Science of the Total Environment 548–549 (2016) 463–471

Contents lists available at ScienceDirect

Science of the Total Environment

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

Ionizing radiation, antioxidant response and oxidative damage: A meta-analysis

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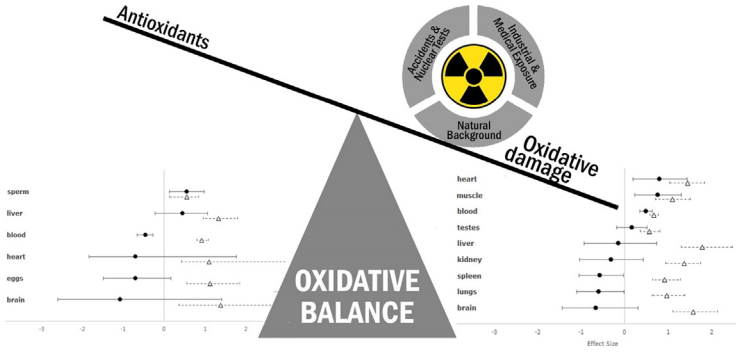
HIGHLIGHTS

- There is interest in variation in metabolic effects of chronic low-dose ionizing radiation
- A random effect meta-analysis of effect sizes of radioactive contamination was performed
- We found significant effects of radiation on oxidative damage and antioxidant response
- We found significant heterogeneity among biological matrices, species and age classes

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 July 2015
Received in revised form 6 January 2016
Accepted 6 January 2016
Available online xxxx

Editor: D. Barcelo

Keywords:
Chernobyl
Fukushima
Eastern Urals Trace
Antioxidant activity
Radioactive contamination
Oxidative stress
ROS

ABSTRACT

One mechanism proposed as a link between exposure to ionizing radiation and detrimental effects on organisms is oxidative damage. To test this hypothesis, we surveyed the scientific literature on the effects of chronic low-dose ionizing radiation (LDIR) on antioxidant responses and oxidative damage. We found 40 publications and 212 effect sizes for antioxidant responses and 288 effect sizes for effects of oxidative damage. We performed a meta-analysis of signed and unsigned effect sizes. We found large unsigned effects for both categories (0.918 for oxidative damage; 0.973 for antioxidant response). Mean signed effect size weighted by sample size was 0.276 for oxidative damage and −0.350 for antioxidant defenses, with significant heterogeneity among effects for both categories, implying that ionizing radiation caused small to intermediate increases in oxidative damage and small to intermediate decreases in antioxidant defenses. Our estimates are robust, as shown by very high fail-safe numbers. Species, biological matrix (tissue, blood, sperm) and age predicted the magnitude of effects for oxidative damage as well as antioxidant response. Meta-regression models showed that effect sizes for oxidative damage varied among species and age classes, while effect sizes for antioxidant responses varied among species and biological matrices. Our results are consistent with the description of mechanisms underlying pathological

Abbreviations: LDIR, low-dose ionizing radiation; NCRP, National Council on Radiation Protection and Measurements; INES, International Nuclear and Radiological Event Scale; NPP, Nuclear Power Plant; ROS, reactive oxygen species; RNS, reactive nitrogen species.

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http://dx.doi.org/10.1016/j.scitotenv.2016.01.027

Lipid peroxidation
Ecology
Evolution

effects of chronic exposure to LDIR. Our results also highlight the importance of resistance to oxidative stress as one possible mechanism associated with variation in species responses to LDIR-contaminated areas.

1. Introduction

Low-dose ionizing radiation (LDIR) is the type of low-rate chronic irradiation that does not induce adverse toxic effects (National Council on Radiation Protection (NCRP), 1987). However, exposure to LDIR can accelerate cellular senescence via increasing activity of reactive oxygen species (ROS) and disruption of biopolymers (Loseva et al., 2014). Because the power of exposure decreases with the distance to the source, a bigger potential hazard comes from radiological agents being ingested or inhaled.

