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SHORT COMMUNICATION

Neurocognitive Function in Aged Survivors Exposed to Atomic Bomb Radiation In Utero: The Radiation Effects Research Foundation Adult Health Study

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Although some adverse effects on neurocognitive function have been reported in children and adolescents irradiated prenatally during the atomic bombings and the Chernobyl nuclear accident, little information is available for effects on the elderly. Here we evaluate the effects of prenatal exposure to atomic bomb radiation on subjective neurocognitive function in aged survivors. To evaluate neurocognitive impairment, we mailed the Neurocognitive Questionnaire (NCQ), a self-administered scale, to prenatally exposed survivors, including clinic visitors and non-visitors at the time of the 2011 and 2013 Adult Health Study (AHS) examinations. We received replies from 444 individuals (mean age, 66.9 ± 0.6 years). After adjusting for sex, city, and educational background, we found no significant effects of radiation, clinic visit, or interaction between radiation and clinic visit on the scores of the 4 NCQ factors of metacognition, emotional regulation, motivation/organization, and processing speed. Even in analyses considering gestational age at the time of the bombings, none of the 4 NCQ factor scores was related to maternal uterine dose. There remains the limitation that this study consisted of healthy survivors, but we found no significant radiation effect on late-life cognition in people prenatally exposed to atomic bomb radiation.

INTRODUCTION

The Radiation Effects Research Foundation (RERF) has conducted many studies to elucidate the effects of prenatal radiation exposure on childhood growth and development. Studies of the central nervous system and neurocognitive function suggested adverse effects related to dose and gestational age that included intellectual impairment, epileptic seizures, small head size, and decreased intelligence quotient scores and academic performance (*1*, *2*).

After the Chernobyl nuclear power plant accident, studies in several countries reported intellectual impairment, a tendency toward behavioral and emotional disorders, lower IQ, and poorer school outcomes in prenatally exposed children compared to controls (*3–5*) while other studies found no relationship between cognitive function in children and putative radiation exposures (*6*, *7*). Decreased verbal memory and executive functioning were reported in prenatally exposed adolescents (*8*), as were decreased full-scale IQ and verbal IQ scores in adolescents exposed to low-dose radiation before gestational week 16 (*9*).

Few epidemiological studies, however, have been conducted on the effects of prenatal radiation exposure on late-life neurocognitive function. In the RERF Adult Health Study (AHS), no significant radiation effects by atomic bombings were found among elder survivors exposed in utero on objective cognitive function assessed with the Cognitive Abilities Screening Instrument (CASI) (*10*). However, there remained a concern about selection bias in that the eligible population was limited to clinic visitors for AHS. We designed the present study to investigate the association between prenatal radiation exposure and subjective neurocognitive function in aged in utero survivors, including both clinic visitors and non-visitors.

MATERIALS AND METHODS

Study Subjects and Exposed Radiation Dose

In 1978, 1,021 in utero survivors who were born between the day of the atomic bombings and the end of April 1946 and lived in either Hiroshima or Nagasaki in 1950, and their controls, were selected as a sub-cohort of the AHS cohort. Approximately 90% of this sub-cohort was alive at the beginning of the study in 2011 (*10*). The AHS is an ongoing clinical program that conducts biennial clinical examinations and semi-annual mail surveys (*11*).

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TABLE 1
Demographic Characteristics of Subjects

	Total of the subjects	Control group (<5 mGy)	Low-dose group (5-<250 mGy)	High-dose group (>=250 mGy)
Age at evaluation, mean (SD)	66.9 (0.6)	66.9 (0.6)	67.0 (0.6)	66.7 (0.6)
Sex, No. (%)				
Female	234 (52.7%)	131 (53.0%)	80 (54.4%)	23 (46.0%)
Male	210 (47.3%)	116 (47.0%)	67 (45.6%)	27 (54.0%)
City, No. (%)				
Hiroshima	358 (80.6%)	188 (76.1%)	132 (89.8%)	38 (76.0%)
Nagasaki	86 (19.4%)	59 (23.9%)	15 (10.2%)	12 (24.0%)
Educational background, No. (%)				
Primary school	49 (11.0%)	26 (10.5%)	18 (12.2%)	5 (10.0%)
High school	128 (28.8%)	71 (28.7%)	37 (25.2%)	20 (40.0%)
College/University	51 (11.5%)	35 (14.2%)	10 (6.8%)	6 (12.0%)
Missing	216 (48.6%)	115 (46.6%)	82 (55.8%)	19 (38.0%)
AHS clinical examination, No. (%)				
Visitors	227 (51.1%)	132 (53.4%)	69 (46.9%)	26 (52.0%)
Non-visitors	217 (48.9%)	115 (46.6%)	78 (53.1%)	24 (48.0%)
Gestational age at the time of bombing, No. (%)				
15 weeks	168 (37.8%)	92 (37.2%)	54 (36.7%)	22 (44.0%)
16–25 weeks	131 (29.5%)	69 (27.9%)	47 (32.0%)	15 (30.0%)
26 weeks	145 (32.7%)	86 (34.8%)	46 (31.3%)	13 (26.0%)

