore recognized for the induction of mental retardation or a reduction in IQ when exposure occurs during corticogenesis—that is, in the period 8–15 weeks postovulation (Otake *et al.* 1987, 1988, 1989, Schull *et al.* 1988, Ishimaru *et al.* 1989).

Although ionizing radiation produces small heads and mental retardation, it is only one among many agents that can cause similar effects. Actually, the developmental time at which an agent responsible for such effects is applied is often more important than the nature of the agent itself (UNSCEAR 1986). Contrary to most teratological malformations, where the period of vulnerability is short, often a week or less in humans, the developing brain and calvarium are characterized by a relatively long period of vulnerability to injury, lasting weeks or months in humans and other slowly growing animals. It is not clear, however, whether an atypically small head is an independent teratogenic effect or merely secondary to the effect of radiation on the developing brain itself, since the bones forming the cranial vault are commonly thought to develop in close association with the development of the brain and dura. Nor is it clear what small head size may imply with respect to the nature of radiation-related brain damage.

The purposes in this study were threefold: first, to examine the relationship of small head size to dose in specific trimesters or at fixed postovulatory ages (weeks after fertilization); second, to evaluate the relationship of small head size to anthropometric measurements such as standing height, body weight, sitting height, and chest circumference; and, finally, to examine the correlation of small head size, with or without severe mental retardation, to IQ scores.

2. Materials and methods

2.1. *Study population*

The prenatally exposed population used in this report is the PE-86 *In Utero* Clinical Sample. The

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study population consists of the 1598 persons (Hiroshima 1250, Nagasaki 348) used by Otake *et al.* (1987) in an analysis of severe mental retardation—the 1613 cases of the original clinical study sample (PE-86) of prenatally exposed survivors and non-exposed subjects (Wood *et al.* 1967) minus 10 subjects with unknown Tentative 1965 Dosimetry Revised (T65DR) dose and five subjects born outside the birth date restriction of 6 (Hiroshima) or 9 (Nagasaki) August 1945 to 31 May 1946. The DS86 doses are available for 1566 of these individuals (1242 in Hiroshima and 324 in Nagasaki). Among these 1566 individuals, 1473 had the circumference of their head measured at least once between ages 9 and 19. Their head and other anthropometric measurements were obtained at the time of their annual clinical examinations from 1954 to 1964. The present study focuses on this group of 1473 subjects.

A small head is defined as one with a circumference smaller than 2 standard deviations below the mean observed at the specific age at measurement based on the criteria for small heads at ages 9 to 19 indicated in Table 1a. It should be noted that these individuals have often been described as 'microcephalic'. This term seems inappropriate, however, since, first, microcephaly denotes a clinically recognizable smallness of the head (which is often misshapen as well), and, second, the clinical diagnosis generally is applied to individuals whose head is smaller (often 3 standard deviations or more below the mean) than the size viewed as atypical here. Accordingly, we use the expression 'atypically small head', or merely 'small head' to include all individuals satisfying the criteria described above.

Twenty-six of the 30 cases diagnosed as severe mental retardation before age 17—that is, who were found to be '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' (Otake *et al.* 1987) are included among the 1473 study subjects. Three of the four severely mentally retarded cases not included died before 1954, that is, before age 9. The one remaining case, a non-exposed individual, survives, but she did not have a physical examination between ages 9 and 19. Among the 1473 individuals studied, 62 had small heads as defined previously. It should be noted that the criteria differ between males and females for the same chronological age, ranging from a difference of −0·98 to 1·34 cm (Table 1b). The correlation between small-head-size cases determined using age- and sex-specific criteria and cases determined using age-specific criteria with the sexes combined is described briefly in §4.

2.2. *D86 dosimetry*

Maternal uterine absorbed doses, based on the DS86 dosimetry system (Version 3) (interoffice memorandum 1989), are used in the present study since fetal doses are not available. The DS86 Version 3 dose estimates in Hiroshima and Nagasaki were computed in July 1989. These new estimates provide better doses for distal survivors in the open at the time of the bombings (ATB) of Hiroshima and Nagasaki, and for survivors shielded by terrain or in factories. When detailed shielding histories are available the DS86 dose estimates are derived from a 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 (Roesch 1987). For those survivors whose shielding histories were incomplete, free-in-air

Table 1a. Age-specific criterion for small head sizes

Age ATE	Number of subjects	Mean (cm)	Variance	Standard deviation (SD)	Criterion[a] (cm)
9	430	50·46	2·56	1·60	47·26
10	964	50·98	2·26	1·50	47·98
11	906	51·47	2·39	1·55	48·37
12	919	51·93	2·82	1·68	48·57
13	306	52·61	2·92	1·71	49·19
14	286	53·29	2·91	1·71	49·88
15	760	53·91	2·64	1·63	50·65
16	1054	54·20	3·09	1·76	50·69
17	1207	54·50	2·79	1·67	51·16
18	1087	54·65	2·62	1·62	51·41
19	806	54·70	2·84	1·69	51·33

ATE = at the time of examinations.
[a]The head circumference was two SDs or more below the age-specific mean.

Table 1b. Age-sex specific criterion for small head sizes

Age ATE	Number of subjects	Mean (M) (cm)	Variance	Standard deviation (SD)	Criterion <(M − 2 × SD) (cm)
9	235	50·74	2·81	1·68	47·38
	(195)	(50·12)	(2.05)	(1·43)	(47·26)
10	515	51·22	2·50	1·58	48·05
	(449)	(50·72)	(1·87)	(1·37)	(47·99)
11	485	51·61	2·66	1·63	48·35
	(421)	(51.30)	(2·03)	(1·43)	(48·45)
12	496	51·89	3·49	1·87	48·15
	(423)	(51·97)	(2·04)	(1·43)	(49·11)
13	166	52·45	3·59	1·90	48·66
	(140)	(52·80)	(2·08)	(1·44)	(49·92)
14	160	53·07	3·21	1·79	49·49
	(126)	(53·57)	(2·41)	(1·55)	(50·47)
15	417	54·03	2·95	1·72	50·59
	(343)	(53·76)	(2·24)	(1·50)	(50·77)
16	563	54·44	2·80	1·67	51·10
	(491)	(53·92)	(3·28)	(1·81)	(50·30)
17	631	54·91	2·44	1·56	51·79
	(576)	(54·06)	(2·83)	(1·68)	(50·70)
18	569	55·15	2·32	1·52	52·10
	(518)	(54·11)	(2·40)	(1·55)	(51·01)
19	396	55·33	2·38	1·54	52·24
	(410)	(54·10)	(2·56)	(1·60)	(50·90)

ATE = at the time of examinations.
Figures in parentheses show results in females.

kerma was estimated using regression coefficients, and to obtain absorbed doses the free-in-air estimates were corrected using the mean building and body transmission factors derived from those individuals with detailed exposure information.