Industrial and military use of radioactive materials has led to their release to ecosystems. Early monitoring studies of humans and biota following atomic bomb testing as well as radiation-related accidents (e.g. in Kyshtym, Russian Federation), suggested elevated health risks and mortality rates in humans and some mammals associated with high acquired doses after chronic exposure to LDIR (Sakata et al., 2012; Lushnikova et al., 1997; Mozolin et al., 2008; Shoikhet et al., 1999; Grigorkina and Olenev, 2013; Grigorkina and Pashnina, 2007). These studies also suggested that the effects of direct exposure to ionizing radiation were exacerbated by incorporation of soluble radioactive elements (Ivannikov et al., 2002). Recent ecological studies of the Chernobyl and Fukushima catastrophes confirmed this, and demonstrated high variability in such effects among taxa. Along with a high frequency of morphological abnormalities (Akimoto, 2014; Hiyama et al., 2012, 2013; Møller et al., 2007) and tumors (Møller et al., 2013), and an overall decline in population abundances (Møller and Mousseau, 2007a, 2007b, 2009; Møller et al., 2012), these effects included high rates of genetic aberrations in somatic (Alamri et al., 2012; Bonisoli Alquati et al., 2010a; Møller et al., 2013) and germline cells (Ellegren et al., 1997). Moreover variation exists across species in their biochemical and genetic responses to increasing environmental radiation (Galván et al., 2014; Hinton et al., 2007).

Overall, attempts to rigorously monitor human populations in Ukraine, Belarus and Russia following the Chernobyl accident have been scattered at best (Edwards et al., 2004; Yablokov et al., 2009). Nonetheless, these studies showed that workers involved in the cleanup operations (the so-called 'liquidators'), who were exposed to much higher doses than evacuated civilians, demonstrated elevated frequencies of genetic abnormalities (Moysich et al., 2002; Sevan'kaev et al., 2005), solid cancers and cardio-vascular diseases (Cardis and Hatch, 2011; Serdiuk et al., 2011). An elevated fraction of evacuated adolescents and young adults suffered from thyroid cancer (Demidchik et al., 2007). At the same time, epidemiological studies with small cohorts and small and non-representative control groups carried out years after the catastrophe did not yield sufficient evidence to support the hypothesis of radiation-associated mortality linked to the Chernobyl accident (Serdiuk et al., 2011; Weinberg et al., 2001).

These findings emphasize the need to study variation in health effects in the context of chronic exposure to LDIR. Results of such studies are important and may be used in radiation protection and for defining safety requirements, particularly given the current debates about the shape of dose–response curves describing radiation-related effects and the severity of radiation injury (Ryan, 2012).

When absorbed by living cells, ionizing radiation can induce direct breakage in the chemical bonds of biological macromolecules. Ionizing radiation can also affect proteins, nucleic acids and complex lipids as a result of the generation of reactive oxygen species (ROS) via radiolysis of water or alteration of mitochondrial functions (Kam and Banati, 2014). ROS are a diverse group of chemical species, which naturally occur in cells, where they perform important signaling functions (Azzam et al., 2011; Murphy et al., 2011). ROS activity is controlled by a number of enzymatic and non-enzymatic antioxidants. The inability to balance the increased generation of ROS by antioxidant mechanisms results in oxidative stress, a complex stressor for cells that manifests as increased oxidative molecular damage to biomolecules, e.g. oxidation of lipids, oxidative modification of nitrogenous bases etc. (Halliwell and Gutteridge, 2007; Jones, 2006). In turn, oxidative damage may promote the emergence of pathological states, accelerated cell aging and apoptosis (Halliwell and Gutteridge, 2007; Spitz et al., 2004). In numerous invertebrate and vertebrate species, oxidative damage may result in reduced growth, fertility and survival (Costantini, 2014).

The association between LDIR and the generation of reactive species has been widely described (Azzam et al., 2011; Smith et al., 2012). The role of ionizing radiation in generation of ROS is well explained as the correlation between genetic damage and oxidative damage (e.g. Costantini, 2014; Galván et al., 2014). Oxidative damage might be one mechanism underlying several of the detrimental effects of radiation. The root of the controversy relates to the manifestation of a given symptom or morbidity as a consequence of the three-way interaction of increased concentrations of ROS, decreased activity of antioxidant enzymes, and genetic damage associated with increased background radiation (Spitz et al., 2004), especially when disease is followed by another medical condition, like malnutrition, inflammatory disease or respiratory malfunction. However, it is important to note that radionuclides do not only generate damage through radiation, but also through their catalytic activity (the Fenton reaction) (Halliwell and Gutteridge, 2007). In addition, while several studies have documented increased oxidative damage and reduced antioxidant defenses in humans and wild populations of animals chronically exposed to LDIR (e.g. Bonisoli Alquati et al., 2010b), other studies have shown the potential for animals to adapt their antioxidant system to chronic exposure to LDIR (Galván et al., 2014). In addition, theoretical calculations and lack of accurate dosimetry have called into question findings of increased oxidative stress from exposure to LDIR (Smith et al., 2012).

