Environment International 136 (2020) 105371

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence

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ARTICLE INFO

Handling Editor: Paul Whaley

Keywords:
Ionizing radiation
Low dose
Neurodevelopment
Epidemiology
Child health

ABSTRACT

Background: The neurodevelopmental effects of high doses of ionizing radiation (IR) in children are well established. To what extent such effects exist at low-to-moderate doses is unclear. Considering the increasing exposure of the general population to low-to-moderate levels of IR, predominantly from diagnostic procedures, the study of these effects has become a priority for radiation protection.
Objectives: We conducted a systematic review of the current evidence for possible effects of low-to-moderate IR doses received during gestation, childhood and adolescence on different domains of neurodevelopment.
Data sources: Searches were performed in PubMed, Scopus, EMBASE and Psychinfo on the 6th of June 2017 and repeated in December 2018.
Study eligibility criteria: We included studies evaluating the association between low-to-moderate IR doses received during gestation, childhood and adolescence, and neurodevelopmental functions.
Study appraisal and synthesis methods: Studies were evaluated using the Cochrane Collaboration's risk of bias tool adapted to environmental sciences. A qualitative synthesis was performed.
Results: A total of 26 manuscripts were finally selected. Populations analyzed in these publications were exposed to the following sources of IR: atomic bomb (Hiroshima and Nagasaki), diagnostic/therapeutic radiation, and Chernobyl and nuclear weapon testing fallout.

There was *limited* evidence for an association between low-to-moderate doses of IR and a decrease in general cognition and language abilities, that is, a causal interpretation is credible, but chance or confounding cannot not be ruled out with reasonable confidence. Evidence for a possible stronger effect when exposure occurred early in life, in particular, during the fetal period, was *inadequate*. Evidence for an association between IR and other specific domains, including attention, executive function, memory, processing speed, visual-spatial abilities, motor and socio-emotional development, was *inadequate*, due to the very limited number of studies found.
Limitations, conclusions, and implications of key findings: Overall, depending on the domain, there was limited to inadequate evidence for an effect of low-to-moderate IR doses on neurodevelopment. Heterogeneity across studies in terms of outcome and exposure assessment hampered any quantitative synthesis and any stronger conclusion. Future research with adequate dosimetry and covering a range of specific neurodevelopmental outcomes would likely contribute to improve the body of evidence.
Systematic review registration number: The systematic review protocol was registered in PROSPERO (registration number CRD42018091902).

Abbreviations: CI, confidence interval; IQ, intelligence quotient; IR, ionizing radiation; MRI, magnetic resonance imaging; OR, odds ratio; SD, standard deviation; SR, systematic review; WAIS, wechsler adult intelligence scale

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https://doi.org/10.1016/j.envint.2019.105371
Received 24 May 2019; Received in revised form 22 November 2019; Accepted 27 November 2019
Available online 30 January 2020

1. Introduction

Neurodevelopment is a continuous process that starts during prenatal life and extends until young adulthood (Gogtay et al., 2004). Ionizing radiation (IR) at high doses is a well-known risk factor for neurodevelopmental impairment, with the evidence being mainly based on epidemiological studies of childhood brain cancer survivors (Armstrong et al., 2010; de Ruiter et al., 2013; Mulhern et al., 2004). Whether low and moderate doses (defined, respectively, as 100 mGy and below and 100 to 2000 mGy for photon radiation (MELODI, 2019; National Research Council (U.S.), 2006)), can also induce such detrimental effects is under debate. Research on health effects of low-to-moderate doses of IR is considered a priority for radiation protection (MELODI, 2019; Kreuzer et al., 2017) given the current context of increased exposure in the general population. Since the 1980's, the average annual IR dose to the general population of the US, from all sources, has nearly doubled, predominantly because of the increase in medical radiation exposure, which now accounts for approximately half of the average annual IR dose (NCRP Report No, 160, 2009). Similar increases have also been observed in other high income countries (UNSCEAR, 2013, 2008). Research in the low IR dose range is also critical, because, in the unlikely event of another major nuclear accident like that at the Chernobyl nuclear power plant, a large part of the population may receive low levels of radiation doses (Cardis et al., 2006; Cardis and Hatch, 2011).

The carcinogenic effect of IR at moderate doses is well established and the current focus in radiation protection cancer research is in effects at low doses, in order to assess whether the assumptions made for radiological protection concerning the possible magnitude of an effect at low doses are correct. For non-cancer outcomes, the situation is different. Evidence for effects of moderate IR doses (in the range of several hundred mGy) on the vascular system and lens opacities has been increasing in recent years. The effects are not yet firmly established, and much work is underway to assess whether these effects exist and what the underlying mechanisms may be. This is also the case for neurodevelopment effects, though much less work has been conducted on this topic to date. Indeed, an important research priority in the 2019 Strategic Research Agenda of the European MELODI platform (MELODI, 2019), is to evaluate the risk of non-cancer effects, including neurodevelopment effect, at low to moderate dose and to understand possible mechanisms for these effects.

Neurodevelopment refers to the process of acquisition of functional skills, abilities and knowledge, such as cognitive, emotional, and motor skills, that takes place during brain maturation and it is a crucial aspect of an individual's health and wellbeing. We aimed to provide a synthesis of the current evidence for low-to-moderate IR induced neurodevelopmental effects using a Systematic Review (SR) methodology (The Cochrane Collaboration, 2011).

Several SR and *meta*-analysis have been published in the field of radiation protection research (Berrington de Gonzalez et al., 2013; Little et al., 2010; Lorenz et al., 2018), none of them addressing neurodevelopment as an outcome. Here, we propose an innovative SR methodology, in the field of radiation epidemiology, by including risk of bias evaluation tool (Johnson et al., 2014; Morgan et al., 2019; Savitz et al., 2019; The Cochrane Collaboration, 2011), integrated in the synthesis of results (Popay et al., 2006; The Cochrane Collaboration, 2011), together with characterization of the confidence in the findings (Guyatt et al., 2011; Lewin et al., 2018).

The objectives of the present SR are (1) to identify and synthesize all research studies involving humans who have received low-to-moderate IR doses during gestation, childhood, or adolescence (when the brain is still under development); (2) to draw evidence-based conclusions from these studies on the possible effects of low to moderate doses on functional aspects of neurodevelopment; and (3) identify research gaps and recommend appropriate methodology to guide ongoing and future research in this area.

2. Methods

A systematic review protocol was written according to the PRISMA-P 2015 checklist (Moher et al., 2015) and registered in PROSPERO (Booth et al., 2011) (registration number CRD42018091902 (Pasqual et al., 2018)).

2.1. Eligibility criteria

We defined the criteria for inclusion of studies using the PECOs (Population, Exposure, Comparator, Outcome and study design) statement (Johnson et al., 2014; The Cochrane Collaboration, 2011), which guides the selection of relevant studies (Table 1).

The population (P) of interest in the present SR was composed by humans exposed to IR during gestation and/or childhood and/or adolescence.

The exposure (E) was low-to-moderate IR dose to the brain, defined, for the purpose of this study, as doses below 5 Gy. Such doses are well below the brain dose absorbed during cranial radiotherapy (Armstrong et al., 2010; Berrington de Gonzalez et al., 2013; Xu et al., 2008). We then checked if the mean absorbed dose to the brain was of the order of 100 mGy ensuring we could assess the effect of low-to-moderate IR dose in a sizeable portion of the population. In radiation epidemiology, studies addressing this dose-range include the following populations: atomic bomb survivors, populations exposed as a result of the Chernobyl accident, patients exposed to medical radiation (diagnostic, as well as therapeutic exposure for benign and malignant diseases in organs distant from the brain), and the general population exposed to background radiation.

Several comparisons (C) were relevant for inclusion, such as: a) comparison between exposed and unexposed subjects, b) comparison between different categories of dose or proxies of dose (such as radiation treatment site), and c) studies using dose as a continuous variable.

The outcomes (O) considered in this study were neurodevelopmental functions organized in a hierarchical framework (Forns et al., 2012) as follows: 1) the *cognition domain* including five sub-domains: attention, executive function, language, learning and memory, and visual-spatial abilities; 2) the *psychomotor domain* including fine and gross motor abilities; and 3) the *social-emotional domain* comprising social competence, attachment, adaptive behavior, and emotional competence. In this SR we focused on all these functional domains measured through validated cognitive testing (primary endpoints). Definitions of each domain are described in details elsewhere (Forns et al., 2012; Youngstrom et al., 2010).

Surrogate outcomes of the neurodevelopment (such as academic achievement or prevalence of mental disorder) were considered as secondary endpoints, as were pathophysiological brain features assessed by neuroimaging tools (Horton et al., 2014; Saykin et al., 2013).

Only observational studies evaluating long-term neurodevelopment radiation effects (evaluated at least 3 years after exposure) were considered. Language of the articles was restricted to English and no restriction was applied to year of publication.

2.2. Information source

Systematic searches were performed in the main electronic biomedical and psychological sciences databases: PubMed, Scopus, EMBASE, and Psychinfo. We also scanned the reference lists of the studies included, as well as relevant reviews identified through the search and relevant Radiation Protection reports.

2.3. Search strategy and selection of studies

The search strategy reflected the PECO structure detailed above (Table 1). Thus, it was formulated as "Population AND Exposure AND Outcome". The search terms used in each database (PubMed, Scopus,

Table 1
Study selection criteria.

PECOs elements	PECO question formulation*: Among human population that during fetal life/childhood / adolescence were exposed to low-to- moderate doses of IR what is the effect of such levels of dose on neurodevelopment, compared to populations who were not exposed (or were exposed to lower dose levels)? Criteria
Population	
	Studies involving humans exposed during gestation/childhood/ adolescence or studies in which: a) the majority (80%) of the population were exposed during gestation/childhood/adolescence; b) results are reported separately for adults and children/adolescence
Exposure	
	Studies evaluating exposure to ionizing radiation: • Where a dose estimation was reported (cut-off point: cumulative absorbed dose to the brain of 5 Gy) • Where individual doses were not used, but reasonable surrogate measures were used, this applies mainly to the following sources of exposure: medical diagnostic / therapeutic exposure; A-bomb exposure; Chernobyl/ accidental exposure
Comparator	
	a) Comparison between exposed and unexposed subjects, b) Comparison between different categories of dose or proxies of dose (such as radiation treatment site, territories with different contamination levels) c) Studies using a continuous exposure were also included.
Outcome	
	Studies reporting neuropsychological developmental outcomes: • Cognitive outcomes: cognition, intelligence, results from neuropsychological tests, processing speed, attention, language, executive function, learning and memory and visual abilities (visual spatial abilities) • Psychomotor: gross motor skills and fine motor skills • Social-emotional domain: social competence, attachment, adaptative behavior, emotional competence, social skills and social behavior • Surrogate measure of cognitive outcomes. **Studies providing results of neuroimaging parameters as outcomes:** • Structural magnetic resonance imaging (MRI): whole brain volume, volume of specific regions, cortical thickness; Diffusion Tensor Imaging (DTI): fractional anisotropy (measures white matter integrity), mean diffusivity • Functional MRI (fMRI): BOLD (Blood Oxygen Level Dependent); signaling comparison • Computer Tomography Scan: Signs of pathological features (i.e. microbleeds, vasculopathy) or connectivity issues • Positron Emission Tomography (PET-CT scan) • Neuronal activation (electrical /metabolic activity) • Magnetic resonance spectroscopy: Relative metabolite concentration (spectrum of different brain metabolites) • Any outcome not included above but obtained using one of the listed neuroimaging techniques to assess it
Study design	
	• Longitudinal prospective and retrospective observational studies (case-control /cohort studies) • Cross-sectional studies

* Formulation of the PECO question follows recent recommendations by Morgan et al., (Morgan et al., 2018)

EMBASE, and Psychinfo) are provided in Supplementary Table S1. The search was performed on the 6th of June 2017 and repeated in December 2018 to integrate studies potentially published during the review process.

Studies eligibility criteria (Table 1) were defined by EP and MBB, tested on a sample of 20 papers and refined accordingly, until an adequate inter-reviewer agreement, measured with the Cohen's kappa (*K*) coefficient (K > 0.8 was considered a good inter- reviewer agreement).

Studies of potential interest were selected in parallel by EP and MBB using a two-step process: first, by screening the title and the abstract of all the search results and, second, by screening the full text of the records identified in the first step as compliant with the eligibility criteria. The results obtained by each reviewer were compared after each step.

2.4. Management of study records

The study records were managed through CADIMA (Kohl et al., 2018), an open access online tool specifically developed for evidence synthesis in environmental sciences. Once the studies were selected, we collected details on the study publication, study characteristics, exposure assessment, outcome measurement and information for the risk of bias assessment. Data collection was done by EP and revised by MBB. The list of variables collected is available in the Supplementary Table S2.

2.5. Risk of bias in individual studies

We first evaluated the risk of bias in each individual study using an adaptation of the Cochrane Collaboration's risk of bias tool (The Cochrane Collaboration, 2011) developed for observational studies in environmental sciences (Johnson et al., 2014; Lam et al., 2016). Scales for assessing quality or risk of bias were not used because they are not supported by empirical evidence (Savitz et al., 2019; The Cochrane Collaboration, 2011).

We evaluated the following sources of bias: recruitment, blinding, exposure assessment, confounding, outcome assessment, selective reporting, conflict of interest and any other bias of interest (i.e. use of an insensitive instrument for outcome measurement). For each source of bias, we rated the risk of bias as "low", "probably low", "probably high" or "high". A clear definition of each bias source and the judgment criteria are provided in Supplementary Table S3. The bias assessment was individually performed by the two reviewers (EP and MBB) and results were discussed with other co-authors (ITC and EC) to reach consensus.

To help identify important confounders of the relationship between brain dose and neurodevelopmental effects, we examined recent reviews or *meta*-analysis of specific environmental or socio-demographic factors associated with the outcomes of interest. In Supplementary Table S4 we summarized the main findings and rated the potential for confounding in the association between IR and neurodevelopment.

Finally, we derived an overall judgment of the risk of bias at the study level, useful for the results synthesis and confidence characterization (Morgan et al., 2019). To do so, for each bias identified, we evaluated the likelihood that it threatened the validity of the study (Savitz et al., 2019). If one bias was identified and judged to potentially compromise study results, the overall risk of bias judgment was "the study presents one major threat to validity". Where more than one source of bias was identified in the study, in addition to evaluating their likelihood of compromising the validity of the study, the correlation between those biases was also taken into account (Savitz et al., 2019). Therefore, for each study four possible ratings were possible (see legend of Fig. 2).