2.3. *Gestational age and trimester 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 trimester or postovulatory 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 (ATB)
= 280 − (date of birth–6 or 9 August 1945),

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, not on the birth reports found in the household registers (koseki) by Otake and Schull (1984). To obtain postovulatory age, G, 14 days were subtracted from the 'days of pregnancy ATB', Y, and age in days was converted to age in weeks by dividing by 7, i.e. $G = (Y - 14)/7$; G was presumed to be zero if it was negative. The trimesters of pregnancy ATB are defined as follows for Hiroshima and, in parenthesis, for Nagasaki:

1st trimester: 7 (10) February 1946–31 May 1946 (about < 12 weeks postovulation)
2nd trimester: 7 (10) November 1945–6 (9) February 1946 (about 12–24 weeks postovulation)
3rd trimester: 6 (9) August 1945–6 (9) November 1945 (about 25 or more weeks postovulation)

2.4. *Statistical methods*

Two issues regarding the effect of ionizing radiation on the developing head and brain are considered here; namely, the demonstration of an increased risk with increasing dose, based on the observed frequency of occurrence of a response culminating in a measurably small head or severe mental retardation, and the demonstration of the existence of a threshold in the low-dose region (under 20 cGy). Whether a threshold should be expected clearly depends upon the nature of the biological events leading to an atypically small head and central nervous system defects, or retardation of growth and development following exposure to ionizing radiation; these events are presently unknown. In our analysis, various statistical procedures or tests have been employed, including linear and linear-quadratic weighted regression analysis, to examine the relationship between the frequency of small head sizes and DS86 uterine absorbed dose by trimester ATB and by postovulatory age.

Suppose that P is the probability that an individual who had received dose, D, will develop a small head. Assume further that N_j is the number of independent individuals examined in the jth dose category of whom r_j are affected. If the r_j are binomially distributed, then the likelihood of observing the entire data set is

$$L_j = \Pi_j \binom{N_j}{r_j} (P_j)^{r_j} (1-P_j)^{N_j - r_j}.$$

As simple approximations we have fitted two models. One of these models assumes a linear dose-response relationship, that is, $P_j = \alpha + \beta D_j$, and the other assumes a linear-quadratic dose-response relationship $P_j = \alpha + \beta D_j + \gamma D_j^2$, but does not constrain the value of γ to positive terms. Variations of these models, which arise from the assumption of a threshold of risk, specifically $P_j = \alpha + \beta(D_j - T)$ and $P_j = \alpha + \beta(D_j - T) + \gamma(D_j - T)^2$ have also been fitted (again γ was not constrained). The last two models hold only if $(D_j - T) \geq 0$, where T is the threshold of dose. In the frequency data we have used the mean doses in the various dose categories. The parameters of these methods were estimated by the method of maximum-likelihood, assuming the observed number in each cell to be a binomial variate having an expected value based on the model equation. The estimate of the threshold, T, is based on the smallest χ^2 or log-likelihood value obtained through assigning successive incremental values to T. The 95% confidence limits were determined from the same deviance statistic, i.e., $\chi^2 = -2\log[L(X/T^*)/L(X/T)]$, where $T^* = L$ (a 95% lower bound) or U (a 95% upper bound) and T is the maximum-likelihood estimate of the threshold, i.e. $-\log L(X/T^*) = -\log L(X/T) + \chi^2/2$ (Otake 1984).

The relationships between small and 'normal' head sizes that could conceivably be related to the DS86 dose and measurements of standing height, weight, sitting height, and chest circumference were analysed simultaneously by a multivariate analysis of covariance (see Starmer and Grizzle 1968, Seber 1984). The multivariate model used is defined by

$$\mathbf{E(Y)} = \mathbf{X} \cdot \mathbf{B} \text{ and } \mathbf{\Sigma} \otimes \mathbf{I}_n,$$

where $\mathbf{Y}$ is an $n \times p$ matrix of dependent variables containing the physical characteristics observed in the n individuals, $\mathbf{X}$ is an $n \times m$ matrix composed of a known unit coefficient that depends on a general mean and covariate measurements such as sex (male = 1; female = 2) and small head size (small heads = 1; others = 2) as categorical factors, radiation dose, radiation dose squared, or postovulatory age; and $\mathbf{B}$ is an $m \times p$ matrix of parameters in which the p characteristics are each independently distributed in a p-dimensional normal distribution with the same covariance matrix. Furthermore, the rows of $\mathbf{Y}$ are assumed to be independently normally distributed with unknown covariance matrix $\mathbf{\Sigma}$, where $\otimes$ is a Kronecker product and $\mathbf{I}_n$ is an identity matrix. If the notation of the regression analysis applied here is used in accordance with the method of the GLIM system (McCullagh and Nelder 1983), the fitted model is

$$\text{Set of physical measurements } (\mathbf{Y}) = 1 + \text{Sex} + \text{SHS} + \text{Dose} + \text{Age}.$$

The hypothesis can be generalized to $\mathbf{H}_0$: $\mathbf{CBU} = \mathbf{0}$, where $\mathbf{C}(p \times m)$ and $\mathbf{U}(p \times u)$ are arbitrary matrices, to yield the appropriate hypothesis. The multivariate test under an appropriate hypothesis is made by a likelihood ratio statistic, i.e. an asymptotic chi-square statistic.

3. Results

3.1. *DS86 uterine absorbed dose and small head size or severe mental retardation*

Small head size and trimester of exposure. The frequency of individuals with small heads, with and without severe mental retardation, is shown in Table 2a by trimester at exposure and DS86 uterine absorbed dose. Figure 1 gives the proportion of small heads and the 90% confidence limits of the proportion by trimester at exposure. As is evident from Figure 1, the proportion of individuals with small heads in the first trimester unquestionably increases with increasing dose, and does so also in the second trimester, but to a lesser extent. Hardly any increase is observed in the third trimester (data not shown in Figure 1). Of the 26 mentally retarded cases, 15 (58%) had small heads (Table 2b). About 24% of the 62 individuals with a small head size (determined by age-specific criteria) among the 1473 clinical subjects were mentally retarded. This proportion increases to 29% (13/45) when only those subjects exposed to 0·01 Gy or more are considered. These figures, it will be noted, are larger than the 11% (8/71) previously reported by Wood

Table 2a. Small head size in children exposed *in utero* to the atomic bomb by trimester and DS86 uterine absorbed dose