Here we assess the effects of chronic exposure to LDIR from radioactive contamination. We aim at exploring the insights of long-term metabolic processes, such as antioxidant function and oxidative damage, of individuals affected by chronic irradiation caused by radioactive contaminants. We collected exhaustive data from radiobiological studies in the Russian and the English language scientific literature, and combined published evidence into a meta-analysis of the effects of chronic radiation exposure on markers of oxidative damage and antioxidant protection. Our aim was to test whether high environmental radioactivity would lead to higher oxidative damage and lower antioxidant defenses in exposed organisms. Meta-analysis is a powerful tool for quantitatively summarizing research, especially when there is apparent heterogeneity in research findings (Arnqvist and Wooster, 1995; Hedges and Olkin, 1985; Koricheva et al., 2013).

We expected factors related to study design, age and model organism to explain variation across studies and species in the relationship between LDIR exposure and oxidative damage. Hence, we also tested whether different biological matrices and species differed in their response to radiation. Different organs and tissues can be differentially exposed and/or sensitive to radiation exposure, depending on the metabolic fate of radionuclides. Juveniles and adults can also differ in their sensitivity, with individuals at early developmental stages generally being more sensitive to increased radiation because of their immature antioxidant system (Costantini, 2014; Lu and Finkel, 2008) and due to potential hazardness of the damage being accumulated in their stem cell progeny (Liu et al., 2014). Finally, variation across species in

exposure and sensitivity to LDIR would allow us to identify species that can serve as sensitive bio-indicators of the effects of LDIR, and model how such effects translate into potential risk for humans and other species (Møller and Mousseau, 2015).

2. Materials and methods

2.1. Literature search and data sets

We made an exhaustive literature search of both correlative and experimental studies on Web of Science, relying on the following keywords: "radioactive contamination", "increased background radiation", "occupation exposure", "Chernobyl" in combination with "oxidative stress", "reactive oxidative species", "lipid peroxidation", "peroxide radicals" and "antioxidant". Once we located these papers, we tested if they fulfilled our inclusion criteria. We also searched the reference lists of all identified publications in an attempt to locate additional publications. Because many nuclear accidents have occurred in the former Soviet Union, a large number of publications have appeared in Russian, Belorussian and Ukrainian. Although such publications are often neglected or deliberately omitted from meta-analyses, we made a concerted effort to identify such publications.

We included (1) ecological or biomedical surveys of individuals exposed to high environmental radiation levels; (2) studies examining the relationship between acquired dose (external; ingested etc.) and markers of ROS metabolism; (3) studies reporting at least one statistical test, which compared non-exposed and exposed individuals; and (4) studies from which those data could be extracted and converted into effect sizes. Exclusion criteria were (1) studies that involved radiation therapy (e.g. for oncology treatment); (2) studies that concerned treatment of radiation-affected people; and (3) studies that involved short-term exposure to toxic doses of ionizing radiation. We present a PRISMA diagram showing the number of initial publications and the subsequent publications excluded from the final sample of 40 studies (Fig. 1). This resulted in 212 effect sizes for antioxidant response and 288 effect sizes for oxidative damage. All studies found by March 31 2015 were included in the analyses, and all data are reported in Supplementary material Table S1. Copies of most of these papers, some of which are difficult to obtain electronically, have been posted on a website (http://cricket.biol.sc.edu/oxi-stress).

2.2. Method of meta-analyses

A meta-analysis was performed using signed and unsigned effect sizes to estimate a direction and magnitude of LDIR effects on oxidative status. The data were analyzed using the software Meta-Win (Rosenberg et al., 2000). We estimated effect sizes in terms of Hedges *g* by using standard procedures. For data that contained estimated means and standard deviations we used the formula by Hedges and Olkin (1985):

$$g = \frac{M_{\text{experiment}} - M_{\text{control}}}{SD^{*}_{\text{pooled}}}$$

where Hedges pooled standard deviation was estimated as:

$$SD^{*}_{\text{pooled}} = \sqrt{\frac{(n_1-1)SD_1^2 + (n_2-1)SD_2^2}{n_1+n_2-2}}$$

where sample standard deviations were SD_1 and SD_2 and sample sizes were n_1 and n_2 respectively for the two samples. If a standard error