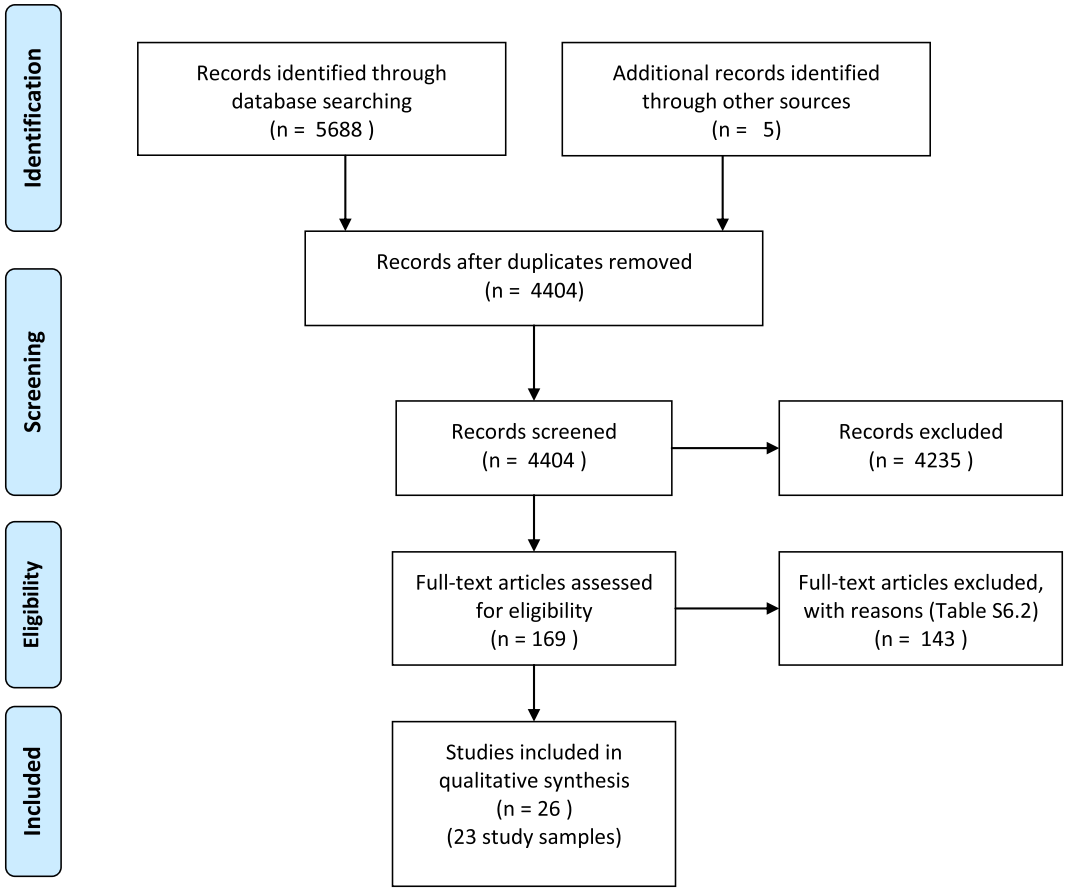

Fig. 1. Flow diagram showing the results of the literature search and screening process. See text for explanation on the divergence between number of studies and number of samples.

2.6. Data synthesis and confidence characterization

Because manuscripts presented strong heterogeneity and did not consistently report quantitative measures that could be pooled in a *meta*-analysis, a qualitative synthesis was performed following the methods indicated in the Cochrane collaboration handbook (Higgins and Green, 2011) and in Popay et al. (Popay et al., 2006). For each neurodevelopmental domain, we built a table reporting the effect estimates from each study. Whenever possible, we transformed the reported results to allow comparison between studies (i.e. translation to IQ scale, calculation of an Odds Ratio from a beta coefficient, etc.). We then summarized, at study level, the direction of the effect using a standardized binary metric (Popay et al., 2006; The Cochrane Collaboration, 2011). Overall, each study was assigned one of these two conclusive statements: "No evidence of an effect reported" (with the symbol ✗) or "Evidence of a decreased neurodevelopmental function associated with IR exposure" (⇩). As a second step, we evaluated the overall direction of the effect suggested across studies (Popay et al., 2006; The Cochrane Collaboration, 2011).

To characterize the confidence in the results for each specific neurodevelopmental domain, we adopted the GRADE approach (Guyatt et al., 2011), using its adaptation to the environmental field (Johnson et al., 2014), and the CERQual methodology (Lewin et al., 2018). Briefly, we evaluated the elements that could affect the level of confidence in the study results. Among the elements that could downgrade the strength of evidence were: (1) presence of methodological concerns; (2) inconsistency of results; (3) low relevance of the studies with respect to the PECO inclusion criteria; (4) inadequacy of the data (few studies/low sample size); and (5) absence of effect estimates and associated confidence intervals. Elements that could upgrade the strength of the evidence were the presence of an effect of large magnitude and of a dose-response relationship. The strength of the available evidence was then rated using an adaptation to the outcomes under study of the IARC Monographs classification of possible human carcinogens as: sufficient, limited, inadequate, and evidence suggesting lack of an effect (see Table 4) (IARC, 2019), following agreement by all co-authors.

3. Results

3.1. Search results

Our search produced 5688 records. Four additional records were identified by screening the reference list of the selected papers and an additional one was identified when the search was repeated in December 2018. After duplicate removal, 4404 titles and abstracts were screened, and 169 records were selected for full-text screening. This resulted in inclusion of 26 full-texts (Fig. 1). The list of records rejected in the title/abstract and full-text screening can be found in Supplementary Tables S5 and S6 respectively. The final list of selected papers can be found in the Supplementary Table S6. The reasons for exclusion of full texts are also reported in Supplementary Table S6. Briefly, 78 full texts were excluded on the basis of the exposure criterion; 12 because of a combination of exposure and outcome criteria; six due to both study design and exposure criteria; 4 because of the population criterion; and 7 for not fulfilling other combinations of criteria. Two did not present primary data and two were found to be duplicates. 14 studies were not accessible and 18 were not written in English. In some studies, from the same original study sample, two separate manuscripts were published evaluating different outcomes, a different follow-up time, or a different subsample (Igumnov and Drozdovitch, 2000; Kolominsky et al., 1999).

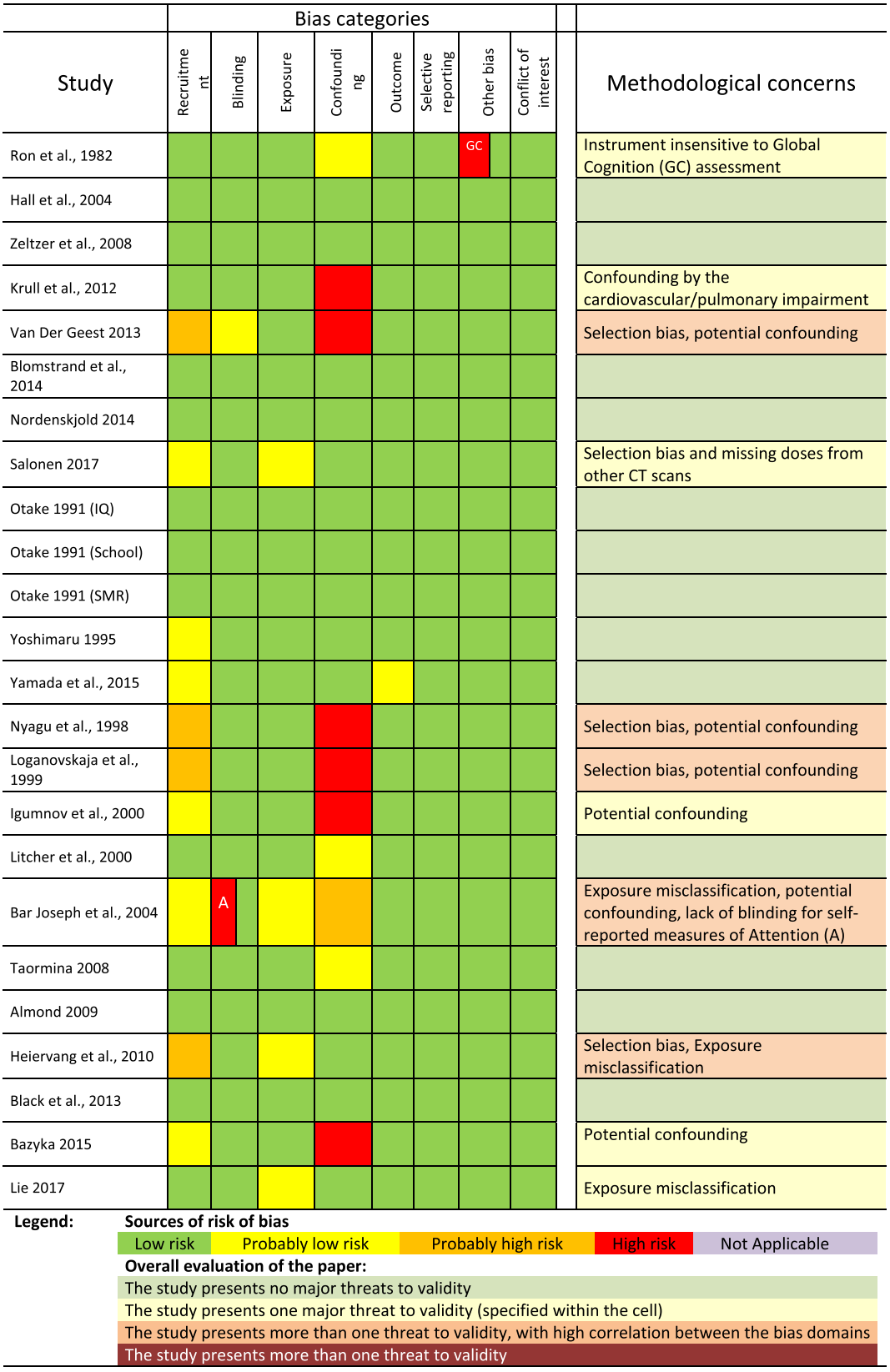

Fig. 2. Results of the evaluation of the risk of the major categories of bias by studies.

Inversely, a single manuscript (Otake et al., 1991) reported results from three different study samples. The resulting number of study samples analyzed in the present review is therefore 23, as reported in Table 2.

3.2. Study characteristics and risk of bias evaluation

Table 2 summarizes the main study characteristics, detailing the population, the type of exposure and dose distribution (where

Table 2
Characteristic of selected studies.

Reference	Methods				Exposure			Outcome	
	Study design	Study population and location	Sample size	Sex (Male %)	Type of exposure	Age at exposure	Dose distribution	Outcome	Age at outcome measurement
Medically exposed population									
Ron et al., 1982	Cohort	Tinea capitis cohort (Israel)	27,084 (10842 irradiated matched to 10,842 controls and to 5400 siblings)	49%	Radiotherapy for benign disease	Mean = 7 years	Mean brain dose ranged from 0.7 to 1.6 Gy (Ron et al., 1988)	General cognition (score of military test); Proxy (education achievement; mental diseases)	10-20 years for education achievement analysis; 17 years for IQ; 9-34 for mental diseases
Hall et al., 2004	Cohort	Cutaneous haemangioma cohort (Sweden)	2,816	100%	Radiotherapy for benign disease	Mean = 7 months	Median dose to the brain = 20 mGy (range 0-2800 mGy)	General cognition & cognitive domains [V,L] (score of military test); Education achievement	18 years
Zeltzer et al., 2008	Cohort	Childhood cancer survivors (United States and Canada)	7,147	49%	Radiotherapy for malignant disease	Median = 7 years (range 0-20)	No radiotherapy 33.6%; Radiotherapy other then cranial 35%; Cranial radiotherapy 30%	Socio-emotional domains (Self-reported test)	32 years (median)
Krull et al., 2012	Cohort	Childhood HL survivors (United States)	62	NR	Radiotherapy for malignant disease	Mean = 15 years	39% < 30 Gy and 61% > 30 Gy to the thorax (*)	General cognition; brain pathological features (MRI)	42.2 years
van der Geest et al., 2013	Cohort	Childhood cancer survivors (The Netherlands)	1,092 (652 childhood cancer survivors; 440 controls)	56%	Radiotherapy for malignant disease	Median = 6 years	7% of survivors received limbs/ abdomen radiotherapy (very low brain dose)	Socio-emotional domains (self-reported test)	23 years (median)
Blomstrand et al., 2014	Cohort	Cutaneous haemangioma cohort (Sweden)	3,030	100%	Radiotherapy for benign disease	Median = 5 months	Median dose to the brain = 20 mGy	General cognition & cognitive domains [V, L] (score of military test); Education achievement	18 years
Nordenskjöld et al., 2015	Cohort	Maternal x-ray pelvimetry cohort (Sweden)	46,066	51%	Diagnostic x-ray exposure	In uterus	3.5% exposed to pelvimetry (estimated fetal dose 1.5 mGy)	Education achievement	15 years
Salonen et al., 2018	Cohort	CT scan exposed cohort (Sweden)	147	54%	Diagnostic x-ray exposure (CT-scan)	Mean = 11 years (2.77y)	For a single head CT-scan, the estimated brain dose is 30 and 50 mGy (Lee et al., 2018).	Cognitive domains [A, E, LM, P, V]; Motor domain	17.8 years
Fallout from the atomic bombings in Hiroshima and Nagasaki									
Otake et al., 1991 IQ analysis	Cohort	Atomic bomb survivors (Japan)	1,673	NR	Gamma-rays and neutrons from the atomic blast	In uterus	Fetus dose < 0.01 Gy 72%; 0.01-0.09 Gy 14.5%; 0.1-0.49 Gy 10%; 0.5-1 Gy 2.5%; > 1Gy 1%	General cognition (IQ)	10-11 years
Otake et al., 1991 School performance	Cohort	Atomic bomb survivors (Japan)	1,090	NR	Gamma-rays and neutrons from the atomic blast	In uterus	Fetus dose < 0.01 Gy 69%; 0.01-0.09 Gy 16.5%; 0.1-0.49 Gy 11%; 0.5-1 Gy 2%; > 1Gy 1%	Proxy of neurodevelopment	10-11 years
Otake et al., 1991 SMR analysis	Cohort	Atomic bomb survivors (Japan)	1,598	NR	Gamma-rays and neutrons from the atomic blast	In uterus	Fetus dose < 0.01 Gy 69%; 0.01-0.09 Gy 13%; 0.1-0.49 Gy 13%; 0.5-1 Gy 3%; > 1Gy 2%	Proxy of neurodevelopment	Less than 17 years
Yoshimaru et al., 1995	Cohort	Atomic bomb survivors (Japan)	888	47%	Gamma-rays and neutrons from the atomic blast	In uterus	Fetus dose < 0.01 Gy 72%; 0.01-0.09 Gy 11%; 0.1-0.49 Gy 13%; 0.5-1 Gy 2.5%; > 1Gy 1.5%	Motor domains (MO)	15-16 years
Yamada et al., 2015	Cohort	Atomic bomb survivors (Japan)	1,844	30%	Gamma-rays and neutrons from the atomic blast	> 13 years old (Maximum 33 years old)	Mean (SD): 434 (727) mGy; 15% above 1 Gy brain dose	General cognition (CASI score)	Between 60 and 80 years old