Dose group[a] (Gy)	Mean dose (Gy)	Subjects	Small head size (%)	Small head size with severe mental retardation (%)	Normal head size with severe mental retardation (%)
All trimesters					
<0·01	0·000	1010	17 (1·68)	2 (0·20)	6 (0·59)
0·01–0·09	0·053	205	8 (3·90)	1 (0·49)	2 (0·98)
0·10–0·49	0·229	197	19 (9·64)	1 (0·51)	1 (0·51)
0·50–0·99	0·632	38	8 (21·05)	3 (7·89)	0 (0·00)
1·00+	1·302	23	10 (43·48)	8 (34·78)	2 (8·70)
Total	—	1473	62 (4·21)	15 (1·02)	11 (0·75)
1st trimester					
<0·01	0·000	310	7 (2·26)	0 (0·00)	1 (0·32)
0·01–0·09	0·053	66	3 (4·55)	0 (0·00)	1 (1·52)
0·10–0·49	0·229	67	13 (19·40)	0 (0·00)	1 (1·49)
0·50–0·99	0·629	10	6 (60·00)	2 (20·00)	0 (0·00)
1·00+	1·565	6	5 (83·33)	3 (50·00)	0 (0·00)
Total	—	459	34 (7·41)	5 (1·09)	3 (0·65)
2nd trimester					
<0·01	0·000	397	5 (1·26)	0 (0·00)	3 (0·76)
0·01–0·09	0·055	71	3 (4·23)	1 (1·37)	1 (1·37)
0·10–0·49	0·231	69	4 (5·80)	1 (1·15)	0 (0·00)
0·50–0·99	0·641	20	2 (10·00)	1 (5·00)	0 (0·00)
1·00+	1·202	12	5 (41·67)	5 (41·67)	1 (8·33)
Total	—	569	19 (3·34)	8 (1·41)	5 (0·88)
3rd trimester					
<0·01	0·000	303	5 (1·65)	2 (1·32)	2 (0·66)
0·01–0·09	0·051	68	2 (2·94)	0 (0·00)	0 (0·00)
0·10–0·49	0·229	61	2 (2·94)	0 (0·00)	0 (0·00)
0·50–0·99	0·615	8	0 (0·00)	0 (0·00)	0 (0·00)
1·00+	1·229	5	0 (0·00)	0 (0·00)	1 (20·0)
Total	—	445	9 (2·02)	2 (0·45)	3 (0·67)

[a]Doses have been rounded to the nearest cGy.

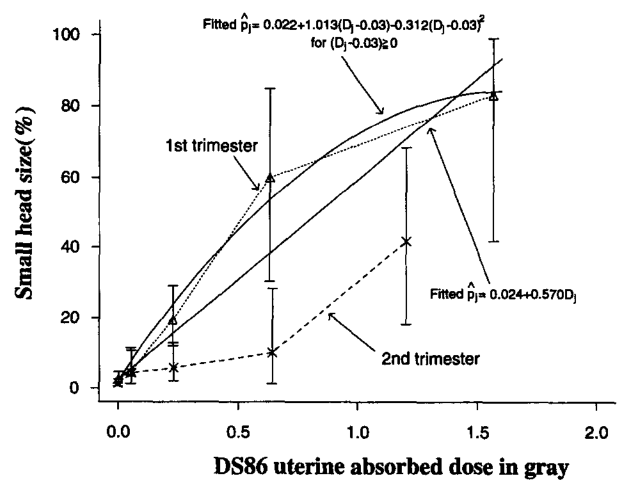

Figure 1. Proportion of small head size cases and 90% confidence limits by DS86 dose and trimester.

et al. (1967). However, these authors based their judgement on measurements obtained at age 17, and used as their criterion a head circumference that was equal to or smaller than 1·75 standard deviations from the mean of the control (this corresponds to the lower 5% of a normal distribution).

Most (86%) of the individuals with small heads were exposed in the first or second trimester—55% in the former period and 31% in the latter. The risk of an atypically small head and severe mental retardation observed among individuals exposed to 0·01 Gy or more is 57% (8/14) in the second trimester, but only 19% (5/27) in the first trimester. Of the 13 individuals with atypically small heads and severe mental retardation exposed to 0·01 Gy or more, 62% (8/13) were exposed in the second trimester and 38% (5/13) in the first trimester.

Table 2b. Small head size in children exposed *in utero* to the atomic bomb by gestational week and DS86 uterine absorbed dose

Dose group[a] (Gy)	Mean dose (Gy)	Subjects	Small head size (%)	Small head size with severe mental retardation (%)	Normal head size with severe mental retardation (%)
0–7 weeks					
<0·01	0·000	195	5 (2·56)	0 (0·00)	1 (0·51)
0·01–0·09	0·051	43	3 (6·97)	0 (0·00)	0 (0·00)
0·10–0·49	0·242	32	6 (18·75)	0 (0·00)	0 (0·00)
0·50–0·99	0·555	4	2 (50·00)	0 (0·00)	0 (0·00)
1·00+	1·818	2	1 (50·00)	0 (0·00)	0 (0·00)
Total	—	276	17 (6·16)	0 (0·00)	1 (0·36)
8–15 weeks					
<0·01	0·000	233	3 (0·14)	0 (0·00)	2 (0·86)
0·01–0·09	0·055	45	1 (2·22)	1 (2·22)	1 (2·22)
0·10–0·49	0·214	57	11 (19·30)	1 (1·75)	1 (1·75)
0·50–0·99	0·659	14	6 (42·86)	3 (21.43)	0 (0·00)
1·00+	1·346	11	8 (72·73)	7 (63·64)	0 (0·00)
Total	—	360	29 (8·06)	12 (3·33)	4 (1·11)
16–25 weeks					
<0·01	0·000	297	4 (1·35)	0 (0·00)	1 (0·34)
0·01–0·09	0·056	53	2 (3·77)	0 (0·00)	1 (1·89)
0·10–0·49	0·239	50	0 (0·00)	0 (0·00)	0 (0·00)
0·50–0·99	0·652	15	0 (0·00)	0 (0·00)	0 (0·00)
1·00+	1·190	6	1 (16·67)	1 (16·67)	2 (33.33)
Total	—	421	7 (1·66)	1 (0·24)	4 (0·95)
26+ weeks					
<0·01	0·000	285	5 (1·75)	2 (0·70)	2 (0·70)
0·01–0·09	0·050	64	2 (3·13)	0 (0·00)	0 (0·00)
0·10–0·49	0·229	58	2 (3·45)	0 (0·00)	0 (0·00)
0·50–0·99	0·561	5	0 (0·00)	0 (0·00)	0 (0·00)
1·00+	1·094	4	0 (0·00)	0 (0·00)	0 (0·00)
Total	—	416	9 (2·16)	2 (0·48)	2 (0·48)

[a]See footnote to Table 2a.

Small head size and postovulatory age at exposure. The proportion of individuals with small heads is shown in Table 2b for four postovulation periods, namely, 0–7 weeks, 8–15 weeks, 16–25 weeks, and 26+ weeks. These intervals reflect different phases in the normal development of the human brain. The proportion of individuals with small heads increases with increasing dose only in the first two periods, and an especially sharply rising trend is seen in the 8–15-week interval (Figure 2).

3.2. *IQ values for small-head cases with or without severe mental retardation*

The Appendix gives the IQ values which were available for the 73 cases with small head size and/or severe mental retardation, and their DS86 uterine dose estimates and gestational age (weeks). As is evident from the Appendix, the IQ values for five severely mentally retarded cases with small heads varied within a range of 56 to 78 with a mean IQ of 63·8 and standard deviation of 8·5. The IQ values for seven severely mentally retarded cases without small heads fluctuated within a range of 56 to 88 with a mean IQ of 69·0 and standard deviation of 12·0. On the other hand, the IQ values for the 31 cases with small heads only ranged from 61 to 140 with an IQ mean of 96·3 and standard deviation of 19·8. The mean IQ and standard deviation for the overall sample are 107·8 and 16·4, respectively. No significant difference was observed between the first two IQ means given above, but both are significantly smaller than the mean for individuals with small heads without severe mental retardation. The mean IQ of individuals with a small head without