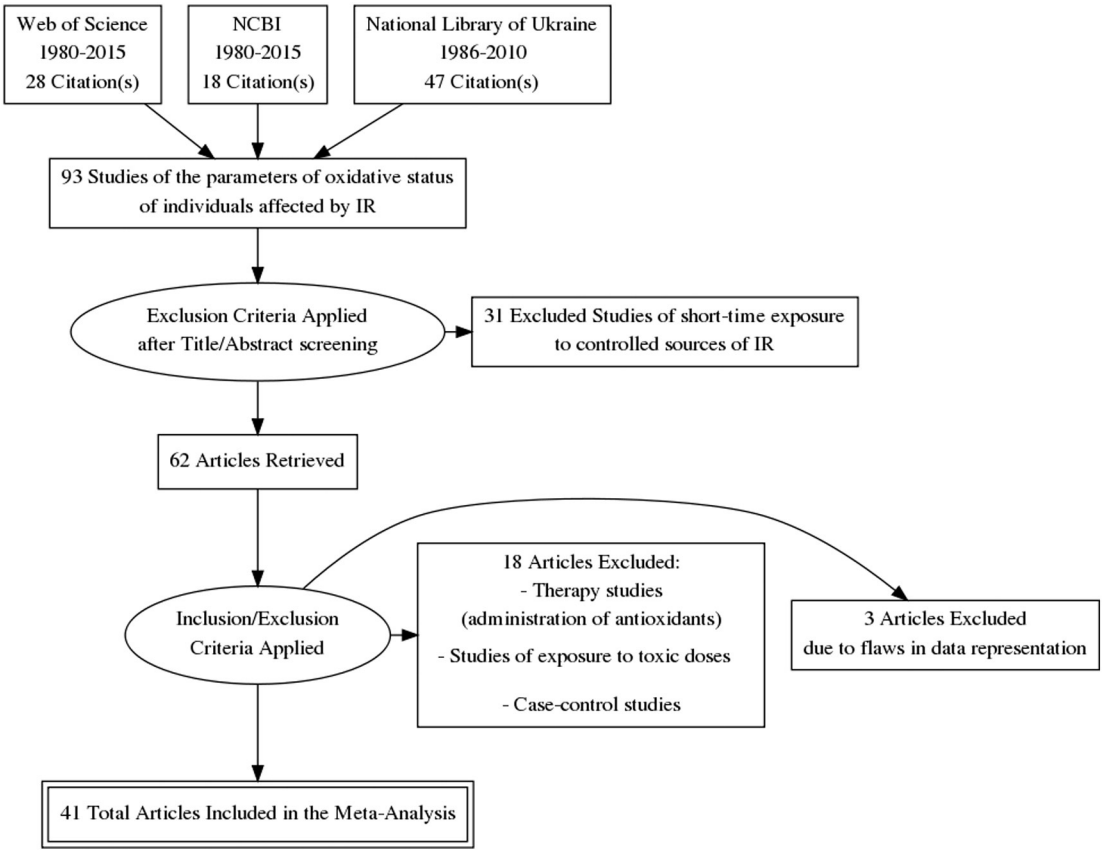

Fig. 1. The PRISMA flow diagram (http://prisma.thetacollaborative.ca/) of the initial publications and the subsequent number of papers retained for the meta-analysis.

was reported, it was simply transformed into *SD* as follows:

$$SD = \frac{SE}{\sqrt{n}}.$$

For transformation of *F*-values and Pearson's correlation coefficient *r* we estimated effect sizes in terms of Cohen's *d* using equations in Rosenthal (Rosenthal, 1994). In particular, we converted *F*-values from a one-way ANOVA (or the main effect of a two- or more way ANOVA; here ionizing radiation) into Cohen's *d*:

$$d = \sqrt{F\left(\frac{n_i + n_c}{n_i n_c}\right)\left(\frac{n_i + n_c}{n_i + n_c - 2}\right)}.$$

Pearson's *r* was converted into Cohen's *d* as:

$$d = \frac{2r}{\sqrt{1-r^2}}.$$

Likewise, the variance of Cohen's *d* was defined as follows:

$$\sigma_d^2 = \left(\frac{n_i + n_c}{n_i n_c} + \frac{d^2}{2(n_i + n_c - 2)}\right)\left(\frac{n_i + n_c}{n_i + n_c - 2}\right)$$

where n_i and n_c were the sample sizes of the two samples. Cohen's *d* can be converted into Hedges *g* relying on Hedges and Olkin (1985):

$$g \approx d\left(1 - \frac{3}{4(n_i + n_c) - 9}\right).$$

Because there was considerable heterogeneity in the number of effect sizes per study, and because of differences in effect size among studies, we used random effect meta-analysis to account for such heterogeneity (Raudenbush, 1994). Variables used in random effect models were subsequently entered in meta-regressions with study as a random effect, and the three fixed effects of species, biological matrix and age as predictors. These models were subsequently reduced by eliminating all predictors that did not explain part of the variance at a level of $P < 0.10$. We used $P < 0.10$ to avoid excluding factors with overall weak effects. Full models including all three predictors all resulted in similar conclusions. All analyses were made using JMP (SAS Institute Inc., 2012).