(*continued on next page*)

Table 2 (*continued*)

Reference	Methods				Exposure			Outcome	
	Study design	Study population and location	Sample size	Sex (Male %)	Type of exposure	Age at exposure	Dose distribution	Outcome	Age at outcome measurement
Environmental disaster exposure									
Nyagu et al., 1998	Cohort	Chernobyl evacuees (Ukraine)	1,339	52%	Evacuees (30 km zone) & children living in strict control zones and moderate contamination areas (with Cs deposition density > 37 kBq/m^2) (#)	In uterus	40% in the exposed group (21% of which were evacuees, 43% residents of contaminated areas), 60% from clean territories	General cognition (IQ), Social-emotional (parent reporting)	6-8 years old
Loganovskaja and Loganovsky, 1999	Cohort	Chernobyl evacuees (Ukraine) (randomly selected from Nyagu (1998)	100	53%	Evacuated from the 30 km exclusion zone of Chernobyl power plant (#)	In uterus	50% evacuee; 50% non-exposed	General cognition (IQ), Social-emotional (parent reporting, emotional/ behaviour disorders)	9-10 years
Igumnov and Drozdovitch, 2000; Kolominsky et al., 1999	Cohort	Chernobyl evacuees (Belarus)	500	51%	Evacuated in 1991–93 from areas with a ^{137}Cs soil deposition density ranging from 100 to 15400 kBq/m^2 ($)	In uterus	50% evacuees (< = 3 Gy to the thyroid) living in Minsk; 50% non-evacuee (Cs deposition density < = 200 Bq/m^2) Mean thyroid dose 0.39 and 0.01 Gy respectively	General cognition (IQ), Social-emotional and motor domain (emotional/behaviour disorders)	6-7 year (First exam); 10-12 years (Second exam)
Bromet et al., 2000; Litcher et al., 2000; Taormina et al., 2008	Cohort	Chernobyl evacuees (Ukraine)	600	48%	Evacuated from the 30 km exclusion zone of Chernobyl power plant (#)	In uterus or < 15 months	50% evacuees living in Kiev; 50% non-evacuees from same classroom as evacuees	**Bromet 2000**: [SE] domain **Litcher 2000:** General cognition & cognitive domains [A, LM], Proxy (school achievement) **Taormina 2008:** Cognitive domains [A, L, LM, V]	**Litcher 2000 & Bromet 2000:** 10-12 years old **Taormina 2008**: Follow up at 19 years of age of Litcher and Bromet 2000 study.
Bar Joseph et al., 2004	Cohort	Chernobyl fallout exposed emigrants (Israel)	1,629	52%	Emigrated from Gomel region and other Belarus areas contaminated with ^{137}Cs	In uterus & up to 4 years at the time of the accident	41% from Gomel (average ^{137}Cs deposition density: 40 to 1480 kBq/m^2). Others from area with < 37 kBq/m^2	General cognition	12-18 years
Almond et al., 2009	Cohort	Chernobyl fallout exposure (Sweden)	562,637	NR	Born between 1983 and 1988 in areas of Sweden with different contamination levels	In uterus	3% from highly contaminated area (^{137}Cs deposition density: 44.2 kBq/m^2). Highest dose to Swedish population estimated to be 4 mGy (Edvarson and Moberg, 1991)	Proxy (School achievement)	16 years
Heiervang et al., 2010a, 2010b	Cohort	Chernobyl fallout exposure (Norway)	178	49%	Norway residents born soon after the Chernobyl accident. Mean external radiation estimate for the exposed areas is 0.935 mSv	In uterus or < 18 months	48% of participants were residents in the most contaminated areas (average dose 0.94 mGy; the comparison group lived in areas of low contamination (average dose 0.01 mGy)	Heiervang et al., 2010a: General cognition (IQ) & cognitive domains [L, V]; Heiervang et al., 2010b: Cognitive domains [A, E, L, P,V]	Median 18.4 years (range 16.3-20 y)
Black et al., 2013	Cohort	Nuclear weapon testing in the Russian Arctic Archipelago 1955-62 (Norway)	603,294	49%	Born between 1956 and 1966. Residents of areas with different contamination levels	In uterus (8-16 weeks of gestation)	Mean (SD) total beta radiation ground deposition for the men sample: 59.76 (91.01) kBq/m^2); for women: 64.77 (98.39) kBq/m^2 (@)	General cognition (score of military test); Education achievement	Adolescence to young adulthood
Bazyka et al., 2015	Cohort	Chernobyl accident exposure (State Registry of Ukraine)	205	48%	Born in areas with different contamination levels in Ukraine	In uterus	Prenatal mean equivalent brain dose = 17.1 (7.1) mGy in exposed and 0.8 (0.02) in non-exposed group	Proxy (mental disorder prevalence) (**)	25-27 years

(*continued on next page*)

Table 2 (*continued*)

Reference	Methods				Exposure			Outcome	
	Study design	Study population and location	Sample size	Sex (Male %)	Type of exposure	Age at exposure	Dose distribution	Outcome	Age at outcome measurement
Lie et al., 2017	Cohort	Chernobyl fallout exposure (Norway)	166,967 exposed 148,744 non-exposed	NR	Exposure during the 5th gestational month	In uterus	Exposed category: < 0.01 mSv 52.5%; 0.01-0.015 31.7%; 0.016-0.023 mSv 11%; > =0.024 mSv 5.2% (##)	Proxy (mental disorder prevalence, school achievement)	Mental retardation (5 years); high school completion (20 y), school grade (16 y)

SMR: Severe Mental Retardation; IQ Intelligence Quotient, HL Hodgkin Lymphoma; NR Not Reported.
([]) In squared brackets domains are identified as following: A attention, E executive function, L language, LM learning & memory, P processing speed, V visual-spatial, SE Socio-Emotional
(*) For a Mantle field radiation therapy the dose to the brain is estimated to vary between 0 and 9 % that of the target dose (depending on the machine type median brain absorbed dose is estimated to be between 0 and 2% of the target dose) (Shamsaldin et al., 1998).
(#) The average effective dose received by people evacuated from the 30 Km zone is about 33 mGy; for areas of 137Cs deposition density > 555 KBq/m2 the estimated effective dose is about 50 mGy and for areas with 137Cs deposition density above 37 kBq/m^2 is about 10 mGy (Cardis et al., 2006).
($) Thyroid dose to the fetus from I-131 was estimated. The mean thyroid dose in the exposed group was 0.39 Gy, and 0.04 Gy in the control group. Brain dose was not estimated but expected to be very low as most of the I-131 dose is deposited in the thyroid. The choice of the thyroid as a target organ in studying neurodevelopment is due to the hypothesis that the thyroid plays a role in neurodevelopment.
(@) Annual dose from nuclear testing fallout in Norway ranged from 150 mGy (coastal and low-density population areas) to 4 mGy (Oslo).
(**) The study also reported results of a number of neuropsychological tests. However, comparison includes the cleanup worker group and it is reported in a graph, thus it is difficult to draw conclusions in this systematic review. Only comparison of prevalence of disease is considered here.
(##) Average combined external and internal dose was estimated as the monthly dose in each municipality over a period of 36 months. Average cumulative doses in the month 5 after the accident were assigned to each participant on the basis of mother's residential history.

available), and the outcomes studied.

There was heterogeneity across studies in terms of exposure type and outcome assessment. Eight studies assessed effects of medical radiation exposure either after treatment for benign diseases, diagnostic imaging or cancer radiotherapy to anatomical areas other than the brain. Eleven studies addressed IR exposure from the Chernobyl accident, and one from nuclear weapon testing. Five studies were based on the atomic bomb survivor's cohort. Regarding the exposure window, fourteen studies assessed prenatal exposure, ten assessed childhood exposure and two adolescent exposure.

The risk of bias assessment (The Cochrane Collaboration, 2011) is summarized in Fig. 2 and detailed in Supplementary Table S7. Sources of bias that presented particular concerns across studies were: "Confounding", "Recruitment" and "Exposure assessment". Considering the evaluation of methodological concerns at study level (last column of Fig. 2), 13 (50%) studies were considered free of major threats to validity, 6 presented one major threat to validity and the others were found to have more than one methodological concern.

3.3. Synthesis of the evidence

Effect measures, as extracted from the manuscripts included in this SR, were grouped by each specific outcome under evaluation: the results for the general cognition domain are shown in Table 3; those for the cognition sub-domains (e.g. attention, executive function), socio-emotional and motor skills domains are presented in Supplementary Table S8. The proxy measures of neurodevelopment (education achievement, presence of specific mental disorders, and evaluation of specific pathological features) are outlined in Supplementary Table S9. Analysis by period of exposure (*in utero* versus post-natal and by weeks of gestation) are shown in Supplementary Table S10.

For all the domains and proxy measures, the synthesis and characterization of the evidence is presented in Table 4.

3.3.1. Cognition domain

3.3.1.1. Global cognitive domain

3.3.1.1.1. Synthesis of results and evaluation of the evidence

Overall, we found that there was *limited* evidence for a decrease in global cognitive function after low-to-moderate doses of IR (Table 4). Evidence was based on 13 relevant studies, 6 of them of good quality, including a total of 276,253 subjects (Table 3). Causal interpretation is credible, with some evidence of a dose-response relationship with a decrease of 4 to 5 IQ points following a 250 mGy brain dose. However, chance or confounding could not be ruled out with reasonable confidence.

3.3.1.1.2. Description of the studies contributing to the evidence

Table 3 summarizes the exposure and outcome measures used, as well as the results of the studies. The majority of the studies (10/14) indicate a lower IQ score with an increased IR exposure.

3.3.1.1.2.1. Outcome characteristics

Instruments used to measure global cognition were various scales of the Intelligence Quotient (IQ) (Black et al., 2013; Blomstrand et al., 2014; Hall et al., 2004; Nyagu et al., 1998; Otake et al., 1991; Ron et al., 1982; Yamada et al., 2015), including the Wechsler Intelligence Scale (Heiervang et al., 2010a; Igumnov and Drozdovitch, 2000; Krull et al., 2012a), the Raven matrices test (Bar Joseph et al., 2004; Loganovskaja and Loganovsky, 1999) and other measurements of verbal and non-verbal intelligence (Litcher et al., 2000). Four of the studies used an IQ score obtained during military recruitment (Black et al., 2013; Blomstrand et al., 2014; Hall et al., 2004; Ron et al., 1982). While Black, Blomstrand, and Hall used the IQ-scale continuously, Ron and collaborators used the army classification "apt" and "not apt to become an officer", a categorization which may not be sensitive enough to detect little changes in IQ points. Most of the studies measured IQ during childhood/adolescence, with the exception of Krull et al. (during adulthood) and Yamada (in elderly). Results by Yamada et al. might

Table 3
Summary of reported associations between ionizing radiation exposure and "global cognition" domain.

Reference*	Exposure	Age at exposure / Age at outcome assessment	Total N (lowest dose category N)	Outcome	Summary of results (transformed in a standardized score)$	Direction of the effect
Atomic bomb survivors						
Otake, Schull and Yoshimaru, 1991	Continuous	Prenatal / 11-12 years	1,202 (862)	Change in IQ score per 0.01 Gy	β = -0.158	⇩
Yamada et al., 2015	Continuous	Adolescence & young adulthood / 60-80 years	1,844 (728)	Change in CASI score per 0.01 Gy	β = 0.064	✗
Medically exposed populations						
Hall et al., 2004	Categorical: frontal and posterior brain dose	Early life / 18 years	2,211 (638)	Military test (*Technical instruction*)	Mean difference in test results (> 250 mGy vs 0 dose)**: -0.33** points in IQ scale*	⇩
Blomstrand et al., 2014	Categorical: hippocampus dose	Early life / 18 years	3,030 (825)	Military test *Combine score* *Technical ability* *Logical ability*	Mean difference in test results (> 250 mGy vs 0 dose) in IQ scaleˆ: -0.28 -1.9 -0.20	⇩
Ron et al., 1982	Irradiated vs non-irradiated	Childhood / 17 years	5,005 (2730 comparison group)	% of subjects in the low IQ category (not apt to be officers during military service)	Prevalence comparison: Magnitude not reported **p < 0.05**	⇩
Krull et al., 2012	Categorical	Childhood / mean 42.2 years	62 (24)	WASI - intelligence domain (less than 30 Gy to the thorax mantle-field radiation vs above)	Magnitude not reported p > 0.05	✗
Environmental exposure						
Black et al., 2013	Continuous (ground & air β-radioactivity residential levels) from weapons testing	Prenatal1 / 8-44 years	260,766 (NR)	Change in mean IQ score obtained from a military test per 1 increment in ground level β-radioactivity	Mean difference in IQ scores per total dose: **-0.04**	⇩
Litcher et al., 2000a	Chernobyl evacuees' vs non-evacuated class-mates	Prenatal & early life/ 10-12 years	600 (300)	Symbolic Relations subtest (nonverbal intelligence)	Mean difference in test score: -0.06	⇩
Igumnov and Drozdovitch, 2000	Chernobyl evacuees' vs non-evacuees	Prenatal / 6–7 years	500 (250)	WISC-III ^{UK} IQ score	Mean difference in score: **-0.36**	⇩
Complementary: Kolominsky, Igumnov and Drozdovitch, 1999		Prenatal / 10–12 years			Mean difference in score: -0.1	
	Individual thyroid doses	Prenatal / 6-7 and 10-11 years	138 (66)	WISC-III ^{UK} IQ score	Pearson's r = 0.15 at 6-7 years; Pearson's r = 0.17 at 10-11 years	✗
Heiervang et al., 2010b	Exposed versus unexposed	Prenatal & early life / 16-20 years	178 (94)	WASI (combined scores)	Mean difference in score: **-0.33**	⇩
Nyagu, Loganovsky and Loganovskaja, 1998	Chernobyl evacuees' vs non-evacuees	Prenatal / 6-8 years	1,339 (795)	% of subject in very low IQ category (IQ < 70)	Comparison of prevalence = **2.44%**	⇩
Loganovskaja and Loganovsky, 1999	Chernobyl evacuees' vs non-evacuees	Prenatal / 9-10 years	100 (50)	% of subject in low IQ category (70 < IQ < 90)	Comparison of prevalence for the Draw a man test = **15%**; Raven coloured matrices = **10%**; BPVS = **10%**	⇩