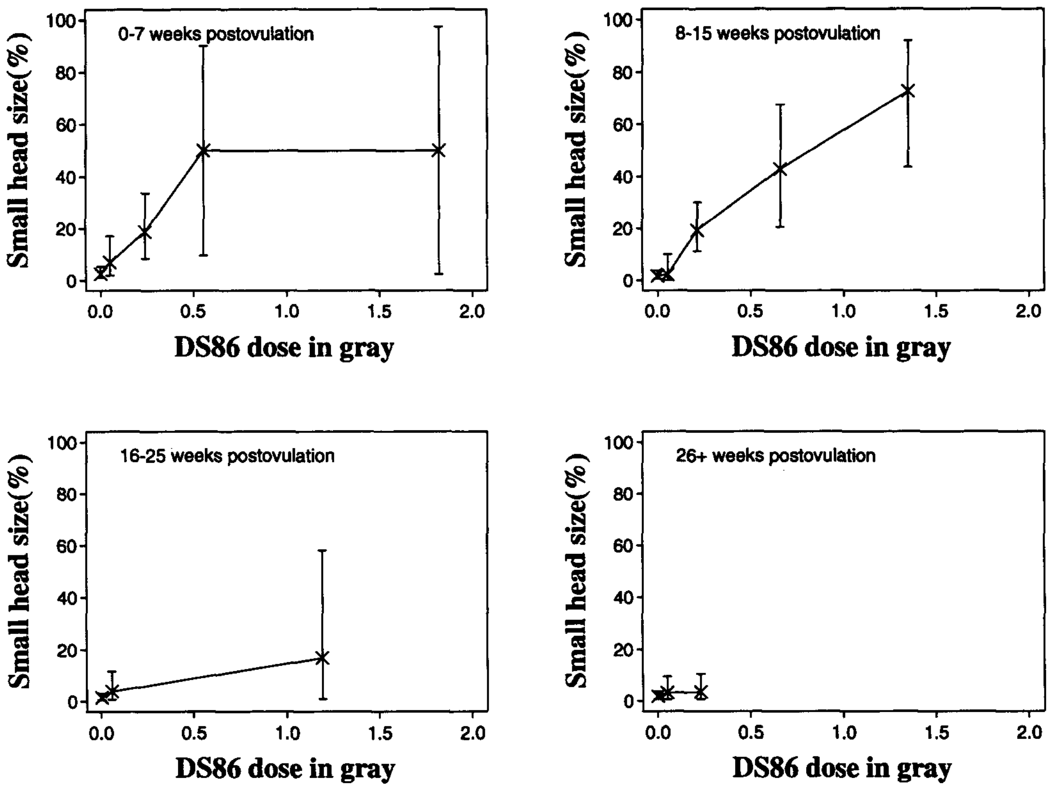

Figure 2. Proportion of small head size cases and 90% confidence limits by DS86 dose and gestational age (weeks).

severe mental retardation does not differ significantly from the mean for the entire sample.

3.3. *Dose-response relationship and small head size*

Various dose-response models, with and without a threshold, have been fitted to the data by trimester and postovulatory age (Table 3). A significant radiation-related effect on the frequency of individuals with small heads is noted only in the first and second trimesters, and for the 0-7-week and 8-15-week postovulatory periods. 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 (Table 3 and Figures 1 and 3). The linear term is significant and the quadratic term suggestive. No excess risk for small head size is seen in the third trimester or among individuals exposed at ≥ 16 weeks postovulation. The estimated threshold, based either on a linear or a linear-quadratic threshold dose-response model, 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.

3.4. *Relationship between small and 'normal' head sizes and physical measurements of growth, DS86 dose and postovulatory age at exposure*

The relationship of small head size to exposure to ionizing radiation and postovulatory age was evaluated using four physical measurements of growth and development—standing height, weight, sitting height, and chest circumference. These four variables are highly correlated. Accordingly, the four measurements were evaluated as a set using a multivariate analysis with DS86 dose and postovulatory age as covariates, and sex and small head size as categorical factors. The means and standard deviations of the four physical measurements, the DS86 dose, and postovulatory age in weeks are given in Tables 4a and 4b by sex and small head size, with and without severe mental retardation, but only for two age groups, namely ages 10 and 18. A retardation in growth, as judged by the physical measurements, is observed among individuals with small heads, with or without severe mental retardation, when their values are compared with those of individuals with 'normal' heads. These findings are similar to those of Ishimaru *et al.* (1989), who have reported that measurements of head circumference, height, and body weight at age 18 among members

Table 3. A linear or linear-quadratic dose–response relationship of small heads and the estimated threshold with 95% lower bound by trimester and postovulation

	Estimate of parameters				
Item[a]	$\hat{\alpha}$ (S_α)	$\hat{\beta}$ (S_β)	$\hat{\gamma}$ (S_γ)	Threshold (lower, upper)	Log-likelihood value
All ages: L	0·021	0·329**		0	−217·98
	(0·004)	(0·052)		(0, 0·06)	(−219.98)
L-Q	0·017	0·351**	−0·028[N.S.]	0	−217·95
	(0·004)	(0·099)	(0·107)	(0, 0·09)	(−219·90)
1st trimester: L	0·024	0·570**		0	−89·66
	(0·008)	(0·066)		(0, 0·07)	(−87·67)
L-Q	0·022	1·013**	−0·312[Sugg]	0·03	−88·26
	(0·008)	(0·242)	(0·176)	(0, 0·18)	(−90·20)
2nd trimester: L	0·013	0·247**		0	−70·28
	(0·007)	(0·074)		(0, 0·23)	(−72·52)
L-Q	0·014	0·167[N.S.]	0·0010[N.S.]	0	−70·07
	(0·006)	(0·136)	(0·0016)	(0, 0·22)	(−72·03)
3rd trimester: L	0·019	0·017[N.S.]		0	−44·06
	(0·007)	(0·057)		(0, —)	(—)
0–7 weeks: L	0·030	0·426**		0	−55·26
	(0·012)	(0·091)		(0, 0·13)	(−57·31)
L-Q	0·026	0·826**	−0·307[N.S.]	0	−53·88
	(0·011)	(0·291)	(0·203)	(0, 0·22)	−56·44
8–15 weeks: L	0·013	0·579**		0	−65·98
	(0·007)	(0·077)		(0, 0·10)	(−68·14)
L-Q	0·013	0·977**	−0·336[N.S.]	0·04	−65·01
	(0·007)	(0·263)	(0·228)	(0, 0·15)	−67·30
16–25 weeks: L	0·014	0·030[N.S.]		0	−35·16
	(0·006)	(0·041)		(0, —)	(—)
≥26 weeks: L	0·021	0·031[N.S.]		0	−43·45
	(0·008)	(0·072)		(0, —)	(—)
0–15 weeks: L	0·020	0·545**		0	−121·19
	(0·006)	(0·067)		(0, 0·06)	(−123·34)
L-Q	0·019	0·875**	−0·282[Sugg]	0·02	−119·83
	(0·006)	(0·193)	(0·163)	(0, 0·14)	(−121·89)
≥16 weeks: L	0·017	0·027[N.S.]		0	−78·76
	(0·005)	(0·036)		(0, —)	(—)

[a]Linear (L) and linear-quadratic (L-Q).