We interpreted our data as follows: positive ES for an oxidative marker and negative ES for a marker of antioxidant response would indicate a negative impact of LDIR. Likewise, the effect of LDIR would be considered positive if oxidative damage decreased (negative ES for oxidative marker) and when enzymatic and non-enzymatic antioxidants increased (positive ES for antioxidant marker), respectively (Costantini and Møller, 2009; Costantini et al., 2011). The analysis of the unsigned effect sizes was performed to determine the magnitude of effect regardless of its direction. Some biomarkers express radiation effects by being up-regulated, while others are down-regulated. Thus, using absolute effect sizes avoids effects on different biomarkers canceling each other out. Effect sizes were considered to be small (Hedges $g = 0.2$, explaining 1% of the variance), intermediate ($g = 0.5$, explaining 9% of the variance) or large ($g = 0.8$, explaining 25% of the variance) as suggested by Cohen (1988).

3. Results

3.1. Markers of response to LDIR: response in antioxidants and oxidative metabolism

In the meta-analysis we included enzymatic and non-enzymatic markers of antioxidant response to LDIR. We extracted studies of effects on catalase (CAT, $n = 55$), superoxide dismutase (SOD, $n = 36$), glutathione (GSH, $n = 17$), and glutathione peroxidase (GPX, $n = 14$), as for non-enzymatic markers there were effects on vitamin A (VitA, $n = 18$), vitamin E (VitE, $n = 18$), and carotenoids ($n = 9$). Overall, studies of enzymatic antioxidants accounted for 55% of all markers of antioxidant response.

Markers of oxidative stress included effects on ROS concentration ($n = 21$) and their metabolites — diene and triene conjugates ($n = 157$), thiobarbituric acid reactive species (TBARS, $n = 81$), and reduced glutathione (GSSG, $n = 17$). Here, metabolic markers accounted for 89% of all markers of oxidative stress (Supplementary material Table S1).

3.2. Variation in effects between relatively high and low doses acquired by humans

Our analysis included studies on humans that were participating in the cleanup operations after the Chernobyl accident. For some cleanup workers maximum estimated exposure was 200 mSv (Lyashenko et al., 2000, Supplementary material Table S1). We compared them to the effects found in studies on other human individuals that were not directly involved in the event, but were also exposed to LDIR. Our analysis suggests none to very small difference between the two groups of studies (antioxidant response: $F = 0.1$, d.f. $= 1, 124$, $P = 0.752$; oxidative damage: $F = 0.59$, d.f. $= 1, 97$, $P = 0.444$).

3.3. Summary statistics, mean effect sizes and evidence for publication bias

Mean effect size for oxidative damage due to radiation and weighted by sample size was 0.277, with a fail-safe number that exceeded 709 (Table 1; Fig. F1). The absolute magnitude of oxidative damage was large, and estimated at 0.918. In comparison, mean effect size for antioxidant response weighted by sample size was −0.350 (absolute ES = 0.983), and the fail-safe number was more than 1600 (Table 1). In total, sample size was 17,332 for 212 effect sizes from studies of antioxidant response, and 13,953 for 288 effect sizes from studies of oxidative damage. There was significant heterogeneity for effect sizes for both oxidative damage and antioxidant response (Table 2, Fig. F1).

Effect size was significantly but weakly positively correlated with sample size for Kendall's rank order correlation for oxidative damage ($\tau = 0.171$, $P < 0.0001$), but not for antioxidant response ($\tau = -0.010$, $P = 0.84$). The correlation between effect sizes and their variances was also significant but weak for oxidative damage ($\tau = -0.149$, $P = 0.0002$), but not for antioxidants ($\tau = -0.061$, $P = 0.19$). The correlation between effect size and publication year was not significant for oxidative damage ($r = -0.007$, $P = 0.87$) or for antioxidants ($r = 0.021$, $P = 0.67$).