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Table 3 (*continued*)

Reference*	Exposure	Age at exposure / Age at outcome assessment	Total N (lowest dose category N)	Outcome	Summary of results (transformed in a standardized score)$	Direction of the effect
Bar Joseph et al., 2004	Proxy: residence address at the time of the accident	Prenatal and early life / 12-18 years	1,629 (554)	Raven Standard Progressive Matrices Test	Mean (SD) score among areas: -Highly exposed areas = **57 (29);** -Unexposed regions: a. Other Belarus areas = **58 (30);** b. Moscow & St Petersburg = **64 (30)**	✗

*Colors indicate the overall methodological concern based on the risk of bias evaluation: Green = no major threats to validity; Yellow = one major threat to validity; Orange = more than one threat to validity correlated between them; Red = more than one threat to validity.
$ Transformation of the mean difference into a standardized score has been calculated with the following formula: Standardized score = Mean difference/SD. Thus, we obtained a score which is expressed in number of SD changes. Reported differences refer to the difference between the highest versus lower exposure categories. In **Bold** within the table: p-value < 0.05.
^ IQ was measured in stanine scale (mean 5 and SD 2). We converted in IQ points scale (mean 100 and SD 5) by multiplying the stanine scale result by 7.5 (Blomstrand et al., 2014a).
BPVS British Picture Vocabulary test: The examiner said a word and the child had to indicate the image that illustrated that meaning among 4 pictures presented. **CASI** Cognitive Abilities Screening Instrument, it is a validated screening test for cognitive function and has a score 0-100 (comparable to IQ test). Here they used the short version with a score range 0-49. Higher score means higher cognitive capacity. **IQ Score** Intelligence testing based on an improved version of the Koga test in Hiroshima and Nagasaki and of Tanaka-B test in Nagasaki only, with a mean value and Standard deviation of 100 and 15. **Pearson's r** Pearson correlation between IQ and dose level **Raven Standard Progressive Matrices Test** consist in filling correctly a geometric pattern with a missing piece. **SMR** Severe Mental Retardation. **Symbolic Relations** is a subtest of the Detroit Test of Learning Aptitudes and consists of completing a visual pattern choosing between six possible images. **WAIS** Wechsler Adult Intelligence Scale-III. **WASI** Wechsler Abbreviated Scale of Intelligence. **WISC-III** ^{UK} Wechsler Intelligence Scale for Children.

capture the process of neurodegeneration, and thus may not be fully comparable with those of the other studies.

3.3.1.1.2.2. Exposure assessment

Exposure was mainly evaluated during fetal/early life. Comparison between results of studies where exposures happened during prenatal and post-natal life is discussed separately (Paragraph 3.5).

Regarding the exposure assessment, no risk of bias was found in the studies conducted in the atomic bomb survivors population (Otake et al., 1991; Yamada et al., 2015). The Dosimetry System 86 (DS86) (Roesch, 1987) used in Otake et al. was used in atomic bomb survivors studies for about 20 years until the 2002 dosimetry system (DS02) (used in Yamada et al.,2015) was implemented (Egbert, 2012). The two dosimetry systems are strongly correlated (Cullings et al., 2006), and no major bias is expected in risk estimates in using the DS86 system (Preston et al., 2004). Also studies of medically exposed subjects (Blomstrand et al., 2014; Hall et al., 2004; Krull et al., 2012a; Ron et al., 1982) generally had adequate exposure assessment as information on radiation treatment was based on medical records. Studies in children after the Chernobyl accident in Belarus and Ukraine compared evacuees and non-evacuees (Igumnov and Drozdovitch, 2000; Litcher et al., 2000; Loganovskaja and Loganovsky, 1999), or offspring of mothers who lived in areas with much different levels of exposure (Bar Joseph et al., 2004; Nyagu et al., 1998), thus, exposure misclassification is not likely. The Norwegian (Heiervang et al., 2010a) study of the consequences of the Chernobyl accident used objective measurement data on contamination levels by official place of residence of the mothers during pregnancy/at birth. Contamination levels were, on average, very much lower than in the studies in the territories most affected by the Chernobyl accidents, with consequently narrow exposure ranges and hence little statistical power to detect an effect if any. Thus, reported results might be due to chance, in particular considering the very low sample size. The Norwegian study of Black et al. (2013), comparing areas with different contamination from the fall-out from atmospheric weapon testing in the 1950′s and 60′s, also resulted in a comparison between very low cumulative fetal dose levels, with, therefore, some risk of exposure misclassification and of chance findings.

3.3.1.1.2.3. Additional methodological considerations

Igumnov et al. (2000), Nyagu (1998) and Loganovskaja (1999), and Litcher et al. (2000) who studied the offspring of mothers evacuated after the Chernobyl accident, did not take properly into account maternal stress during pregnancy which has been related to neurodevelopmental impairment (Graignic-Philippe et al., 2014; Tarabulsy et al., 2014; Van den Bergh et al., 2017). In addition to that, evacuees might also had lower socio-economic status compared to non-evacuees and this was not properly taken into account (Igumnov and Drozdovitch, 2000; Litcher et al., 2000; Loganovskaja and Loganovsky, 1999; Nyagu et al., 1998). Bar Joseph et al. (2004) did not consider the children's baseline health status; although they recognized that the exposed and unexposed differed in this respect.

Results from Krull et al. (2012) were difficult to interpret within the question explored here, because it is impossible to disentangle the effect on cognition due to the cardio-pulmonary impairment from that due to the scatter radiation to the brain, in the absence of a valid estimate of brain dose.

Results from Nyagu (1998), Loganovskaja (1999), Igumnov (2000), and Heiervang (2010) could had also be affected by selection bias. Participation rates were not reported and it might be that people with higher exposure or who had concerns about cognitive problems would have been more likely to participate, biasing results.

3.3.1.2. Attention sub-domain

3.3.1.2.1. Synthesis of results and evaluation of the evidence

Evidence for an association between low dose IR exposure and impairment in the attention domain was judged to be *inadequate* (Table 4) as it was based on only four studies with small sample sizes (1449 subjects in total) (Table S8.1).

Table 4
Synthesis and characterization of the evidence.

Summary of findings	Studies contributing to the finding	Elements for assessing the certainty in the evidence		Certainty in the evidence*	Brief rationale of the rating around the certainty of evidence
		Factors that decrease confidence	Factors that increase confidence		
Cognition domain					
General cognition: Decrease with low-to-moderate IR dose.	**No methodological concerns:** Otake et al., 1991; Yamada et al., 2015; Hall et al., 2004; Blomstrand et al., 2014; Litcher et al., 2000; Black et al., 2013 **Some concerns:** Krull et al., 2012; Ron et al.,1982; Igumnov 2000 **Moderate concerns:** Bar Joseph et al., 2004, Heiervang et al., 2010; Nyagu et al.,1998; Loganovkaja et al.,1999	**Methods:** 7 studies presented some/moderate concerns. **Consistency:** Results consistently indicated lower cognition with increasing exposure. **Relevance:** Krull et al., 2012 were not specifically designed to evaluate the effect of low-to- moderate IR to the brain. **Data adequacy:** Statistical power is an issue for Heiervang et al., 2010 (possible chance finding). **Type of effect estimated:** Results mainly based on simple statistical comparisons (mean or prevalence).	**Magnitude of effect:** Mild. A decrease of around 5 IQ points for an exposure of 250 mGy (Otake, Schull, and Yoshimaru 1991; Hall et al., 2004; Blomstrand et al., 2014) **Dose-response gradient:** Three studies of overall high quality and big sample size showed a dose-response relationship favoring the effect after exposure. (Otake et al., 1991; Hall et al., 2004; Blomstrand et al., 2014)	**Limited**	Finding based also on studies of good quality and large sample size. Overall results were consistent, relevant with respect to the present SR question and based on adequate data, although mainly based on simple statistical comparison. Some evidence of a dose response gradient was found.
Attention: Overall no association with low-to-moderate IR dose	**No methodological concerns:** Taormina et al., 2008 **Some concerns:** Salonen et al., 2018; **Moderate concerns:** Heiervang et al., 2010a	**Methods:** Only one studies of overall good quality. **Consistency:** The majority of studies indicated no effect. **Relevance:** All studies were relevant respect to the PECO question. **Data adequacy:** Serious concern for statistical power in Heiervang et al., 2010[a] and Salonen et al., 2018 (given the low dose distribution). **Type of effect estimated:** Results mainly based on statistical comparison (mean or prevalence).	**Magnitude of effect:** Close to 0 **Dose-response gradient:** Not reported	**Inadequate**	Finding based on low number of studies with small sample size, thus chance cannot be ruled out.
Executive function: No clear indication of an association with IR dose.	**Some concerns:** Salonen et al., 2018; **Moderate concerns:** Heiervang et al., 2010a	**Methods:** No studies of good quality. **Consistency:** One of the two studies reported an association across all executive function sub-domains, the other none. **Relevance:** All studies were relevant respect to the PECO question. **Data adequacy:** Serious concern for statistical power in both studies. **Type of effect estimated:** Results mainly based on simple statistical comparisons (mean or prevalence).	**Magnitude of effect:** Not possible to be evaluated. Results likely due to chance. **Dose-response gradient:** Not reported.	**Inadequate**	Finding based on low number of studies with small sample size, thus chance cannot be ruled out.
Language abilities: decrease with low-to-moderate IR dose.	**No methodological concerns:** Blomstrand et al., 2014; Hall et al., 2004; Taormina et al., 2008 **Moderate concerns:** Heiervang et al., 2010a	**Methods:** Overall studies of good quality. **Consistency:** All but one reported an association. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Four studies contributing to the evidence. Out of them, two (Hall et al., 2004; Blomstrand et al., 2014) had a large sample size. Serious concern for Heiervang et al. **Type of effect estimated:** Results mainly based on simple statistical comparison (mean or prevalence).	**Magnitude of effect:** Mild to very small. Difference in score ranged between 8% and 40% of the SD. **Dose-response gradient:** Some evidence of a dose-response relationship from Blomstrand et al. and Hall et al.	**Limited**	Findings based on studies of overall good quality and on adequate data, although mainly based on simple statistical comparisons. The estimated effect was rather small and there was little evidence of a dose-response gradient.

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Table 4 (*continued*)

Summary of findings	Studies contributing to the finding	Elements for assessing the certainty in the evidence		Certainty in the evidence*	Brief rationale of the rating around the certainty of evidence
		Factors that decrease confidence	Factors that increase confidence		
Learning and memory: No clear indication of an association.	**No methodological concerns:** Litcher et al., 2000b; Taormina et al., 2008 **Some concerns:** Salonen et al., 2018; **Moderate concerns:** Heiervang et al., 2010a	**Methods:** Half of the studies present methodological concern. **Consistency:** Half of the studies reported an association. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Overall low sample size. **Type of effect estimated:** Results mainly based on simple statistical comparison (mean or prevalence).	**Magnitude of effect:** Mild to very small. The difference in score ranged between 11% and 75% of the SD. Odds Ratio for maternally-reported memory problems was quite large (Litcher et al., 2000), however likely due to reporting bias. **Dose-response gradient:** Not reported	**Inadequate**	Finding based on studies with small sample size, thus chance cannot be ruled out.
Visual-Spatial domain: Overall no association with low-to-moderate IR dose.	**No methodological concerns:** Hall et al., 2004; Blomstrand et al., 2014; Taormina et al., 2008 **Some concerns:** Salonen et al., 2018; **Moderate concerns:** Heiervang et al., 2010a	**Methods:** two studies presenting some methodological concern, but of overall low sample size (not really contributing to the finding) **Consistency:** Two over five studies reported an association. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Five studies contributed to the evidence. Out of them, two (Hall et al., 2004 and Blomstrand et al., 2014b) had large sample sizes. **Type of effect estimated:** Results were mainly based on simple statistical comparisons (mean or prevalence)	**Magnitude of effect:** Small. In general, it was close to 0. For the two studies that suggested an effect the difference in score between exposed and unexposed is around 20% of the SD. **Dose-response gradient:** No evidence of a dose-response gradient.	**Inadequate**	Findings based on studies of overall good quality, although reporting simple statistical comparison. The magnitude of effect was small and there was no indication of a dose-response relationship.
Motor and coordination domain					
Fine motor abilities: No clear indication of an association.	**No methodological concerns:** Yoshimaru et al., 1995; **Some concerns:** Igumnov et al., 2000; Salonen et al., 2018	**Methodological:** Some concerns in two studies contributing with low sample size **Consistency:** Two out of three studies reported an association for, at least, one of the tests performed **Relevance:** All studies were relevant to the PECO question **Data adequacy:** One of the 3 studies was based on the atomic bomb survivors' sample (large). The other studies had small sample sizes. **Type of effect estimated:** The A-bomb studies presented beta estimates of the effect.	**Magnitude of effect:** Mild. For a Gy of exposure a decrease of 2 SD point was reported. The OR for any motor developmental disorder was 1.9 (Litcher et al., 2000). **Dose-response gradient:** Reported for one of the tests assessed in Yoshimaru et al., 1995.	**Inadequate**	Findings based on overall few studies, only one of them with sufficient sample size and of good quality.
Socio-emotional domain					
Social competence Overall no association with low to moderate IR dose.	**No methodological concerns:** Zeltzer et al., 2008; Taormina et al., 2008 **Some concerns:** Igumnov et al., 2000	**Methods:** Some concerns in one study due to potential confounding bias (Igumnov 2000) **Consistency:** Overall no association was reported **Relevance:** All but one (Zeltzer et al., 2008) were specifically designed to look at the effect of low-to-moderate IR doses and general cognition. **Data adequacy:** Relevant studies were of small sample size. **Type of effect estimated:** OR of impairment in social function reported in 2/3 study. The others were based on simple mean difference.	**Magnitude of effect:** Mild to small. The only study favoring an association reported an OR of 1.32 **Dose-response gradient:** Not reported	**Inadequate**	Findings based on few studies with overall low sample size. The larger study was less relevant to the PECO question.