[N.S.]$p > 0·10$; [Sugg]$p < 0·10$; *$p < 0·05$; and **$p < 0·01$.

Regression estimate $\hat{\alpha}$ is an intercept and regression estimates $\hat{\beta}$ and $\hat{\gamma}$ are the increase in the frequency of small head size with dose and dose^2 expressed in Gray, respectively. The respective standard errors (S_α, S_β and S_γ) in Gray are shown in parentheses. The threshold and its 95% lower and upper limits are expressed in Gray. Log-likelihood value of the 95% upper estimates is given in parentheses.

of the prenatally exposed sample in Hiroshima and Nagasaki suggest a linear and statistically significant diminution in these measurements with increasing dose.

In order to investigate the possibility of growth retardation using the four physical measurements simultaneously, a multivariate analysis of covariance was attempted using individuals 10–12 and 16–18 years old for whom comparatively large numbers of observations were available (see Table 1a). The results of this analysis are shown in Tables 5a and 5b for individuals with and without severe mental retar-

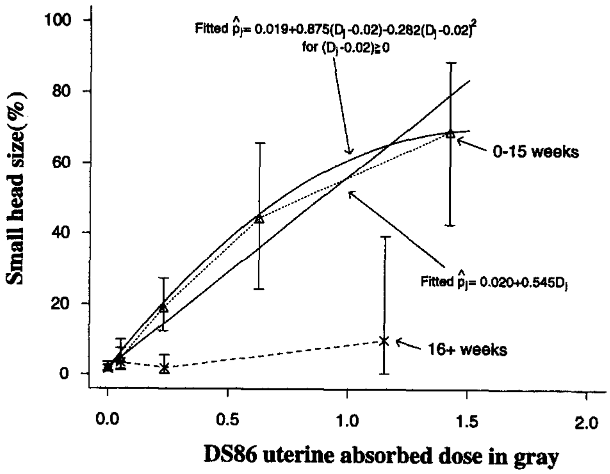

Figure 3. Proportion of small head size cases and 90% confidence limits by DS86 dose and gestational age (weeks).

dation. Growth retardation with increasing radiation dose is observed at almost all ages as judged by the negative estimates of the dose parameters associated with the four measurements. However, a statistically significant retardation, after adjusting for confounding factors based on sex, small head and postovulatory age, is noted only at age 17 with or without inclusion of severe mental retardation and at 18 years of age with the severely mentally retarded cases included. At ages 10 and 16 there is a suggestive growth retardation when the individuals with severe mental retardation are included, but not when these cases are excluded. At all other ages no statistically significant retardation is observed although, as previously noted, at these ages too, growth apparently diminishes as the radiation dose increases. Note, however, that where a statistically significant effect of radiation on growth is not seen, the pubertal growth spurt and its variability in age of onset could increase the generalized variance of the measurements, diminishing the sensitivity of the statistical tests. This conjecture is not supported, however, by a test of the homogeneity of the generalized variances since these cannot be shown to be significantly heterogeneous.

Postovulatory age is statistically significant and negative for all coefficients associated with the four physical measurements, except for chest circumference at age 10, with or without the inclusion of individuals with severe mental retardation in the analysis. As is evident from Tables 4a and 4b, individuals with small heads, with or without the inclusion of the cases with severe mental retardation, exhibit a highly significant retardation of growth and development with postovulatory age at exposure, as judged by the four physical measurements. Why this should be so is not obvious; but the decrease in these four measurements as postovulatory age increases suggests that there may have been some selection for body size in the earlier ages; that is, individuals who survived exposure in the early stages of gestation may have represented healthier pregnancies, on average, and were consequently destined to be larger children or young adults. If this were true it would be reasonable to assume that no postovulatory age effect would be observed if the comparisons were restricted to those sample members who were either not exposed or exposed to doses <0·01 Gy. When the data are so restricted, however, we continue to find a postovulatory age effect; thus the explanation for this finding remains elusive.

The sign of the estimated parameters associated with sex differs significantly with age at examination. Younger females, ages 11–12, tend to be slightly but significantly larger than males, but by ages 16–18 the males are definitely larger. The somewhat larger size of the females in the earlier years undoubtedly reflects the usually earlier onset in females of the adolescent growth spurt, commonly around ages 10–12.

4. Discussion

The harmful effects of irradiation on the human embryonic and fetal brain have been documented in many studies of the survivors exposed prenatally to the atomic bombings of Hiroshima and Nagasaki. Evaluation of the data on severe mental retardation with and without accompanying small head size, IQ score, and school performance among the prenatally exposed atomic bomb survivors has shown the most striking effects on the developing brain to occur among those individuals exposed in the 8–15- and 16–25-week periods postovulation; that is, at a time when the definitive cytoarchitecture of the cortex is emerging and synaptogenesis occurs (Otake *et al.* 1987, 1988, 1989, Schull *et al.* 1988). Studies of the frequency of individuals with seizures have also revealed a significant effect of radiation received in the 8–15-week postovulatory period. Collectively, these investigations suggest that radiation-related damage to the developing brain can manifest itself in various ways, but the picture is still incomplete.

The estimated threshold for the occurrence of small head size, 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 vulnerability

Table 4a. Means and standard deviations, by sex and head size category, for four physical measurements, DS86 dose and gestational weeks at 10 years old

Item	Small head: With severe mental retardation Mean	SD	Small head: Without severe mental retardation Mean	SD	Normal head: With severe mental retardation Mean	SD	Normal head: Without severe mental retardation Mean	SD
Males								
Number of subjects	23		15		481		479	
Standing height (cm)	120·7	7·44	124·0	6·32	127·6	5·22	127·6	5·21
Weight (kg)	21·8	3·94	23·1	3·97	25·8	2·89	25·8	2·89
Sitting height (cm)	67·6	5·61	69·2	6·11	70·4	2·59	70·4	2·59
Chest circumference (cm)	57·5	3·71	58·3	4·23	60·1	2·76	60·1	2·76
Mean DS86 dose (Gy)	0·619	0·568	0·481	0·588	0·063	0·188	0·063	0·188
Gestational week	16·7	10·45	17·0	11·27	19·0	10·36	19·0	10·37
Females								
Number of subjects	16		15		428		423	
Standing height (cm)	122·7	4·47	122·8	4·60	127·5	5·52	127·6	5·42
Weight (kg)	21·9	2·77	21·7	2·80	25·3	3·11	25·3	3·11
Sitting height (cm)	68·5	2·07	68·5	2·15	70·5	2·97	70·6	2·93
Chest circumference (cm)	56·0	3·43	55·8	3·47	58·0	3·03	57·9	3·03
Mean DS86 dose (Gy)	0·067	0·131	0·072	0·134	0·069	0·185	0·066	0·167
Gestational week	16·7	11·86	15·7	11·60	19·6	10·68	19·6	10·68

Table 4b. Means and standard deviations, by sex and head size category, for four physical measurements, DS86 dose and gestational weeks at 18 years old