3.4. Predictors of effect size

We first used Generalized Linear Mixed Models (GLMM) to test for the effects of marker ($F = 32.67$, d.f. $= 1, 491.6$, $P < 0.0001$, antioxidant:

Table 1
Effect size estimates weighted by sample size for antioxidant response and oxidative damage. The table also reports sample size, lower and upper 95% bootstrap confidence intervals, test for heterogeneity (Q_{Total}), *P*-value for heterogeneity test and Rosenthal's failsafe number. Effect sizes shown in bold are significantly different from zero.

	Effect size	N	Lower B-strap CI	Upper B-strap CI	Absolute ES	Q_{Total}	*P*	Rosenthal's failsafe number
Antioxidant response	**−0.35**	212	−0.53	−0.17	**0.9727**	454.33	0.001	1698.2
Oxidative damage	**0.276**	288	0.086	0.37	**0.9184**	735.88	0.001	708.7

Table 2
Effect size estimates and absolute estimates weighted by sample size for antioxidant response and oxidative damage. The table also reports sample size, lower and upper 95% bootstrap confidence intervals. Effect sizes shown in bold are significantly different from zero.

	Effect size	N	Lower B-strap CI	Upper B-strap CI	Absolute effect size	Lower B-strap CI	Upper B-strap CI
Antioxidant response by biological matrix							
Blood	**−0.4558**	**160**	**−0.6467**	**−0.2536**	**0.9237**	**0.7974**	**1.0871**
Liver	0.4574	32	−0.1518	1.1338	**1.3373**	**0.9593**	**1.7977**
Brain	−1.0769	4	−3.5724	0.4507	**1.3899**	**0.3616**	**4.2475**
Heart	−0.7009	2	−3.171	0.4337	**1.1017**	**0.4337**	**3.171**
Eggs	−0.7048	9	−1.5757	0.0749	**1.1296**	**0.5569**	**1.8472**
Sperm	**0.5558**	**3**	**0.1251**	**0.9857**	**0.5554**	**0.1251**	**0.8428**
Oxidative damage by biological matrix							
Blood	**0.4936**	**136**	**0.3533**	**0.6328**	**0.6705**	**0.5856**	**0.778**
Liver	−0.1426	32	−1.0279	0.6498	**1.7837**	**1.3136**	**2.4897**
Brain	−0.6542	20	−1.6221	0.134	**1.5866**	**1.118**	**2.1366**
Lungs	**−0.5896**	**17**	**−1.1671**	**−0.0752**	**0.9667**	**0.6354**	**1.3833**
Heart	**0.8035**	**18**	**0.1717**	**1.4084**	**1.4518**	**1.0392**	**1.8409**
Spleen	**−0.5653**	**17**	**−1.1006**	**−0.0782**	**0.919**	**0.6431**	**1.2882**
Kidney	−0.3142	17	−1.0505	0.4097	**1.3763**	**0.945**	**1.7523**
Muscle	**0.764**	**15**	**0.2166**	**1.2885**	**1.1081**	**0.7184**	**1.5126**
Testes	0.1756	15	−0.1659	0.5277	**0.5654**	**0.3657**	**0.8158**
Antioxidant response by species							
Homo sapiens	**−0.5179**	**149**	**−0.7161**	**−0.3265**	**0.8928**	**0.7543**	**1.0422**
Rattus norvegicus	−0.0369	19	−0.9505	0.8549	**1.6966**	**1.2086**	**2.3345**
Hirundo rustica	**1.0128**	**11**	**0.6021**	**1.4296**	**1.0003**	**0.6147**	**1.4664**
Parus major	**−1.3696**	**6**	**−2.2902**	**−0.5828**	**1.3562**	**0.6100**	**2.1749**
Apodemus agrarius	0.8725	5	−0.7928	3.4625	**1.6896**	**0.5651**	**3.6249**
Mus musculus	**−1.413**	**5**	**−1.616**	**−1.2564**	**1.4121**	**1.2616**	**1.6065**
Microtus oeconomus	−1.2427	4	−4.1036	0.0749	**1.1941**	**0.1109**	**3.2536**
Microtus arvalis	**2.1033**	**4**	0.5600	**5.0518**	**1.9357**	**0.6265**	**4.8408**
Myodes rutilus	2.7442	2	1.4713	4.6699	2.6359	1.4713	4.6699
Apodemus uralensis	0.2167	2	0	0.4337	0.2166	0	0.4337
Apodemus sylvaticus	−0.1701	2	−0.3994	0.0588	0.2289	0.0588	0.3994
Myodes glareolus	−0.0366	2	−0.1693	0.0961	0.1327	0.0961	0.1693
Oxidative damage by species							
Rattus norvegicus	**−0.0428**	**155**	**−0.2114**	0.1690	1.0594	0.934	1.1925
Homo sapiens	**0.523**	**110**	**0.3922**	0.6629	0.6271	0.5265	0.7334
Microtus arvalis	−0.5189	9	−3.5842	1.3470	2.6492	1.5616	4.9091
Bos taurus	**0.4457**	**3**	**0.3406**	**2.4855**	0.4456	0.3406	0.5452
Myodes rutilus	−2.1144	3	−7.4000	0.2310	3.5682	1.5603	7.4
Apodemus agrarius	2.8164	3	1.9291	8.7224	2.6476	1.9937	8.7224
Apodemus uralensis	**2.1756**	**2**	**1.9291**	**2.4273**	2.1736	1.9291	2.4273
Hirundo rustica	0.1737	2	−0.5711	0.9516	0.7541	0.5711	0.9516
Antioxidant response by age							
Adult	**−0.315**	**155**	**−0.5616**	**−0.0822**	**1.1109**	**0.9627**	**1.2776**
Juvenile	**−0.4668**	**55**	**−0.7373**	**−0.2288**	**0.6585**	**0.4831**	**0.9051**
Oxidative damage by age							
Adult	**0.1866**	**275**	**0.0586**	**0.3156**	**0.8481**	**0.769**	**0.9351**
Juvenile	**1.343**	**11**	**0.6638**	**2.3029**	**1.3226**	**0.6534**	**2.1804**