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Table 4 (*continued*)

Summary of findings	Studies contributing to the finding	Elements for assessing the certainty in the evidence		Certainty in the evidence*	Brief rationale of the rating around the certainty of evidence
		Factors that decrease confidence	Factors that increase confidence		
Emotional domain: Overall no association with low-to-moderate IR dose.	**No methodological concerns:** Zeltzer et al., 2008 **Some concerns:** Igumnov et al., 2000 **Moderate concerns:** Nyagu et al., 1998; Loganovskaja et al., 1999; van der Geest et al., 2013	**Methods:** Most of the studies presented methodological concerns. **Consistency:** Three over five studies reported an association. **Relevance:** All but one (Zeltzer et al., 2008) were specifically designed to look at the effect of low-to-moderate IR doses and neurodevelopment. **Data adequacy:** Relevant studies are of small sample size. **Type of effect estimated:** Odds Ratio of impairment in social function reported in 2/5 study. The other based on simple mean/ prevalence difference.	**Magnitude of effect:** Mild to small. ORs ranged between 1 (Zeltzer et al., 2008) to 2.67 (Igumnov and Drozdovitch 2000). **Dose-response gradient:** A study of overall high quality and big sample size showed a dose-response relationship favouring the effect (Otake, Schull, and Yoshimaru 1991). Also Almond et al.,2009 showed a exposure-response positive gradient (decrease in school grades with increase in 137Cs ground deposition)	**Inadequate**	Findings based on few studies with overall low sample size. The larger study was less relevant to the PECO question. Overall, there were methodological concerns, in particular in studies reporting an association.
Proxies of neurodevelopment					
School grade: a decrease in school grade with increasing IR dose.	**No methodological concerns:** Otake et al.1991; Litcher et al., 2000; Almond 2009; Nordenskjöld et al., 2015 **Some concerns:** Lie et al., 2017	**Methods:** Overall, studies of good quality. **Consistency:** A decrease in school grade with increase in exposure consistently reported. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Studies of large sample size. **Type of effect estimated:** All studies based on a risk effect estimate (beta coef., Relative risk).	**Magnitude of effect:** Mild. Difficult to compare across studies as different grade systems were used. In the A-bomb study for a Gy of exposure a decrease in 0.7/5 was estimated. **Dose-response gradient:** A positive dose-response gradient reported.	**Limited**	Findings were consistent and based on studies of overall good quality and large sample sizes. Suggestion of a dose-response relationship.
School achievement: decrease in probability to attend high school with increasing IR dose.	**No methodological concerns:** Ron et al., 1982; Hall et al., 2004; Almond et al., 2009	**Methods:** Overall, studies of good quality. **Consistency:** Association consistently reported. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Studies of large sample size. **Type of effect estimated:** 2/3 study based on risk effect estimates (beta coeff.).	**Magnitude of effect:** Mild to low. Around 10-15% reduction of probability to attending high school (Hall 2004). 3% difference between low and high contaminated area reported by Almond et al., 2009. **Dose-response gradient:** An exposure (level of 137Cs in ground deposition) - response (decreasing probability to attend high school) reported in Almond et al., 2009.	**Limited**	Findings were consistent and based on studies of overall good quality and large sample size. Suggestion of a dose-response relationship.
School achievement: (High school diploma or higher degree): Overall no association with low to moderate IR dose.	**No methodological concerns:** Yamada et al., 2016; Blomstrand et al., 2014; Black et al., 2013; **Some concerns:** Lie et al., 2017	**Methods:** Overall, studies of good quality. **Consistency:** Association reported in 1/3 of the studies. **Relevance:** Yamada et al., was partially relevant to the PECO question (results of the comparison of school attendance presented in the descriptive table as baseline comparison across categories of dose). **Data adequacy:** Studies of large sample size. Although level of exposure compared in Lie et al., 2017 are extremely low, thus statistical power may be low in this study. **Type of effect estimated:** 3/4 studies based on risk effect estimates (beta coef., OR, RRR).	**Magnitude of effect:** Small. 0.4% difference in obtaining high school diploma between low and high contaminated area reported by Black et al.,2013. **Dose-response gradient:** An exposure (level of ^{137}Cs ground deposition) - response (decreasing probability to attend high school) reported in Almond.	**Inadequate**	Results were inconsistent: A large study of good quality reported an association (of small magnitude), and such decrease was not reported in the other studies (large and of good quality).

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Table 4 (*continued*)

Summary of findings	Studies contributing to the finding	Elements for assessing the certainty in the evidence		Certainty in the evidence*	Brief rationale of the rating around the certainty of evidence
		Factors that decrease confidence	Factors that increase confidence		
Prevalence of mental disorder: Increase risk of mental retardation with low-to-moderate IR dose.	**No methodological concerns:** Otake et al., 1991; Yamada et al., 2016; **Some concerns:** Ron et al., 1982; Igumnov et al., 2000; Bazyka et al., 2015; Lie et al., 2017	**Methods:** Most of the studies presented methodological concerns. **Consistency:** Association reported in 4/6 of the studies. **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Studies of large sample size. **Type of effect estimated:** 4/6 studies based on risk effect estimates (beta coeff., OR, RRR).	**Magnitude of effect:** Low to mild. OR (or RR) ranged between 1.1 and 2.5 **Dose-response gradient:** A dose response gradient reported by Otake 1991.	**Limited**	Findings were based on studies of large sample size. Suggestion of a dose-response relationship. However, some studies have some methodological concerns.
Question of vulnerable period of exposure					
Exposure period sensitivity: Overall, there was an indication of higher effect when exposure occurred in uterus	**No methodological concern:** Otake et al., 1991; Yamada et al., 2016; **Moderate concerns:** Heiervang et al., 2010a	**Methods:** Overall, studies of good quality. **Consistency:** The two studies stratified results by week of gestation and consistently indicated higher effects between the 8–16 weeks. **Relevance:** Studies were partially relevant to the PECO question: We reported results overall comparable except for the exposure window. Studies reporting stratification by exposure period were also considered. **Data adequacy:** The A-bomb survivors' population was included. Serious concern for statistical power for Heiervang et al. **Type of effect estimated:** Two studies reported a beta coeff.	**Magnitude of effect:** Not relevant for the judgment **Dose-response gradient:** Not relevant for the judgment	**Inadequate**	Findings based on the two A-bomb survivor studies, however comparison between them may not be fully adequate as outcome was assessed in different period of life.

Coeff. Coefficient; **OR** Odds Ratio; **RR** Relative Risk; **RRR** Relative risk ratio; **SD** Standard deviation; **A-Bomb** Atomic Bomb

***Legend certainty of the evidence as based on IARC monograph preamble (IARC, 2019)**

Sufficient	A causal association between the exposure and the outcome has been established. That is, a positive association has been observed in the body of evidence on radiation dose and the outcome of interest in studies in which chance, bias, and confounding were ruled out with reasonable confidence
Limited	A causal interpretation of the positive association observed in the body of evidence on radiation exposure and the outcome of interest is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.
Inadequate	The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and outcome
Evidence of lack of effect	There are several high-quality studies covering the full range of levels of exposure of interest, which are mutually consistent in not showing a positive association between dose and the studied outcome at any observed level of dose

3.3.1.2.2. Description of the studies contributing to the finding

Three studies (Heiervang et al., 2010b; Litcher et al., 2000; Taormina et al., 2008) evaluated the effects of environmental exposures during the prenatal period, whereas Salonen et al., 2018 evaluated exposure to CT-scan during childhood. Only one study (Heiervang et al., 2010b) reported a lower attention score in the exposed as compared to the unexposed, although results are likely due to chance, as exposure misclassification was likely and the sample size was too small to detect an effect at these very low dose levels. There was also potential for a selection bias as the percentage of identified, contacted and recruited participants was not given, nor is the reason for non-participation. Further, the exposed population (recruited in areas with relatively small populations) may not be comparable to the control (recruited from other areas, including Oslo).

Statistical power was also an issue in Salonen et al. as based on a comparison between having or not having received a CT-scan during a randomized control trial, without taking into account interindividual variability (patient and technical parameters setting) and range of dose (Tueller et al., 2016). In addition, there was concern about a possible misclassification of exposure as only CTs received during the randomized control trial were recorded, hence possibly missing other CTs.

3.3.1.3. Executive function and processing speed sub-domain

3.3.1.3.1. Synthesis of results and evaluation of the evidence

We found *inadequate* evidence for an association between IR exposure and executive function (Table 4) and processing speed. Findings were based only on two small studies (325 total subjects) with methodological concerns (Heiervang et al., 2010b; Salonen et al., 2018) (Table S8.2).

3.3.1.3.2. Description of the studies contributing to the finding

The results of the two studies contributing to the finding were not consistent: Heiervang et al. (2010) reported an association, while Salonen et al. (2018) not (Table S8.2). The two studies had serious concerns regarding statistical power and presented some methodological limitations as described under the "Attention" domain.

3.3.1.4. Language sub-domain

3.3.1.4.1. Synthesis of results and evaluation of the evidence

There was *limited* evidence for an association between IR exposure and impairment in the language domain (Table 4). This assessment was based on four studies including 3814 subjects in total (Blomstrand et al., 2014; Hall et al., 2004; Heiervang et al., 2010b; Taormina et al., 2008). There were no major methodological concerns except for the Heiervang et al. study (see Attention domain above). All studies conducted a comparison of mean test scores across exposure categories. The estimated effect was small and there was some evidence for a dose-response gradient (Table S8.3).

3.3.1.4.2. Description of the studies contributing to the finding

All studies contributing to the above assessment evaluated the effects of exposure during the prenatal period or the first months of life (Table S8.3). The two haemangioma cohort studies (Blomstrand et al., 2014; Hall et al., 2004) reported a difference in the language domain of approximately 5 IQ points between the lowest (0 mGy) and the highest exposure (> 250 mGy) categories. Heiervang et al. (2010) also reported a decrease of around 5 IQ points in the WAIS Vocabulary subtest among those exposed compared to the unexposed; this, however, was likely due to chance as explained above under "Attention" domain. Results of the WAIS "Similarities and Information" subtest reported by Taormina et al. (2008) were null.

3.3.1.5. Learning and memory sub-domain

3.3.1.5.1. Synthesis of results and evaluation of the evidence

Evidence for an association between IR exposure and learning and memory sub-domain was *inadequate* (Table 4). Four studies of overall low statistical power (1449 subjects) (Heiervang et al., 2010b; Litcher et al., 2000; Salonen et al., 2018; Taormina et al., 2008) contributed to this finding (Table S8.4).

3.3.1.5.2. Description of the studies contributing to the finding

Three studies used measures of both verbal and visual memory (Heiervang et al., 2010b; Salonen et al., 2018; Taormina et al., 2008). Salonen et al. (2018) evaluated exposure during childhood, whereas the other authors did it during fetal and early life. Differences reported were generally close to 0, except in the Heiervang et al. (2010) paper, where the differences could have been due to chance finding, as explained above (Attention domain).

Lie et al. (2017), Litcher et al. (2000), Taormina et al. (2008) estimated the OR of memory problems as reported by the mother and participants (not listed in Table S8.4, as standardized measurements were prioritized). Litcher et al. (2000) reported an odds ratio (OR) of mother-reported memory problems of 5.25 (95% Confidence Intervals (CI) = 2.03; 13.55) for the exposed, however, the difference in the memory test score was close to zero. In the follow-up of the study population in Litcher et al. (Taormina et al., 2008), similar higher OR for mother-reported problems were found (OR = 4.2 (95% CI = 2.1; 8.5) in the high educated stratum; and an OR of 2.3 (95% CI = 1.4; 3.6) in the low educated stratum. These findings suggested the presence of maternal concerns about the health effects of Chernobyl on their child, rather than true memory impairment.

3.3.1.6. Visual-spatial sub-domain

3.3.1.6.1. Synthesis of results and evaluation of the evidence

We found *inadequate* evidence for impaired visual-spatial abilities after exposure to low dose IR (Table 4). This conclusion was based on five studies (3,961 total subjects) (Blomstrand et al., 2014; Hall et al., 2004; Heiervang et al., 2010a; Salonen et al., 2018; Taormina et al., 2008) reporting no association (Table S8.5).

3.3.1.6.2. Description of the studies contributing to the finding

Exposure was mainly evaluated *in utero* (Heiervang et al., 2010b; Taormina et al., 2008), and in early in life (Blomstrand et al., 2014; Hall et al., 2004). One small study evaluated the effect of exposure during childhood (Salonen et al., 2018). There were some methodological concerns about Heiervang et al. (2010) and Salonen et al. (2018) (outlined above), however they contributed with low sample size. Visual-spatial abilities were evaluated in the two large haemangioma cohorts (Blomstrand et al., 2014; Hall et al., 2004) and no effect was reported.

3.3.2. Motor domain

3.3.2.1. Fine motor sub-domain

3.3.2.1.1. Synthesis of results and evaluation of the evidence

Evidence for an association between motor impairment and IR exposure was found to be *inadequate* (Table 4), based on only three studies (Igumnov and Drozdovitch, 2000; Salonen et al., 2018; Yoshimaru et al., 1995) including 1535 subjects overall (Table S8.6). There was little evidence for a dose-response.

3.3.2.1.2. Description of the studies contributing to the finding

Yoshimaru et al. (1995) and Igumnov et al. (2000) evaluated the effect of being exposed to IR during prenatal life. Yoshimaru et al. had the largest sample size among the studies evaluating motor skills and reported a decrease in grip strength and repetitive action tests score with increasing radiation exposure; however, this decrease was not confirmed in subsequent sensitivity analysis where the cases with severe mental retardation were excluded. Igumnov et al. (2000) reported an increased OR for motor coordination disorders (ICD-10 code F82) in the Chernobyl-evacuee group. Salonen et al. (2018) did not report any differences in motor performance (finger tapping tests) between exposed and unexposed subjects, however the study had low statistical power as outlined above (Attention domain).

3.3.3. Socio-emotional domain

3.3.3.1. Social competence sub-domain

3.3.3.1.1. Synthesis of results and evaluation of the evidence

Evidence of impairment in the social functioning domain after IR exposure was *inadequate* (Table 4). Only three studies (Igumnov and Drozdovitch, 2000; Taormina et al., 2008; Zeltzer et al., 2008), with total sample size of 5780 subjects, reported a null or a small effect (Table S8.7).

3.3.3.1.2. Description of the studies contributing to the finding

Table S8.7 reported the associations between IR exposure and social functioning impairment. The larger study on this domain (Zeltzer et al., 2008) evaluated social competences in cancer survivors and was considered less relevant to the PECO question, as the main aim of the paper did not coincide with the question explored here. The other two were conducted in Chernobyl evacuees exposed during prenatal life (Igumnov and Drozdovitch, 2000; Taormina et al., 2008). Igumnov et al. reported a 1.32 (95% CI = 0.82; 4.79) increase in risk of social functioning disorders. Overall, no association between the social competence sub-domain and IR was found in Taormina et al. (2008).

3.3.3.2. Emotional development sub-domain

3.3.3.2.1. Synthesis of results and evaluation of the evidence

We found *inadequate evidence* of an association between IR exposure and emotional impairment (Table 4). This finding was based on five studies (7,271 subjects) (Igumnov and Drozdovitch, 2000; Loganovskaja and Loganovsky, 1999; Nyagu et al., 1998; van der Geest et al., 2013; Zeltzer et al., 2008). An association was reported in three studies (Table S8.8) (Igumnov and Drozdovitch, 2000; Loganovskaja and Loganovsky, 1999; Nyagu et al., 1998) which could had been affected by some methodological issues.