Item	Small head: With severe mental retardation Mean	SD	Small head: Without severe mental retardation Mean	SD	Normal head: With severe mental retardation Mean	SD	Normal head: Without severe mental retardation Mean	SD
Males								
Number of subjects	22		17		547		545	
Standing height (cm)	158·3	7·76	160·0	7·74	165·7	5·68	165·7	5·69
Weight (kg)	45·7	6·87	46·1	7·51	54·9	6·71	54·9	6·72
Sitting height (cm)	86·6	3·82	87·0	4·19	90·3	2·95	90·3	2·96
Chest circumference (cm)	74·5	3·99	74·5	4·28	79·5	5·37	79·5	5·38
Mean DS86 dose (Gy)	0·511	0·599	0·393	0·574	0·062	0·187	0·060	0·181
Gestational week	17·1	10·63	16·7	10·70	18·3	10·33	18·3	10·34
Females								
Number of subjects	21		16		496		493	
Standing height (cm)	146·5	6·10	149·0	4·12	154·0	5·11	154·0	5·06
Weight (kg)	41·5	8·36	42·8	6·65	48·9	5·69	48·9	5·68
Sitting height (cm)	82·5	2·56	83·3	1·67	85·6	2·69	85·6	2·68
Chest circumference (cm)	71·0	6·93	71·5	5·92	75·5	5·03	75·5	5·00
Mean DS86 dose (Gy)	0·276	0·445	0·151	0·179	0·064	0·171	0·061	0·154
Gestational week	14·2	10·34	13·3	11·02	18·6	10·66	18·6	10·67

suggest an embryological difference in the development of a small head, on the one hand, and mental retardation on the other. A linear-quadratic dose-response relationship in the first trimester and 0–15 weeks postovulation provided a negative quadratic estimate. The maximum and minimum estimates of DS86 uterine doses of six individuals exposed to ≥1·0 Gy in the first trimester were 2·41 Gy and 1·02 Gy with an average value of 1·57 Gy. As is evident from Figure 1, the frequency of cases with

Table 5a. Results by age of multivariate analysis of covariance when severely mentally retarded cases were included

Item	Estimates of parameters				Asymptotic	
	SH (cm)	WT (kg)	ST (cm)	CC (cm)	χ^2 (d.f.)	*p*-Value
10 years of age						
Overall	122·76	23·09	68·50	57·99	281·5 (16)	<0·001
Sex	−0·09	−0·47	0·15	−2·07	164·9 (4)	<0·001
SHS	5·47	3·51	2·10	2·10	51·7 (4)	<0·001
Dose	−1·97	−1·04	−1·25	−0·74	8·12 (4)	0·087
Gestational age	−0·03	−0·04	−0·01	0·001	49·8 (4)	<0·001
11 years of age						
Overall	127·68	25·33	69·82	60·87	435·82 (16)	<0·001
Sex	1·04	0·50	0·91	−1·39	183·0 (4)	<0·001
SHS	5·72	3·71	3·07	2·61	39·9 (4)	<0·001
Dose	−1·99	−0·91	−0·98	−0·91	7·33 (4)	N.S.
Gestational age	−0·05	−0·06	−0·03	−0·13	203·0 (4)	<0·001
12 years of age						
Overall	133·21	28·14	72·13	63·25	136·0 (16)	<0·001
Sex	2·50	1·73	1·94	0·69	75·6 (4)	<0·001
SHS	5·07	4·12	2·88	2·63	24·0 (4)	<0·001
Dose	−1·96	−0·96	−0·68	−0·96	6·14 (4)	N.S.
Gestational age	−0·03	−0·06	−0·02	−0·06	23·9 (4)	<0·001
16 years of age						
Overall	155·98	44·53	84·44	73·50	732·6 (16)	<0·001
Sex	−9·66	−3·61	−3·61	−1·82	627·9 (4)	<0·001
SHS	8·42	8·83	4·53	4·66	86·2 (4)	<0·001
Dose	−2·01	−0·99	−0·39	−0·64	8·2 (4)	0·084
Gestational age	−0·07	−0·09	−0·03	−0·04	29·4 (4)	<0·001
17 years of age						
Overall	160·12	47·67	86·82	75·17	1190.1 (16)	<0·001
Sex	−11·29	−5·15	−4·38	−4·19	1032·3 (4)	<0·001
SHS	6·11	8·19	3·23	5·48	96·9 (4)	<0·001
Dose	−2·88	−1·82	−0·63	−0·21	20·3 (4)	<0·001
Gestational age	−0·05	−0·10	−0·02	−0·10	67·5 (4)	<0·001
18 years of age						
Overall	160·22	48·84	87·65	76·19	1108·5 (16)	<0·001
Sex	−11·71	−5·97	−4·74	−3·98	911·1 (4)	<0·001
SHS	6·61	7·94	3·18	4·82	75·3 (4)	<0·001
Dose	−2·82	−1·97	−0·85	−0·53	14·7 (4)	0·006
Gestational age	−0·05	−0·10	−0·03	−0·08	34·8 (4)	<0·001

SHS = small head size, SH = standing height, WT = weight, ST = sitting height and CC = chest circumference.

small heads does not increase linearly with an increase in dose above 1·57 Gy. However, the quadratic term was significant in only two of the models presented in Table 3, and even then the level of significance was only suggestive (i.e. $0{\cdot}05 < p < 0{\cdot}10$). The fitted lines for the linear dose–response and linear-quadratic dose–response relationships are given in Figures 1 and 3. As is evident from these figures, the linear-quadratic curve with a threshold is a suggestively better fit than a straight line, but the data are limited, especially at low doses. Apparent linear-quadratic curves for 0–7 weeks and 8–15 weeks postovulation are seen in Figure 2, but they were not statistically significant. This fact supports a linear dose–response relationship for the frequency of cases with small heads.

Mean IQ and its standard deviation (SD) of IQ scores reported by Schull *et al.* (1988) are 63·8 and 8·5 for the severely mentally retarded cases with small heads, and 68·9 and 11·9 for the severely mentally retarded cases without small heads. These values are 96·4 and 19·8 for cases with small heads only. The mean IQ and SD for the overall sample are 107·8 and 16·4, respectively. No significant dif-

Table 5b. Results by age of multivariate analysis of covariance when severely mentally retarded cases were excluded