−0.393 (0.146); oxidative damage: 0.458 (0.155)) and study (variance ratio = 0.002, 95% CI: 0.026, 0.639, 0.227% of total variance; oxidative damage: variance ratio = 0.054, 95% CI: −0.126, 0.233, 0.042% of total variance).

Levels of antioxidant response differed significantly among biological matrices (Fig. 3, Table 2). Two out of five matrices had effect sizes (ES) that differed significantly from zero (Table 2). While blood had an intermediate negative effect, sperm had a significant intermediate positive effect (Table 1). Interestingly, the positive effect for sperm differed significantly from that for eggs, as shown by non-overlapping confidence intervals, and even the sign of mean effect sizes for sperm and eggs was different (Table 1). Biological matrices differed significantly in terms of oxidative damage with significant heterogeneity (Fig. 2, Table 1). However, significant large absolute effect (i.e. magnitude) of antioxidant response and oxidative damage was demonstrated for most matrices (Figs. 2-3, Table 2).

There was significant interspecific variation in antioxidant response (Fig. 5, Table 2). Among the 12 species presented here, six showed effect sizes significantly different from zero, with *Homo sapiens*, *Parus major* and *Mus musculus* showing negative effect sizes, while *Myodes rutilus*, *Microtus arvalis* and *Hirundo rustica* showing positive effect sizes (Table 2). For oxidative damage, three out of seven species (*Apodemus* sp., *Bos taurus* and *H. sapiens*) showed significant positive intermediate to large effect sizes (Fig. 4, Table 2). When we used absolute effect sizes, rather than signed ES, all species had effect sizes significantly different from zero for markers of antioxidant response, while for oxidative damage three species (*Apodemus uralensis*, *Apodemus sylvaticus*, *Myodes glareolus*) did not yield a significant ES.

Age was significantly related to antioxidant response, being 35% weaker in juveniles than in adults (Fig. 6, Table 2). Oxidative damage

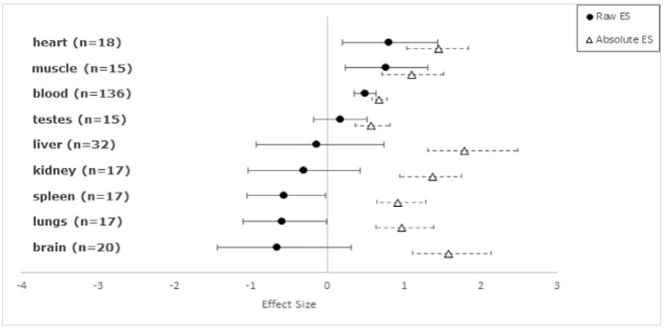

Fig. 2. Forest plot for mean and absolute effect sizes of oxidative damage in biological matrices. Values are means and 95% bootstrap confidence intervals.