We sent the Neurocognitive Questionnaire (NCQ) (*12*) repeatedly in 2011 and 2013 to the in utero survivors who agreed to mail surveys: 570 individuals in 2011 and 540 individuals in 2013 after the RERF Institutional Review Board approved the study. Response rates were 69% for both the 2011 NCQ and 2013 NCQ, without reminders or support from others.

We used the revised DS02R1 maternal weighted absorbed uterine doses (*13*) as surrogates for doses received by the fetuses. Among the 457 individuals who provided 2011 NCQ or 2013 NCQ score, 13 survivors whose maternal weighted absorbed uterine doses were not estimated were excluded from the analysis. Based on those doses, we categorized subjects into 3 groups: control (< 5 mGy), low-dose (5-$<$250 mGy), and high-dose (≥ 250 mGy). The maximum dose in the study subjects was 2,304 mGy and only 5 survivors had doses that were above 1 Gy.

Measurements

We used the NCQ, a self-administered scale, to measure subjective neurocognitive function. The NCQ consists of 25 questions. For each question, subjects were asked to report the frequency of problems experienced in the past 6 months with the following choices: 1 = "never a problem"; 2 = "sometimes a problem"; and 3 = "often a problem". In a previous study (*14*), we identified 4 factors that represented 20 of the 25 NCQ items and labelled them metacognition (Factor 1, 9 items), emotional regulation (Factor 2, 5 items), motivation/organization (Factor 3, 4 items) and processing speed (Factor 4, 2 items) (see Supplemental Table S1; https://doi.org/10.1667/RADE-22-00008.1.S1). We calculated the factor raw score as the sum of scales of completed items for each factor. At least one factor score at the 2011 NCQ or 2013 NCQ was provided from 444 individuals with DS02R1 dose. There is information from 300 survivors from both NCQs, 84 survivors from 2011 NCQ only, and 60 survivors from 2013 NCQ only.

Gestational Age at the Time of the Bombing

We calculated the fetal age at the time of the bombing (ATB) following the method of Otake et al. (*2*): Days of pregnancy ATB = 280 − (date of birth − 6 or 9 August 1945). We obtained gestational age ATB in weeks from "days of pregnancy" and divided it into 3 categories: 0–15 weeks, 16–25 weeks, and $\geq$26 weeks.

Educational Background

We obtained subjects' educational backgrounds by a questionnaire at each survivor's first AHS clinical examination on or after July 1, 1986. We classified educational background into primary school, high school, or college/university. Information on educational background was lacking for 12.3% of clinic visitors and 86.6% of non-visitors. The in utero survivors with clinically diagnosed severe intellectual impairment in childhood did not consent to the mail survey and were not included in the study subjects.

Data Analysis

We converted raw factor scores to T scores with a mean of 50 (SD = 10) in the control group. Higher scores indicated more problems. We assumed that the participant was "impaired" when their T score was 63 or higher, which was the cutoff defined in the Childhood Cancer Survivors Study, approximately corresponding to the highest 10% range of the control's score (*15*). The percentage of individuals with T score $\geq$63 (% impaired) was calculated, and its association with radiation dose was assessed by a multivariable mixed-effects logistic regression model. Since the NCQ was conducted twice, we used both scores for those who answered both questionnaires and assumed a random intercept model to express intra-individual correlations. Separate analyses were conducted for the association between the T scores and radiation dose, utilizing a linear mixed-effects model. Those analyses, adjusted for age at evaluation, sex, city and educational background, were conducted using the categorical variable (low-dose and high-dose groups compared with the control group) and the continuous variable of the radiation dose. We performed separate analysis adjusted for the clinic visitors and interaction term between clinic visitors and radiation dose to check for differences between the associations with radiation between clinic visitors and non-visitors. In addition, differences in the mean T score of the low-dose and high-dose groups compared to the control group were estimated in the analyses stratified by gestational age. In all the analyses, multiple imputation was performed for the missing educational background