3.3.3.2.2. Description of the studies contributing to the finding

The studies on cancer survivors (van der Geest et al., 2013; Zeltzer et al., 2008) did not report any association between radiotherapy to anatomical areas other than the cranium and emotional impairment. However, they were both less relevant to this SR, as the main objective of the two studies was to assess neurocognitive function in childhood cancer survivors.

The studies on Chernobyl evacuees (Igumnov and Drozdovitch, 2000; Loganovskaja and Loganovsky, 1999; Nyagu et al., 1998) reported a higher prevalence of emotional disorders in the evacuee population; however such comparison (evacuees versus non-evacuees) may had been confounded by other factors such as socioeconomic status and maternal stress during pregnancy. Also, some concerns existed regarding the selection of participants and the exposure assessment in the studies from Nyagu (1998) and Loganovskaja (1999), as participation rate was not reported and it could have been higher among the most concerned (the ones who were most exposed, the ones who presented some cognitive impairment).

3.3.4. Proxies of neuropsychological development

3.3.4.1. School performance

3.3.4.1.1. School grade

3.3.4.1.1.1. Synthesis of results and evaluation of the evidence

There was *limited* evidence of a decrease in school grades with increasing radiation exposure (Table 4). This finding was based on five studies (Almond et al., 2009; Black et al., 2013; Lie et al., 2017; Litcher et al., 2000; Nordenskjöld et al., 2015; Otake et al., 1991) with very large sample sizes (761,589 subjects in total) and without major methodological concerns. A dose-response gradient was reported in two of the studies (Almond et al., 2009; Otake et al., 1991).

3.3.4.1.1.2. Description of the studies contributing to the finding

Studies generally summarized school grade in a single score, however, in different ways, thus hampering comparison. Comparison was also difficult because this outcome was assessed at different age points (Table S9.1). In the in-uterus A-bomb survivor's cohort (Otake et al., 1991), a decrease in school grades, for the first year of elementary school, of 0.7 points per 1 Gy was reported (school grades ranged from 0 to 5). Similar results were obtained in other years of elementary school. Lie et al. (2017) found a dose-related decrease in mathematics grades though the doses compared were very low. Therefore, exposure misclassification and statistical power might be an issue here. Almond et al. summed the grades of 16 school subjects for each participant (ranging between 0 and 320) and found a reduction of 0.044 points in total grades for each increase of 1 kBq/m^2 in ^{137}Cs ground deposition. School grades were not associated with radiation exposure in Litcher et al. (2000) and in Nordenskjold et al. (2015).

3.3.4.1.2. School achievement

3.3.4.1.2.1. Synthesis of results and evaluation of the evidence

There was *limited* evidence of a decreased probability of attending high school in relation to radiation exposure (Table 4). This finding was based on three studies of good quality (Almond et al., 2009; Hall et al., 2004; Ron et al., 1982) with a total large sample size (of 569,095 subjects) that consistently reported such an association.

Evidence of a decrease in high school completion or for a higher-level school achievement with increasing exposure was *inadequate* (Table 4). Only one study (Black et al., 2013) out of four good quality studies (Black et al., 2013; Blomstrand et al., 2014; Lie et al., 2017; Yamada et al., 2015) with a total sample size of 593,154 subjects reported an association.

3.3.4.1.2.2. Description of the studies contributing to the finding

Supplementary Table S9.1 reported the results on school achievement associated with IR exposure, stratified by before and after completion of high school. In the two Swedish haemangioma cohorts, Hall et al. (2004) reported a decreasing probability of attending high school with increasing dose. In particular, for an exposure of 50 mGy to the frontal brain, a decrease of around 11 to 14% in the probability of attending high school was found. The decrease was found to be greater for those in the middle socio-economic level (Hall et al., 2004). However, when evaluating completion of a post-high school degree, Blomstrand et al. (2014) did not report any similar decrease. In the *tinea capitis* study, irradiated subjects had a lower score in the high school admission test, compared to non-irradiated (Ron et al., 1982). Similarly, in the Nordic countries studies, Almond et al., (2009) reported that, for each increase of 1 kBq/m^2 in ^{137}Cs ground deposition in the place of birth, the probability of qualification for high school was reduced by 0.053% points. Lie et al. (2017) reported a slight increase in risk of not completing high school in the "highest" exposure group, however the comparison was made between those receiving less than 0.01 mSv (reference group) versus those receiving 0.04 mSv (highest exposure group), thus, being meaningless as both dose group were in a very low dose range. Black et al. (2013) reported a 0.4% reduction in the probability of obtaining a high school diploma for each increase of 1 kBq/m^2 in ^{137}Cs ground deposition.

Two studies evaluated the total number of years of education achieved. In A-bomb survivors exposed in adolescence or young adulthood, Yamada et al. (2016) compared school achievement across different dose categories and found no meaningful differences. Black et al. (2013) reported a reduction of 0.072 and of 0.086 years of total education achieved for each increase of 1 kBq/m^2 in ^{137}Cs ground deposition at the place of birth for males and females, respectively.

3.3.4.2. Presence of mental disorders

3.3.4.2.1. Synthesis of results and evaluation of the evidence

There was *limited* evidence for an increase in mental health disorders after exposure to low-to-moderate IR dose (Table 4). This finding was based on six studies of large sample sizes (total n = 169,103 subjects) (Bazyka et al., 2015; Igumnov and Drozdovitch, 2000; Lie et al., 2017; Otake et al., 1991; Ron et al., 1982; Yamada et al., 2015); however, there were some concerns regarding the methodology used in some of these studies (Bazyka et al., 2015; Igumnov and Drozdovitch, 2000; Ron et al., 1982). The atomic bomb survivor studies suggested a dose-response relationship (Otake et al., 1991).

3.3.4.2.2. Description of the studies contributing to the finding

There was substantial heterogeneity across studies in terms of outcome definition, hampering the comparison of the study results (Supplementary Table S9.2). A higher risk of mental retardation was reported by Otake et al. (1991), Ron et al. (1982) and Lie et al. (2017).

Identification of post-irradiation mental retardation cases in Ron et al. (1982) might not be accurate due to facts that the date of diagnosis for mental retardation was not available. The two Chernobyl evacuee studies also reported a higher prevalence of mental and neurological disorders associated with radiation exposure (Bazyka et al., 2015; Igumnov and Drozdovitch, 2000), however, they did not fully take into account the role of stress in the evacuee mother.

3.3.4.3. Pathophysiological features

In the Supplementary Table S9.3 we reported the findings of radiation-related abnormal brain activity and morphology.

Krull et al. (2012) reported a higher presence of leuco-encephalopathy and hemosiderin deposits (assessed with an MRI) in subjects receiving higher thoracic radiotherapy doses. Loganovskaja et al. reported some differences in brain electric activity, measured with an electroencephalogram, between evacuees and non-evacuees.

3.3.5. Vulnerable exposure period

3.3.5.1. Synthesis of results and evaluation of the evidence

There was *inadequate* evidence of a higher neurodevelopmental effect associated to exposures occurring during fetal life as compared to exposure during adolescence/early adulthood (Table 4). This finding was mainly based on two studies in atomic bomb survivors (Otake et al., 1991; Yamada et al., 2015).

3.3.5.2. Description of the studies contributing to the finding

Supplementary Table S10 reported the results of stratified analysis by period of exposure. In the atomic bomb survivors study, two different analyses were conducted: one on the population exposed *in utero* (Otake et al., 1991) and the other on survivors exposed during adolescence (Yamada et al., 2015). Only the analysis on *in utero*-exposed reported an association, thus, the neurodevelopmental effect of IR might be higher for a prenatal exposure. The two analyses were of good quality. However, they were not fully adequate to specifically answer the question of effect modification by age at exposure because they differed largely in terms of the age at outcome assessment: Otake et al. measured IQ during childhood, whereas Yamada et al. studied cognitive decline in people aged 60-80 years; hence, the comparison was difficult, as radiation may affect cognition differently at the different extremes of the human lifespan.

Concerning the analysis by weeks of gestation, as reported by two studies, (Heiervang et al., 2010b; Otake et al., 1991) (total n = 1286 subjects), a higher effect was consistently reported for the 8 to 16 week of gestation respect to other gestational periods.

4. Discussion

In the present SR we summarized the current evidence on effects of low-to-moderate doses of IR during fetal life, childhood and adolescence on neuropsychological functions. To our knowledge, this is the first SR providing such a synthesis. Overall, we concluded that there was *limited* to *inadequate* evidence for an association between low-to-moderate doses of IR and different domains and sub-domains of neurodevelopment (Table 6).

In particular, we found that there was *limited evidence* for a decrease in general cognition and language domain associated to IR exposure. When considering secondary outcomes, we found *limited* evidence of an association between IR exposure and a decrease in high school attendance and school grades, and of an increased risk of mental retardation.

For the other neurodevelopmental domains, the paucity of studies and the presence of methodological concerns precluded any conclusive assessment and we concluded there was *inadequate* evidence for an effect of low to moderate doses on these outcomes.

Though there was some suggestion of a stronger cognitive effect when exposure occurred early in life, in particular *in utero*, than in adolescence or adulthood, the studies had limitations and we concluded that the reviewed evidence was inadequate.

It should be noted that animal studies have identified the fetal period as the most vulnerable window for radiation-related neurodevelopmental effects (Kempf et al., 2013; Verreet et al., 2015). Among atomic bomb survivors exposed *in utero*, Otake et al. (1991) identified the period between 8 and 16 weeks of gestational age as the most vulnerable period for a radiation-induced neurodevelopment deficit. This may be explained by the embryological development of the brain: organogenesis occurs before week 8 of gestation, period when anatomical malformations may occur (i.e. misfolding of the primitive neural tube) (Moore and Persaud, 2015). In the following period (from 9 weeks of gestational age onwards), organs grow and mature with potential for functional disturbances occurrence (Moore and Persaud, 2015). These observations tend to add credibility to the finding of a stronger effect in early life, which should be investigated further.

4.1. Strengths and limitations of this systematic review

One of the main limitations of our SR was that a quantitative synthesis was not possible with the data collected, given the differences in outcomes, exposure measures, and type of effect estimated. Thus, the present SR could not provide a combined estimate of an effect and a measure of its uncertainty. It was only possible to provide a qualitative synthesis, which, however, helps to draw conclusion to guide both future researches on this topic and radiation protection policies.

One of the main strengths of the present SR was the inclusion of the entire spectrum of neurodevelopmental functions, making a clear distinction in the interpretation of the results between the use of validated neuropsychological instruments and the use of proxies, such as educational achievement. This approach may be taken in consideration in the design of future studies in this topic.

Another original point is that we aimed to conduct an evidence synthesis, that is, using a systematic review methodology, adapted to the environmental science stream, we provided conclusive statements together with the characterization of the strength of the evidence. Such approach meant a transparent critical review of all the included studies. The identification and the discussion of methodological limitations in the studies reviewed may be useful to others when designing and interpreting future studies in this area.

4.2. Radiation protection concerns

4.2.1. Dose-response relationship

Only five studies evaluated whether there was a dose-related effect on the neuropsychological function (Blomstrand et al., 2014; Hall et al., 2004; Otake et al., 1991; Yamada et al., 2015; Yoshimaru et al., 1995). Taken together, these studies indicate a decrease in cognition associated to an increase in radiation exposure of approximately 0.15-0.2 IQ points for each 100 mGy of dose (Blomstrand et al., 2014; Hall et al., 2004; Otake et al., 1991). To contextualize, in a pediatric head CT-scan, the absorbed brain dose is estimated to be between 30 and 50 mGy (Lee et al., 2018). Therefore, if we assume the size of the effect is proportional to the dose, we would expect, hypothetically, an IQ decrease of around 0.45-0.75 IQ points per head CT-scan. Although such a decrease may be considered as clinically irrelevant at the individual level, the public health importance may be relevant, particularly since such type of exposure is dramatically increasing (UNSCEAR, 2008). Moreover, even a small increase in dose from 1 CT could be of importance in a population that may already be at risk of neurodevelopmental impairment, which may be the case for patients with specific neurological diseases diagnosed or followed-up with CT-scans (Journy et al., 2016).

4.2.2. Relevant target organ

The study of radiation-related neurodevelopmental deficits requires estimating doses to the adequate target organ, and there was variation across studies in terms of the organ under study.

The two haemangioma studies (Blomstrand et al., 2014; Hall et al., 2004) estimated the dose absorbed in different parts of the brain and evaluated the association of the dose in each anatomical structure with specific neurodevelopmental outcomes. Such "regional-dose" approach was also implemented in studies of neurodevelopmental function in cranial radiotherapy survivors (Armstrong et al., 2010; Doger de Speville et al., 2017) and is also used in studies of neurodevelopmental function and non-IR exposure (Foerster et al., 2018; Schoeni et al., 2015; Cabré-Riera, 2019). Indeed, if the distribution of dose is heterogeneous in the brain, such an approach will be more powerful as, if the appropriate target area is used, this will reduce dose misclassification. Blomstrand et al. (2014) found that the dose to the hippocampus presented the best correlation with a reduction in the cognitive score, although chance could not be ruled out. However, it is well known that, in cranial radiotherapy patients, a reduction in the dose delivered to the hippocampus results in a lower risk of cognitive impairment (Kazda et al., 2014), suggesting that the hippocampus may be a brain area particularly vulnerable to IR damage.

In the study of evacuees from contaminated territories of Belarus (Igumnov and Drozdovitch, 2000; Kolominsky et al., 1999) thyroid fetal doses were estimated. Thyroid function plays a crucial role in neurodevelopment (Calzà et al., 2015), as illustrated by the link between iodine deficiency and severe mental health dysfunction, known as cretinism. Maternal thyroid function during pregnancy also influences child neurodevelopment (Levie et al., 2018).

It has also been hypothesized that a high radiation dose to the cardiovascular system may have an effect on cognitive function (Krull et al., 2012b; Padovani et al., 2012). Krull and collaborators studied the association between cognition and radiotherapy dose to the thorax, which would have also resulted in low-to-moderate doses to the brain but in much higher doses to the heart and large vessels (Krull et al., 2012a).

4.2.3. Radiation-induced brain morphological changes

We also aimed to include studies addressing morphological or functional features of the brain measured with imaging techniques. Only one study evaluated the possible radiation-related imaging findings (Krull et al., 2012a), although the study design, based on the comparison of participants receiving different dose levels of thoracic radiotherapy, did not allow to draw any conclusion regarding a possible direct radiation effect on the brain structures.