Item	Estimates of parameters				Asymptotic χ^2 (d.f.)	p-Value
	SH (cm)	WT (kg)	ST (cm)	CC (cm)		
10 years of age						
Overall	124·05	23·48	69·07	58·14	247·4 (16)	<0·001
Sex	−0·08	−0·09	0·15	−2·09	162·1 (4)	<0·001
SHS	4·17	3·12	1·53	1·95	34·5 (4)	<0·001
Dose	−0·62	−0·59	−0·53	−0·22	2·13 (4)	N.S.
Gestational age	−0·03	−0·04	−0·01	0·00007	50·4 (4)	<0·001
11 years of age						
Overall	129·24	25·64	70·17	60·93	404·6 (16)	<0·001
Sex	1·10	0·52	0·94	−1·39	182·8 (4)	<0·001
SHS	4·13	3·40	2·70	2·57	27·2 (4)	<0·001
Dose	−0·80	−0·72	−0·48	−0·82	2·49 (4)	N.S.
Gestational age	−0·06	−0·06	−0·03	−0·13	200·5 (4)	<0·001
12 years of age						
Overall	134·19	28·27	72·31	63·28	124·3 (16)	<0·001
Sex	2·55	1·76	1·99	0·72	78·3 (4)	<0·001
SHS	4·00	3·96	2·65	2·61	18·1 (4)	0·002
Dose	−1·34	−0·89	−0·51	−0·90	2·44 (4)	N.S.
Gestational age	−0·03	−0·06	−0·02	−0·06	25·5 (4)	<0·001
16 years of age						
Overall	157·71	45·66	85·03	74·58	697·6 (16)	<0·001
Sex	−9·64	−3·58	−3·60	−1·81	632·3 (4)	<0·001
SHS	6·60	7·64	3·91	3·53	48·8 (4)	<0·001
Dose	−1·19	−0·19	−0·13	−0·11	2·96 (4)	N.S.
Gestational age	−0·06	−0·09	−0·03	−0·04	28·7 (4)	<0·001
17 years of age						
Overall	161·38	48·42	87·24	75·67	1154·0 (16)	>0·001
Sex	−11·26	−5·12	−4·36	−4·20	1029·7 (4)	<0·001
SHS	4·72	7·35	2·76	4·96	65·5 (4)	<0·001
Dose	−1·81	−1·32	−0·20	−0·07	9·52 (4)	0·049
Gestational age	−0·05	−0·10	−0·01	−0·10	66·9 (4)	<0·001
18 years of age						
Overall	161·59	49·19	87·99	76·25	973·0 (16)	<0·001
Sex	−11·63	−5·93	−4·72	−3·99	899·6 (4)	<0·001
SHS	5·12	7·55	2·81	4·76	50·3 (4)	<0·001
Dose	−1·92	−1·27	−0·47	−0·12	6·39 (4)	N.S.
Gestational age	−0·05	−0·10	−0·03	−0·08	35·7 (4)	<0·001

SHS = small head size, SH = standing height, WT = weight, ST = sitting height and CC = chest circumference.

ference exists between the first two IQ means identified above, but both are significantly smaller than the mean for the individuals with small heads without severe mental retardation. The mean IQ of individuals with small heads without severe mental retardation does not differ significantly from the mean for the entire sample.

Of 30 cases of severe mental retardation clinically identified before age 17, 18 (60%) had small heads, as defined previously (Otake *et al.* 1987). Small head size, as described in this 1987 paper by Otake and his colleagues, was determined using a sex-specific criterion of at least 2 standard deviations below the mean observed between ages 16 and 19. In the present study, age-specific critera based on the sexes combined were used for ages 9–19. Consequently, two severely mentally retarded cases were changed from 'normal' head size to small head size, and one severely mentally retarded case was altered from small head size to 'normal' head size. Twenty-six cases of severe mental retardation are included in the present study. Of these, 15 (58%) had atypically small heads, and 12 (80%) of the 15 were exposed in the period 8–15 weeks postovulation. When criteria based on age and sex were used, 14 (54%) of the 26 individuals with severe mental retardation were classified as having atypically small heads. Using these same age- and sex-specific criteria, two mentally retarded cases were changed from the small-head category to 'normal', and one mentally retarded case from 'normal' to small heads. The classification of the remaining 23 mentally retarded individuals is unchanged whichever criteria are used.

Overall, when age-specific criteria for the sexes combined are used to identify small head size, 62 individuals among the 1473 are so classified, whereas when age- and sex-specific criteria are employed, there are 64 small-head cases. Fifty-six individuals were classified as having small heads whichever criteria were used; thus, the consistency is 90·3% (56/62 cases), using age-specific criteria with the sexes combined and 87·5% (56/64 cases) using age–sex-specific values. In the first instance the remaining six cases (one male and five females) were judged to have small heads based on measurements obtained when they were 17 or 18 years of age (except for the male where the classification rested on the measurement at age 13) and their head circumferences were smaller than the head sizes expected at maturity, whereas the eight remaining cases (one male and seven females), using age-sex-specific criteria, were classified as having small heads based on measurements at ages 11–13 except for the male, for whom the measurement occurred at age 16. Among the seven females their head sizes were somewhat larger than the 'cut-point' based on a specific age criterion at maturity.

Of the 17 persons with small heads in the 0–7-week period, 12 without severe mental retardation are in the ≥0·01 Gy group. One (50·0%) of the two individuals with small heads exposed to ≥1·00 Gy and two (50·0%) of the four exposed to 0·50–0·99 Gy were judged to be mentally normal. However, of the 29 individuals with small heads in the 8–15 week period, 26 received a dose of ≥0·01 Gy or more, and 12 (46·2%) had severe mental retardation. Seven (87·5% of the eight individuals with small heads who were exposed to ≥1·00 Gy had severe mental retardation. Thus, 12 (80%) of the 15 individuals with atypically small heads and severe mental retardation ocurred in the period 8–15 weeks post-ovulation. In the 16–25-week period only one (33·3%) of the three individuals with small heads in the ≥0·01 Gy group had severe mental retardation and he is in the ≥1·00 Gy group.

It warrants noting that these findings with respect to age at exposure accord well with those of Miller and Blot (1972) when allowance is made for the difference in dosimetry (they used the T65 maternal kerma) and some subsequent small changes in the data. They observed 'a progressive increase with dose in the frequency of the abnormality (small head circumference) among persons whose mothers were exposed before the 18th week of pregnancy'.

The rubric 'small head size' may, indeed probably does, cover various different developmental 'abnormalities'. Among the indivduals with small heads and severe mental retardation, for example, some clearly invite the clinical diagnosis of microcephaly, since the head is not only unusually small but misshapen. Still others, more commonly, have heads proportionate in all dimensions, albeit small. Moreover, since head size varies in all populations, it can be assumed that some of the individuals here designated as having small heads merely represent the lower extreme of normal variability. Indeed, based on the criterion for small head size used here, if head sizes are approximately normally distributed, some 2·5% of 'normal' individuals would be so classified.

Since the mean IQ and its standard deviation among the 47 individuals having small head without severe mental retardation approximate the values seen in the entire clinical sample, it is conceivable

Table 6. Excess number of individuals with small heads expected by an assumed 2·5% of 'normal' distribution

Item	Gestational weeks			
	0–7	8–15	16–25	26+
Subjects	276	360	421	416
Normal developmental heads	269	351	410	406
Expected small heads	7	9	11	10
Observed small heads	17	29	7	9
Observed small heads with severe mental retardation	0	12	1	2
Observed small heads without severe mental retardation	17	17	6	7

that a significant fraction of these individuals are the 'normals' to whom we allude. Accordingly, we have attempted to estimate the excess number of individuals with small heads ostensibly attributable to exposure to ionizing radiation (see Table 6). As will be seen, among the 62 individuals with small heads, some 37 would be expected normally, and the observed and expected numbers agree reasonably well when exposure occurred in the 16th week or later. However, there is a striking excess before this time—where 16 are expected 46 were actually observed, an excess of 30 cases. If it is assumed that the small head size among those individuals with severe mental retardation are secondary to brain damage, this leaves 18 cases (34 observed minus 16 expected) that might represent radiation-related instances of growth retardation without accompanying mental impairment.