TABLE 2
Association of Radiation Exposure and NCQ 4 Factors

	Control group (<5 mGy)	Low-dose group (5-<250 mGy)	High-dose group (>=250 mGy)
F1 – Metacognition			
Total of the subjects	245	143	49
Adjusted mean T score (95% CI)	52.7 (49.4, 56.0)	53.5 (50.4, 56.9)	52.8 (48.5, 57.2)
P value	ref.	0.42	0.94
Percentage impaired (95%CI)	9.0 (6.4, 12.2)	14.2 (10.0, 19.3)	8.9 (3.6, 17.4)
P value	ref.	0.12	0.88
F2 – Emotional regulation			
Total of the subjects	246	139	50
Adjusted mean T score (95% CI)	55.2 (51.9, 58.6)	54.4 (51.2, 57.8)	54.8 (50.6, 59.1)
P value	ref.	0.48	0.82
Percentage impaired (95%CI)	10.6 (7.8, 14.1)	12.4 (8.4, 17.5)	7.4 (2.8, 15.4)
P value	ref.	0.94	0.42
F3 – Motivation/Organization			
Total of the subjects	247	145	50
Adjusted mean T score (95% CI)	52.4 (49.4, 55.6)	52.4 (49.5, 55.7)	52.5 (48.3, 56.8)
P value	ref.	0.96	0.96
Percentage impaired (95%CI)	10.1 (7.4, 13.5)	12.7 (8.7, 17.6)	13.6 (7.0, 23.0)
P value	ref.	0.54	0.42
F4 – Processing speed			
Total of the subjects	246	145	50
Adjusted mean T score (95% CI)	52.6 (49.5, 56.0)	53.4 (50.4, 56.9)	52.7 (48.5, 57.1)
P value	ref.	0.46	0.94
Percentage impaired (95% CI)	7.5 (5.2, 10.5)	9.9 (6.5, 14.4)	8.5 (3.5, 16.8)
P value	ref.	0.80	0.92

information. The educational backgrounds were estimated by multinomial logistic regression model adjusted for age at evaluation, sex, city, radiation dose, and clinic visits in the Bayesian full likelihood. Non-informative prior, i.e. normal prior, distribution with a mean of 0 and SD of 100 was assumed for the radiation effects and the other regression coefficients. We used OpenBUGS version 3.2.3 (https://github.com/jsta/openbugs); MCMC software to fit the linear mixed-effects model, the mixed-effects logistic regression model, and the multiple imputation, and R version 4.0.1 for the demographic characteristics. A P value less than 0.05 was considered statistically significant.

RESULTS

There were 444 in utero survivors [mean age (SD), 66.9 (0.60) years], including 227 clinical visitors [mean age (SD), 66.9 (0.61) years] and 217 non-visitors [mean age (SD), 66.9 (0.59) years], who provided at least one factor score at either administration and had an estimated radiation dose. The demographic characteristics by radiation dose category were shown in Table 1. Heterogeneity for city ratio by radiation dose category was statistically significant (P value is 0.003.) but not for other characteristics.

Adjusted mean T scores and the percent impaired for any factor did not differ significantly between the control group and the low- and high-dose groups (Table 2). The estimates and 95% Bayesian confidence intervals of the radiation dose and demographic factors for 4 NCQ factors, where radiation dose was treated as continuous values, did not show a significant association between the T scores and radiation dose, either (see Supplementary Table S2; https://doi.org/10.1667/RADE-22-00008.1.S1). Also, there was no significant difference in T scores between clinic visitors and non-visitors and no difference in the association with radiation between clinic visitors and non-visitors (results not shown). We observed no significant increase or decrease in mean T score compared to the control group in either the low- or high-dose group at any gestational age ATB (Fig. 1).