Schull et al. (1991) used MRI to study five cases of mentally retarded atomic bomb survivors, exposed at the prenatal stage (Schull et al., 1991; Schull and Otake, 1999). Signs of failure in migration of neurons (grey ectopic areas) and signs of abnormal brain architecture (macrogyria and mega cisterna magna) were reported among these subjects (Schull and Otake, 1999). Imaging studies on cranial radiotherapy survivors, who received doses much higher than those studied here, generally report white matter damage (Correa et al., 2004; Jacola et al., 2016; Reddick et al., 2003), cerebral microbleeds (Roddy et al., 2016), and a reduction of the hippocampus volume (Ma et al., 2016). The inclusion of non-ionizing radiation imaging tools, such as MRI scan, in research studies could help advance the understanding of the pathophysiology of neurodevelopmental impairment after radiation exposure (Horton et al., 2014; Saykin et al., 2013).

4.3. Conclusions and research recommendations

Overall, the number of large-scale studies of good quality was low for each specific aspect of neurodevelopment evaluated. Furthermore, some of the studies reviewed had low statistical power to detect an effect and inadequate dosimetry, if any. Future studies, larger in size, with careful individual dose reconstruction and collection of information on potential confounding factors would be helpful to reduce uncertainty about the potential effects of low ionizing radiation doses on neurodevelopment in young people as well as in cognitive decline in the elderly.

The field of neuropsychology has evolved during the past years and new specific and validated tests are currently available. Computerized tests have been implemented in several epidemiological studies (Conklin et al. 2013; Sunyer et al., 2015; López-Vicente et al., 2016) with ample benefit in terms of efficiency and standardization for the data collection and statistical analysis. It is important to plan a battery of tests that includes several domains at different levels of hierarchy. Processing speed, executive function, attention and memory should be prioritized because the available scientific evidence suggests they are affected by high dose radiation (i.e. cranial radiotherapy) (Krull et al., 2018; Ullrich and Embry, 2012) and may, therefore, also be affected at lower dose levels.

In conclusion, there is, at the time of this review, *limited* to *inadequate* evidence of an effect of low to moderate ionizing radiation doses on neurodevelopment. However, the possibility of neurodevelopmental effect of low-to-moderate doses of radiation needs to be addressed given the ever growing and evolving IR imaging technologies and resulting dose increases in pediatric radiology. Such research is important both from a research perspective to better characterize a possible association in terms of magnitude of effect, specific domain and brain structure damage; and from a public health and radiological protection perspective to ensure adequate protection of the pediatric and young adult population.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgement

ISGlobal is a member of CERCA programme, Generalitat de Catalunya.

The present publication has been funded by the project KIDMEDRAD (PI16/00120), funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF, "A way to make Europe").

We thank Dr. Liudmilla Liutsko for her help in understanding the social context of populations affected by Chernobyl disaster.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105371.

References

Almond, D., Edlund, L., Palme, M., 2009. Chernobyl's subclinical legacy: prenatal exposure to radioactive fallout and school outcomes in Sweden. Q. J. Econ. 124, 1729–1772. https://doi.org/10.1162/qjec.2009.124.4.1729.

Armstrong, G.T., Jain, N., Liu, W., Merchant, T.E., Stovall, M., Srivastava, D.K., Gurney, J.G., Packer, R.J., Robison, L.L., Krull, K.R., 2010. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. Neuro-Oncol. 12, 1173–1186. https://doi.org/10.1093/neuonc/noq104.

Bar Joseph, N., Reisfeld, D., Tirosh, E., Silman, Z., Rennert, G., 2004. Neurobehavioral and cognitive performances of children exposed to low-dose radiation in the Chernobyl accident: the Israeli Chernobyl health effects study. Am. J. Epidemiol. 160, 453–459. https://doi.org/10.1093/aje/kwh231.

Bazyka, D.A., Loganovsky, K.M., Ilyenko, I.M., Chumak, S.A., Bomko, M.O., 2015. Gene expression, telomere and cognitive deficit analysis as a function of Chornobyl radiation dose and age: from in utero to adulthood. Probl. Radiatsiinoi Medytsyny. Ta

Radiobiolohii. 20, 283–310.
Berrington de Gonzalez, A., Gilbert, E., Curtis, R., Inskip, P., Kleinerman, R., Morton, L., Rajaraman, P., Little, M.P., 2013. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int. J. Radiat. Oncol. Biol. Phys. 86, 224–233. https://doi.org/10.1016/j.ijrobp.2012.09.001.
Black, S.E., Bütikofer, A., Devereux, P.J., Salvanes, K.G., 2013. This is only a test? Long-run impacts of prenatal exposure to radioactive fallout (working paper no. 18987). Nat. Bureau Econ. Res. https://doi.org/10.3386/w18987.
Blomstrand, M., Holmberg, E., Aberg, M.A.I., Lundell, M., Björk-Eriksson, T., Karlsson, P., Blomgren, K., 2014. No clinically relevant effect on cognitive outcomes after low-dose radiation to the infant brain: a population-based cohort study in Sweden. Acta Oncol. Stockh. Swed. 53, 1143–1150. https://doi.org/10.3109/0284186X.2014.899434.
Booth, A., Clarke, M., Ghersi, D., Moher, D., Petticrew, M., Stewart, L., 2011. An international registry of systematic-review protocols. Lancet Lond. Engl. 377, 108–109. https://doi.org/10.1016/S0140-6736(10)60903-8.
Cabré-Riera, A., 2019. Estimated whole-brain radiofrequency electromagnetic fields dose and brain morphology in preadolescents (submitted for publication).
Calzà, L., Fernández, M., Giardino, L., 2015. Role of the thyroid system in myelination and neural connectivity. Compr. Physiol. 5, 1405–1421. https://doi.org/10.1002/cphy.c140035.
Cardis, E., Hatch, M., 2011. The chernobyl accident — an epidemiological perspective. Clin. Oncol. 23, 251–260. https://doi.org/10.1016/j.clon.2011.01.510.
Cardis, E., Howe, G., Ron, E., Bebeshko, V., Bogdanova, T., Bouville, A., Carr, Z., Chumak, V., Davis, S., Demidchik, Y., Drozdovitch, V., Gentner, N., Gudzenko, N., Hatch, M., Ivanov, V., Jacob, P., Kapitonova, E., Kenigsberg, Y., Kesminiene, A., Kopecky, K.J., Kryuchkov, V., Loos, A., Pinchera, A., Reiners, C., Repacholi, M., Shibata, Y., Shore, R.E., Thomas, G., Tirmarche, M., Yamashita, S., Zvonova, I., 2006. Cancer consequences of the Chernobyl accident: 20 years on. J. Radiol. Prot. Off. J. Soc. Radiol. Prot. 26, 127–140. https://doi.org/10.1088/0952-4746/26/2/001.
Conklin, H.M., Ashford, J.M., Di Pinto, M., Vaughan, C.G., Gioia, G.A., Merchant, T.E., Ogg, R.J., Santana, V., Wu, S., 2013. Computerized assessment of cognitive late effects among adolescent brain tumor survivors. J. Neurooncol. 113, 333–340. https://doi.org/10.1007/s11060-013-1123-5.
Correa, D.D., DeAngelis, L.M., Shi, W., Thaler, H., Glass, A., Abrey, L.E., 2004. Cognitive functions in survivors of primary central nervous system lymphoma. Neurology 62, 548–555.
Cullings, H.M., Levenson, Z.B., Funamoto, S., Teranishi, S., 2006. Changes in atomic bomb survivors' dosimetry with the new dosimetry system DS02. Hoken Butsuri 41, 261–271.
de Ruiter, M.A., van Mourik, R., Schouten-van Meeteren, A.Y.N., Grootenhuis, M.A., Oosterlaan, J., 2013. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. Dev. Med. Child Neurol. 55, 408–417. https://doi.org/10.1111/dmcn.12020.
Doger de Speville, E., Robert, C., Perez-Guevara, M., Grigis, A., Bolle, S., Pinaud, C., Dufour, C., Beaudré, A., Kieffer, V., Longaud, A., Grill, J., Valteau-Couanet, D., Deutsch, E., Lefkopoulos, D., Chiron, C., Hertz-Pannier, L., Noulhiane, M., 2017. Relationships between regional radiation doses and cognitive decline in children treated with cranio-spinal irradiation for posterior fossa tumors. Front. Oncol. 7, 166. https://doi.org/10.3389/fonc.2017.00166.
Edvarson, K., Moberg, L., 1991. External doses in Sweden from the Chernobyl fallout. Swedish Radiation Protection Institute, Sweden.
Egbert, S.D., 2012. The 2002 dosimetry system (DS02) and available fluences for organ dose calculations. Radiat. Prot. Dosim. 149, 21–27. https://doi.org/10.1093/rpd/ncr297.
Foerster, M., Arno, Thielens, Wout, Joseph, Marloes, Eeftens, Martin, Röösli, 2018. A prospective cohort study of adolescents' memory performance and individual brain dose of microwave radiation from wireless communication. Environ. Health Perspect. 126. https://doi.org/10.1289/EHP2427.
Forns, J., Aranbarri, A., Grellier, J., Julvez, J., Vrijheid, M., Sunyer, J., 2012. A conceptual framework in the study of neuropsychological development in epidemiological studies. Neuroepidemiology 38, 203–208. https://doi.org/10.1159/000337169.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. USA 101, 8174–8179. https://doi.org/10.1073/pnas.0402680101.
Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A.-Y., Tordjman, S., 2014. Effects of prenatal stress on fetal and child development: a critical literature review. Neurosci. Biobehav. Rev. 43, 137–162. https://doi.org/10.1016/j.neubiorev.2014.03.022.
Guyatt, G.H., Oxman, A.D., Schünemann, H.J., Tugwell, P., Knottnerus, A., 2011. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J. Clin. Epidemiol. 64, 380–382. https://doi.org/10.1016/j.jclinepi.2010.09.011.
Hall, P., Adami, H.-O., Trichopoulos, D., Pedersen, N.L., Lagiou, P., Ekbom, A., Ingvar, M., Lundell, M., Granath, F., 2004. Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. BMJ 328, 19. https://doi.org/10.1136/bmj.328.7430.19.
Heiervang, K.S., Mednick, S., Sundet, K., Rund, B.R., 2010a. Effect of low dose ionizing radiation exposure in utero on cognitive function in adolescence. Scand. J. Psychol. 51, 210–215. https://doi.org/10.1111/j.1467-9450.2010.00814.x.
Heiervang, K.S., Mednick, S., Sundet, K., Rund, B.R., 2010b. The Chernobyl accident and cognitive functioning: a study of Norwegian adolescents exposed in utero. Dev. Neuropsychol. 35, 643–655. https://doi.org/10.1080/87565641.2010.508550.
Higgins, J., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. ed. The Cochrane Collaboration.
Horton, M.K., Margolis, A.E., Tang, C., Wright, R., 2014. Neuroimaging is a novel tool to understand the impact of environmental chemicals on neurodevelopment. Curr. Opin. Pediatr. 26, 230–236. https://doi.org/10.1097/MOP.0000000000000074.
IARC, I.A. of C., 2019. Preamble to the IARC Monographs on the evaluation of carcinogenic risk to humans. World Health Organization, Lyon, France.
Igumnov, S., Drozdovitch, V., 2000. The intellectual development, mental and behavioural disorders in children from Belarus exposed in utero following the chernobyl accident. Eur. Psychiatry J. Assoc. Eur. Psychiatr. 15, 244–253.
Jacola, L.M., Krull, K.R., Pui, C.-H., Pei, D., Cheng, C., Reddick, W.E., Conklin, H.M., 2016. Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 34, 1239–1247. https://doi.org/10.1200/JCO.2015.64.3205.
Johnson, P.I., Sutton, P., Atchley, D.S., Koustas, E., Lam, J., Sen, S., Robinson, K.A., Axelrad, D.A., Woodruff, T.J., 2014. The navigation guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ. Health Perspect. 122, 1028–1039. https://doi.org/10.1289/ehp.1307893.
Journy, N.M., McHugh, K., Harbron, R.W., Pearce, M.S., Berrington De Gonzalez, A., 2016. Medical conditions associated with the use of CT in children and young adults, Great Britain, 1995–2008. Br. J. Radiol. 89, 20160532. https://doi.org/10.1259/bjr.20160532.
Kazda, T., Jancalek, R., Pospisil, P., Sevela, O., Prochazka, T., Vrzal, M., Burkon, P., Slavik, M., Hynkova, L., Slampa, P., Laack, N.N., 2014. Why and how to spare the hippocampus during brain radiotherapy: the developing role of hippocampal avoidance in cranial radiotherapy. Radiat. Oncol. Lond. Engl. 9, 139. https://doi.org/10.1186/1748-717X-9-139.
Kempf, S.J., Azimzadeh, O., Atkinson, M.J., Tapio, S., 2013. Long-term effects of ionising radiation on the brain: cause for concern? Radiat. Environ. Biophys. 52, 5–16. https://doi.org/10.1007/s00411-012-0436-7.
Kohl, C., McIntosh, E.J., Unger, S., Haddaway, N.R., Kecke, S., Schiemann, J., Wilhelm, R., 2018. Online tools supporting the conduct and reporting of systematic reviews and systematic maps: a case study on CADIMA and review of existing tools. Environ. Evid. 7, 8. https://doi.org/10.1186/s13750-018-0115-5.
Kolominsky, Y., Igumnov, S., Drozdovitch, V., 1999. The psychological development of children from Belarus exposed in the prenatal period to radiation from the Chernobyl atomic power plant. J. Child Psychol. Psychiatry 40, 299–305.
Kreuzer, M., Auvinen, A., Cardis, E., Durante, M., Harms-Ringdahl, M., Jourdain, J.R., Madas, B.G., Ottolenghi, A., Pazzaglia, S., Prise, K.M., Quintens, R., Sabatier, L., Bouffler, S., 2017. Multidisciplinary European Low Dose Initiative (MELODI): strategic research agenda for low dose radiation risk research. Radiat. Environ. Biophys. https://doi.org/10.1007/s00411-017-0726-1.
Krull, K.R., Hardy, K.K., Kahalley, L.S., Schuitema, I., Kesler, S.R., 2018. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 36, 2181–2189. https://doi.org/10.1200/JCO.2017.76.4696.
Krull, K.R., Sabin, N.D., Reddick, W.E., Zhu, L., Armstrong, G.T., Green, D.M., Arevalo, A.R., Krasin, M.J., Srivastava, D.K., Robison, L.L., Hudson, M.M., 2012. Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30, 3618–3624. https://doi.org/10.1200/JCO.2012.42.6841.
Lam, J., Sutton, P., Kalkbrenner, A., Windham, G., Halladay, A., Koustas, E., Lawler, C., Davidson, L., Daniels, N., Newschaffer, C., Woodruff, T., 2016. A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. PLoS ONE 11. https://doi.org/10.1371/journal.pone.0161851.
Lee, C., Journy, N., Moroz, B.E., Little, M., Harbron, R., McHugh, K., Pearce, M., Berrington de Gonzalez, A., 2018. Organ dose estimation accounting for uncertainty for pediatric and young adult ct scans in the united kingdom. Radiat. Prot. Dosimetry. https://doi.org/10.1093/rpd/ncy184.
Levie, D., Korevaar, T.I.M., Bath, S.C., Dalmau-Bueno, A., Murcia, M., Espada, M., Dineva, M., Ibarluzea, J.M., Sunyer, J., Tiemeier, H., Rebagliato, M., Rayman, M.P., Peeters, R.P., Guxens, M., 2018. Thyroid function in early pregnancy, child IQ, and autistic traits: a meta-analysis of individual participant data. J. Clin. Endocrinol. Metab. 103, 2967–2979. https://doi.org/10.1210/jc.2018-00224.
Lewin, S., Booth, A., Glenton, C., Munthe-Kaas, H., Rashidian, A., Wainwright, M., Bohren, M.A., Tunçalp, Ö., Colvin, C.J., Garside, R., Carlsen, B., Langlois, E.V., Noyes, J., 2018. Applying GRADE-CERQual to qualitative evidence synthesis findings: introduction to the series. Implement. Sci. IS 13, 2. https://doi.org/10.1186/s13012-017-0688-3.
Lie, R.T., Moster, D., Strand, P., Wilcox, A.J., 2017. Prenatal exposure to Chernobyl fallout in Norway: neurological and developmental outcomes in a 25-year follow-up. Eur. J. Epidemiol. 32, 1065–1073. https://doi.org/10.1007/s10654-017-0350-z.
Litcher, L., Bromet, E.J., Carlson, G., Squires, N., Goldgaber, D., Panina, N., Golovakha, E., Gluzman, S., 2000. School and neuropsychological performance of evacuated children in Kyiv 11 years after the Chornobyl disaster. J. Child Psychol. Psychiatry 41, 291–299.
Little, M.P., Tawn, E.J., Tzoulaki, I., Wakeford, R., Hildebrandt, G., Paris, F., Tapio, S., Elliott, P., 2010. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. Radiat. Environ. Biophys. 49, 139–153. https://doi.org/10.1007/s00411-009-0250-z.
Loganovskaja, T.K., Loganovsky, K.N., 1999. EEG, cognitive and psychopathological abnormalities in children irradiated in utero. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 34, 213–224.
López-Vicente, M., Forns, J., Suades-González, E., Esnaola, M., García-Esteban, R.,