Can these latter individuals be distinguished from those expected by chance? To explore this possibility we have indicated in Figure 4 the location of the 47 cases of small head size without mental retardation in a bivariate plot of standing height versus sitting height expressed as age- and sex-standardized deviates based upon the full sample of 1473 individuals. Note that the individuals with small heads but no apparent mental retardation do not cluster uniquely but are disproportionately represented among the lower values defined by either the 95% or 99% probability ellipse (37 of the 47 cases), suggesting that the small head size reflects a more generalized growth retardation attributable either to radiation or other causes. Three individuals lie outside the 99% ellipse, but only one of these three received a dose of known biological consequence. Specificially, the DS86 doses absorbed by the mother's uterus are 0, 0·05 and 0·49 Gy. This fact, in concert with the other observations we have described, leads us to believe that small head size is not an unique teratogenic effect, but is secondary either to mental retardation or to a more generalized limitation of growth without clinically recognizable mental retardation.

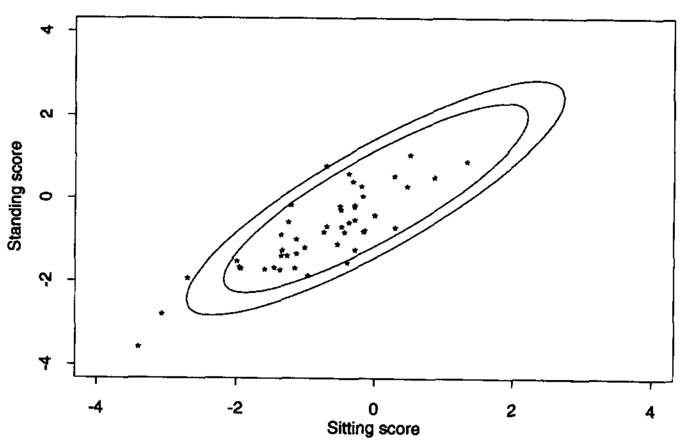

Figure 4. Relationship of the standardized scores for standing and sitting heights among 47 cases with small heads only. The inner ellipse presents the 95% probability limits, and the outer ellipse the 99% limits of standardized scores based on the full sample of 1473 individuals. The standardized score was calculated individually for standing and sitting heights from 9 to 19 years old.

It has been argued that the measurement of the head circumference of an individual exposed prenatally could be a simple, but useful, screening device in the event of accidents such as that which occurred at Chernobyl. Our numbers suggest, however, that although this strategy may be useful it would not be particularly sensitive. The frequency of false negatives (individuals with severe mental retardation but 'normal' head circumferences) would be about 40%, and the frequency of false positives (individuals with small heads arising solely as a result of normal variation) would be almost 60%. However, it should be noted that these assertions are based on measurements made 9 or more years after exposure, and it is not clear whether they are equally valid for measurements made sooner.

As previously stated, the picture of the effects of prenatal exposure to ionizing radiation on physical and mental growth and development is not complete. The *in utero* studies at the Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, have played, and will undoubtedly continue to play, an important role in this still-unfolding story of the effects of exposure to A-bomb radiation on the developing human fetus.

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Appendix. Seventy-three cases with small head size or severe mental retardation

No.	Sex	Gestational age (weeks)	Trimester	DS86 (Gy)	Small head size	Severe mental retardation	IQ	Cause of death (ICD)	Date of death
1	F	1	1	0·000	0	1	—		
2	F	31	3	0·000	0	1	79		
3	M	6	1	1·230	1	0	65		
4	F	25	3	1·770	0	1	60		
5	M	9	1	1·147	1	1	62		
6	M	16	2	0·000	1	0	88		
7	F	22	2	0·000	1	0	95		
8	M	12	2	1·179	1	1	—	(3209)[a]	14 Mar. 1962
9	M	4	1	0·489	1	0	85		
10	M	11	1	0·715	1	0	120		
11	M	15	2	1·462	1	1	78		
12	M	8	1	2·228	1	0	83		
13	F	15	2	NIC	0	1	56		
14	M	13	2	NIC	0	1	76		
15	M	31	3	0·126	1	0	88		
16	M	20	2	0·000	0	1	—	(3459)[b]	19 Sept. 1956
17	M	10	1	0·316	1	0	90		
18	M	6	1	0·572	1	0	115		
19	M	36	3	0·045	1	0	88	(953)[c]	11 Feb. 1968
20	F	36	3	NIC	1	0	103		
21	F	15	2	0·062	1	1	—		
22	F	5	1	0·110	1	0	83		
23	M	15	2	0·611	1	1	—	(011)[d]	30 Aug. 1958
24	M	8	1	0·868	1	1	64		
25	F	7	1	0·444	1	0	105		
26	F	5	1	0·035	1	0	79		
27	F	6	1	0·041	1	0	107		
28	M	12	2	0·617	1	0	96		
29	M	30	3	0·169	1	0	120		
30	F	31	3	0·000	1	1	—	(3459)[b]	26 Mar. 1966
31	M	9	1	1.358	1	1	—		
32	M	19	2	1·229	0	1	64		
33	F	13	2	1·642	1	1	56		
34	M	10	1	1·024	1	1	—		
35	M	36	3	NIC	1	1	—		
36	F	13	2	0·294	1	1	—		
37	F	8	1	0·557	1	0	—		
38	M	8	1	0·135	0	1	—		
39	F	5	1	0·136	1	0	—		
40	F	2	1	NIC	1	0	126		
41	F	2	1	NIC	1	0	111		
42	F	36	3	NIC	1	0	116		
43	M	32	3	NIC	1	0	97		
44	F	20	2	0·027	0	1	88		
45	F	8	1	0·243	1	0	89		
46	M	26	3	NIC	0	1	60		
47	F	21	2	NIC	1	0	76		
48	M	22	2	1·081	1	1	59		
49	F	12	2	1·391	1	1	—		
50	M	29	3	NIC	1	0	118		
51	F	25	2	NIC	1	0	61		
52	F	24	2	0·025	1	0	140		
53	M	9	1	0·689	1	1	—		
54	M	12	2	0·285	1	0	113		
55	F	17	2	0·027	1	0	51		
56	F	11	1	NIC	1	0	98		
57	F	8	1	0·262	1	0	89		
58	M	8	1	0·376	1	0	91		
59	F	15	2	0·202	1	0	—		
60	M	14	2	0·176	1	0	—		
61	F	8	1	0·170	1	0	—		
62	F	7	1	0·000	1	0	—		
63	F	4	1	0·141	1	0	—		
64	F	10	1	0·354	1	0	—		
65	M	2	1	0·355	1	0	—		
66	F	11	1	0·000	1	0	—		
67	F	6	1	0·000	1	0	—	(953)[c]	12 Jan. 1974
68	M	9	1	0·305	1	0	—		
69	M	11	1	0·052	0	1	—		
70	M	15	2	0·000	1	0	—		
71	M	7	1	0·550	1	0	—	(4319)[e]	8 Dec. 1960
72	F	0	1	0·038	1	0	—		
73	M	6	1	0·000	1	0	—		

NIC denotes 'not in city'.
[a]Meningitis due to unspecified bacterium; [b]epilepsy; [c]suicide; [d]pulmonary tuberculosis; [e]cerebral haemorrhage.
ICD = International Classification of Diseases.

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