DISCUSSION

Since adverse effects of in utero radiation exposure on cognitive function in childhood were observed in previous RERF studies (*1*, *2*), we hypothesized that such exposure might affect cognitive function in old age. To test this hypothesis, we evaluated subjective cognitive function using NCQ. Yamada et al. also evaluated objective cognitive function using CASI and reported no obvious radiation effects on neurocognitive function in this group, although selection bias related to AHS clinic visits was mentioned as a limitation of the CASI survey (*10*). The NCQ survey, which was conducted for clinic visitors and non-visitors, independently of the CASI survey, reinforced the CASI results showing that in utero survivors who did not suffer from severe neurocognitive function decline in childhood

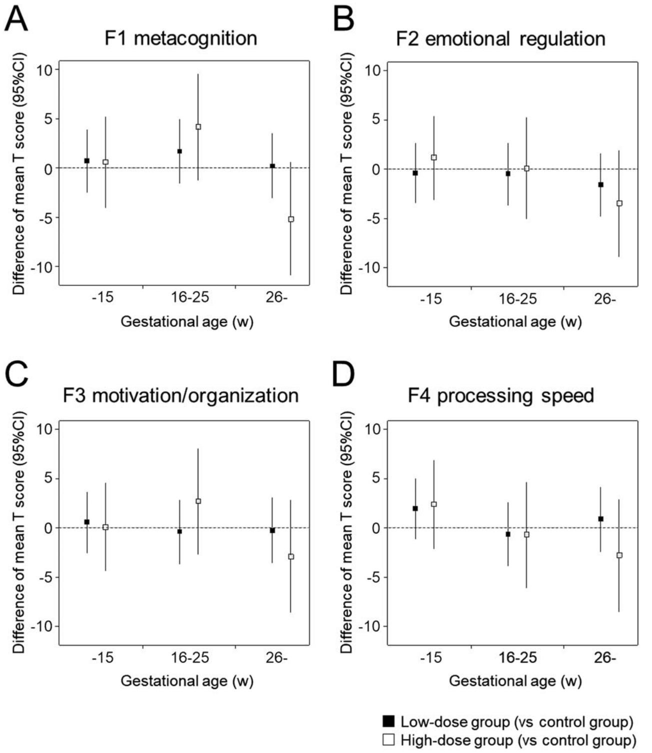

FIG. 1. Association of radiation exposure with 4 NCQ factors by gestational age ATB. (■) and (□) are posterior medians of the difference of mean T score in both the low-dose group and the high-dose group compared with the control group, respectively. The bars are 95% Bayesian confidence intervals. Panel A: F1 metacognition, panel B: F2 emotional regulation, panel C: F3 motivation/organization, panel D: F4 processing speed.

revealed no apparent effects of radiation exposure on their cognitive function in old age.

In the present study population, that consists mostly of survivors exposed to less than 1 Gy except for 5 survivors exposed to 1 Gy or higher, there is no significant association between the T scores of the NCQ factors and radiation dose, either when the radiation doses are separated into categories or treated as continuous values. To our knowledge, we are not aware of there being any other studies on the cognitive function of elder individuals exposed in utero. In this regard, this study is considered valuable.

LIMITATION

Although the decline in subjective or objective cognitive function accelerates with increasing age, the decline is only slight in those under 70 years of age without dementia. (*14*, *16*) The average age of the subjects is 66.9 years, which may be too young to investigate whether fetal radiation exposure accelerates cognitive decline in old age. The NCQ is a self-assessment questionnaire, and the study participants are those who survived at least until 2011 and were able to answer the questions themselves. This may mean a healthy survivor effect remains. In addition, the possibility that erroneous answers due to misunderstanding or false answers may be included cannot be denied.

CONCLUSION

This is the first study using the NCQ to investigate the effects of radiation exposure on subjective neurocognitive function in aged A-bomb survivors exposed in utero, but we could not provide evidence that prenatal radiation exposure adversely affected late-life neurocognitive function. Studies on older people exposed in utero to radiation from non-A-bomb sources will be needed.

SUPPLEMENARY MATERIALS

Table S1. List of NCQ items for the four factors.

Table S2. Association of demographic factors and radiation exposure with estimates of T score for four NCQ factors

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