Álvarez-Pedrerol, M., Júlvez, J., Burgaleta, M., Sebastián-Gallés, N., Sunyer, J., 2016. Developmental trajectories in primary schoolchildren using n-back task. Front. Psychol. 7, 716. https://doi.org/10.3389/fpsyg.2016.00716.
Lorenz, E., Scholz-Kreisel, P., Baaken, D., Pokora, R., Blettner, M., 2018. Radiotherapy for childhood cancer and subsequent thyroid cancer risk: a systematic review. Eur. J. Epidemiol. 33, 1139–1162. https://doi.org/10.1007/s10654-018-0467-8.
Ma, Q., Wu, D., Zeng, L.-L., Shen, H., Hu, D., Qiu, S., 2016. Radiation-induced functional connectivity alterations in nasopharyngeal carcinoma patients with radiotherapy. Medicine (Baltimore) 95. https://doi.org/10.1097/MD.0000000000004275.
MELODI, 2019. MELODI Strategic Research Agenda. MELODI. http://www.melodi-online.eu/m_docs_sra.html (accessed 19 December 2019).
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 1. https://doi.org/10.1186/2046-4053-4-1.
Moore, K., Persaud, T.V.N., 2015. The Developing Human, 10th ed. Saunders.
Morgan, R.L., Thayer, K.A., Santesso, N., Holloway, A.C., Blain, R., Eftim, S.E., Goldstone, A.E., Ross, P., Ansari, M., Akl, E.A., Filippini, T., Hansell, A., Meerpohl, J.J., Mustafa, R.A., Verbeek, J., Vinceti, M., Whaley, P., Schünemann, H.J., 2019. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. Environ. Int. 122, 168–184. https://doi.org/10.1016/j.envint.2018.11.004.
Morgan, R.L., Whaley, P., Thayer, K.A., Schünemann, H.J., 2018. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ. Int. 121, 1027–1031. https://doi.org/10.1016/j.envint.2018.07.015.
Mulhern, R.K., Merchant, T.E., Gajjar, A., Reddick, W.E., Kun, L.E., 2004. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol. 5, 399–408. https://doi.org/10.1016/S1470-2045(04)01507-4.
National Research Council (U.S.) (Ed.), 2006. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. National Academies Press, Washington, D.C.
NCRP Report No. 160, 2009. Ionizing Radiation Exposure of the Population of the United State.
Nordenskjöld, A.C., Palme, M., Kaijser, M., 2015. X-ray exposure in utero and school performance: a population-based study of X-ray pelvimetry. Clin. Radiol. 70, 830–834. https://doi.org/10.1016/j.crad.2015.04.002.
Nyagu, A.I., Loganovsky, K.N., Loganovskaja, T.K., 1998. Psychophysiologic aftereffects of prenatal irradiation. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 30, 303–311.
Otake, M., Schull, W.J., Yoshimaru, H., 1991. Brain damage among the prenatally exposed. J. Radiat. Res. (Tokyo) 32, 249–264. https://doi.org/10.1269/jrr.32.SUPPLEMENT_249.
Padovani, L., André, N., Constine, L.S., Muracciole, X., 2012. Neurocognitive function after radiotherapy for paediatric brain tumours. Nat. Rev. Neurol. 8, 578–588. https://doi.org/10.1038/nrneurol.2012.182.
Pasqual, E., Bosch de Basea, M., Cardis, E., 2018. The neurodevelopmental effects of the exposure of the developing brain to low dose ionizing radiation: a systematic review.
Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., 2006. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews 92.
Preston, D.L., Pierce, D.A., Shimizu, Y., Cullings, H.M., Fujita, S., Funamoto, S., Kodama, K., 2004. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat. Res. 162, 377–389.
Reddick, W.E., White, H.A., Glass, J.O., Wheeler, G.C., Thompson, S.J., Gajjar, A., Leigh, L., Mulhern, R.K., 2003. Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. Cancer 97, 2512–2519. https://doi.org/10.1002/cncr.11355.
Roddy, E., Sear, K., Felton, E., Tamrazi, B., Gauvain, K., Torkildson, J., Buono, B.D., Samuel, D., Haas-Kogan, D.A., Chen, J., Goldsby, R.E., Banerjee, A., Lupo, J.M., Molinaro, A.M., Fullerton, H.J., Mueller, S., 2016. Presence of cerebral microbleeds is associated with worse executive function in pediatric brain tumor survivors. Neuro-Oncol. 18, 1548–1558. https://doi.org/10.1093/neuonc/now163.
Roesch, W.C., 1987. US-Japan joint reassessment of atomic bomb radiation dosimetry in Hiroshima and Nagasaki. DS86. Dosimetry System 1986. Vol. 1. Radiation Effects Research Foundation, Hiroshima (Japan), Japan.
Ron, E., Modan, B., Boice, J.D., Alfandary, E., Stovall, M., Chetrit, A., Katz, L., 1988. Tumors of the brain and nervous system after radiotherapy in childhood. N. Engl. J. Med. 319, 1033–1039. https://doi.org/10.1056/NEJM198810203191601.
Ron, E., Modan, B., Floro, S., Harkedar, I., Gurewitz, R., 1982. Mental function following scalp irradiation during childhood. Am. J. Epidemiol. 116, 149–160.
Salonen, E., Nyman, H., Kizling, I., Geijerstam, J.-L.A., Flodmark, O., Aspelin, P., Kaijser, M., 2018. Cognitive function following head CT in childhood: a randomized controlled follow-up trial. Acta Radiol. Stockh. Swed. 1987 (59), 221–228. https://doi.org/10.1177/0284185117708471.
Savitz, D.A., Wellenius, G.A., Trikalinos, T.A., 2019. The Problem with mechanistic risk of bias assessments in evidence synthesis of observational studies and a practical alternative: assess the impact of specific sources of potential bias. Am. J. Epidemiol. https://doi.org/10.1093/aje/kwz131.
Saykin, A.J., de Ruiter, M.B., McDonald, B.C., Deprez, S., Silverman, D.H.S., 2013. Neuroimaging biomarkers and cognitive function in non-CNS cancer and its treatment: current status and recommendations for future research. Brain Imaging Behav. 7, 363–373. https://doi.org/10.1007/s11682-013-9283-7.
Schoeni, A., Roser, K., Röösli, M., 2015. Memory performance, wireless communication and exposure to radiofrequency electromagnetic fields: a prospective cohort study in adolescents. Environ. Int. 85, 343–351. https://doi.org/10.1016/j.envint.2015.09.025.
Schull, W.J., Nishitani, H., Hasuo, K., Kobayashi, T., Goto, I., Otake, M., 1991. Brain abnormalities among the mentally retarded prenatally exposed atomic bomb survivors (RERF report No. RERF TR 13-91). Radiation Effect Reseacrh Foundation, Hiroshima, japan.
Schull, W.J., Otake, M., 1999. Cognitive function and prenatal exposure to ionizing radiation. Teratology 59, 222–226. https://doi.org/10.1002/(SICI)1096-9926(199904)59:4<222::AID-TERA6>3.0.CO;2-M.
Shamsaldin, A., Grimaud, E., Hardiman, C., Diallo, I., de-Vathaire, F., Chavaudra, J., 1998. Dose distribution throughout the body from radiotherapy for Hodgkin's disease in childhood. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 49, 85–90.
Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., López-Vicente, M., Suades-González, E., Foraster, M., Garcia-Esteban, R., Basagaña, X., Viana, M., Cirach, M., Moreno, T., Alastuey, A., Sebastian-Galles, N., Nieuwenhuijsen, M., Querol, X., 2015. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 12, e1001792. https://doi.org/10.1371/journal.pmed.1001792.
Taormina, D.P., Rozenblatt, S., Guey, L.T., Gluzman, S.F., Carlson, G.A., Havenaar, J.M., Zakhozha, V., Kotov, R., Bromet, E.J., 2008. The Chornobyl accident and cognitive functioning: a follow-up study of infant evacuees at age 19 years. Psychol. Med. 38, 489–497. https://doi.org/10.1017/S0033291707002462.
Tarabulsy, G.M., Pearson, J., Vaillancourt-Morel, M.-P., Bussières, E.-L., Madigan, S., Lemelin, J.-P., Duchesneau, A.-A., Hatier, D.-E., Royer, F., 2014. Meta-analytic findings of the relation between maternal prenatal stress and anxiety and child cognitive outcome. J. Dev. Behav. Pediatr. JDBP 35, 38–43. https://doi.org/10.1097/DBP.0000000000000003.
The Cochrane Collaboration, 2011. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. ed.
Tueller, S.J., Deboeck, P.R., Van Dorn, R.A., 2016. Getting less of what you want: Reductions in statistical power and increased bias when categorizing medication adherence data. J. Behav. Med. 39, 969–980. https://doi.org/10.1007/s10865-016-9727-9.
Ullrich, N.J., Embry, L., 2012. Neurocognitive dysfunction in survivors of childhood brain tumors. Semin. Pediatr. Neurol. 19, 35–42. https://doi.org/10.1016/j.spen.2012.02.014.
UNSCEAR, 2013. UNSCEAR 2013 report - Vol. II, ANNEX B [WWW Document]. URL http://www.unscear.org/unscear/en/publications/2013_1.html (accessed 7.31.15).
UNSCEAR, 2008. UNSCEAR 2008 Report-Vol I, Annex A [WWW Document]. URL http://www.unscear.org/docs/reports/2008/09-86753_Report_2008_Annex_A.pdf (accessed 8.12.15).
Van den Bergh, B.R.H., van den Heuvel, M.I., Lahti, M., Braeken, M., de Rooij, S.R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., Schwab, M., 2017. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.07.003.
van der Geest, I.M.M., van Dorp, W., Hop, W.C.J., Neggers, S.J.C.M.M., de Vries, A.C.H., Pieters, R., Aarsen, F.K., van den Heuvel-Eibrink, M.M., 2013. Emotional distress in 652 Dutch very long-term survivors of childhood cancer, using the hospital anxiety and depression scale (HADS). J. Pediatr. Hematol. Oncol. 35, 525–529. https://doi.org/10.1097/MPH.0b013e31829f2799.
Verreet, T., Quintens, R., Van Dam, D., Verslegers, M., Tanori, M., Casciati, A., Neefs, M., Leysen, L., Michaux, A., Janssen, A., D'Agostino, E., Vande Velde, G., Baatout, S., Moons, L., Pazzaglia, S., Saran, A., Himmelreich, U., De Deyn, P.P., Benotmane, M.A., 2015. A multidisciplinary approach unravels early and persistent effects of X-ray exposure at the onset of prenatal neurogenesis. J. Neurodev. Disord. 7, 3. https://doi.org/10.1186/1866-1955-7-3.
Xu, X.G., Bednarz, B., Paganetti, H., 2008. A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction. Phys. Med. Biol. 53, R193–241. https://doi.org/10.1088/0031-9155/53/13/R01.
Yamada, M., Landes, R.D., Mimori, Y., Nagano, Y., Sasaki, H., 2015. Radiation effects on cognitive function among atomic bomb survivors exposed at or after adolescence. Am. J. Med. 129, 586–591. https://doi.org/10.1016/j.amjmed.2015.09.002.
Yoshimaru, H., Otake, M., Schull, W.J., Funamoto, S., 1995. Further observations on abnormal brain development caused by prenatal A-bomb exposure to ionizing radiation. Int. J. Radiat Biol. 67, 359–371.
Youngstrom, E., S. LaKind, J., Kenworthy, L., Lipkin, P.H., Goodman, M., Squibb, K., R. Mattison, D., J. Anthony, B., Gutermuth Anthony, L., 2010. Advancing the Selection of Neurodevelopmental Measures in Epidemiological Studies of Environmental Chemical Exposure and Health Effects. Int. J. Environ. Res. Public. Health 7, 229–268. https://doi.org/10.3390/ijerph7010229.
Zeltzer, L.K., Lu, Q., Leisenring, W., Tsao, J.C.I., Recklitis, C., Armstrong, G., Mertens, A.C., Robison, L.L., Ness, K.K., 2008. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 17, 435–446. https://doi.org/10.1158/1055-9965.EPI-07-2541.