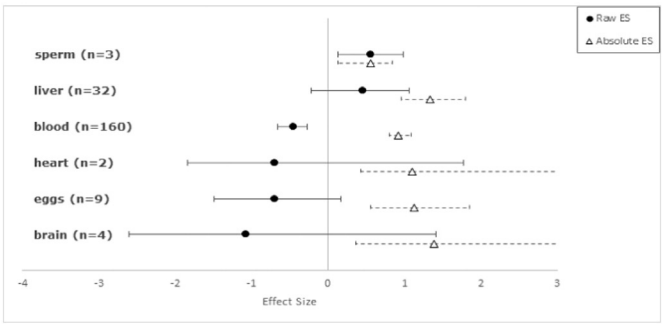

Fig. 3. Forest plot for mean and absolute effect sizes of antioxidant response in biological matrices. Values are means and 95% bootstrap confidence intervals.

in juveniles was six-fold larger than in adults (Table 2). Thus juveniles were more susceptible than adults, likely as a consequence of the weaker antioxidant system of juveniles.

We developed meta-regression models weighted by sample size using study as a random effect. However, none of the random effects accounted for an amount of variance deviating from zero, so instead we used ordinary least squares models. The model for oxidative damage, accounting for 8% of the variance, included significant effects of species and age, but no significant effect of biological matrix (Table 3). The effect of oxidative damage was larger for juveniles than for adults (Table 3). The best-fit model for antioxidant response, accounting for 17% of the variance, included significant effects of species, biological matrix and age, with a larger effect in juveniles than in adults (Table 4).

4. Discussion

The main findings of this study were significant effects of LDIR on the antioxidant status of exposed organisms, with a large magnitude of the mean effect (Table 1). We found significant heterogeneity in effect sizes among species and biological matrices. There were several-fold stronger effects of oxidative damage in juveniles than in adults. There was little or no indirect evidence to suggest publication bias.

We found mean weighted effect sizes for oxidative damage of 0.237 and for antioxidant response of −0.350. The absolute effect sizes were 0.918 and 0.973 respectively. Cohen (1988) regarded a $d = 0.50$ to represent an intermediate effect (equivalent to 6% of the variance). Thus the raw effect sizes that we have estimated here can be considered to be small to intermediate, and the magnitude of effects can be interpreted as large. Møller and Jennions (2002) reported when using Hedges' d an average effect size weighted by sample size across meta-analyses in the biological sciences of 0.721, while the median was 0.595 (in this case the sign of d was also disregarded).

The majority of our studies were extracted from Russian and Ukrainian sources, which are usually not included in Western bibliographical sources. Thus we were able to test for a difference in effect size between these two categories of effects with the eastern literature being more likely to be under-represented than the western literature, which is fully indexed in Web of Science as well as in other search engines. However, we found little or no evidence consistent with expectations for publication bias (Møller and Jennions, 2001). Jennions and Møller (2002) reported a general temporal decline in effect size over time. Here we found a weak and non-significant Pearson correlation between effect size and publication year. We also showed a non-significant correlation between absolute effect sizes and publication year. Begg and Mazumdar (1995) proposed a non-parametric correlation between raw effect size and sample as a test of publication bias, and although we showed significant correlations, they differed in sign and were of small magnitude. Funnel plots arise from the reduction in variance in effect size with increasing sample size (Light and Pillemer, 1984). Again, we found little and inconsistent relationships between variance in effect size and sample size (Fig. F1). Thus there was little evidence suggestive of publication bias.

Antioxidant responses varied among species, biological matrices and age classes. However, a meta-regression only showed a significant effect of species and biological matrices, when the effects of age classes were excluded as an independent predictor. Blood and eggs had intermediate to large negative effects for oxidative damage and antioxidant responses, while there were weak effects for liver, spleen and brain. The direction of the effect was difficult to evaluate due to high variability in markers studied within biological categories. However, this problem can be alleviated when the sign of the effect size is disregarded in the same model. Such analysis showed that all biological matrices had significant effects for individuals exposed to LDIR compared to controls (Figs. 2-3). It was not surprising that brain cells had a large effect. Brain cells have high metabolic activities and significant antioxidant defenses as inferred from the high contents of carotenoids and polyunsaturated fatty acids, which are targets of lipid peroxidation (Barja, 2004; Agostinho et al., 2010; Johnson et al., 2013). The importance of antioxidant defense is confirmed in studies of cancer radiotherapy, where the additional intake of antioxidants decreased the effectiveness of radiation treatment (Lawenda et al., 2008).

Our results also suggest that there might be priority of protection of some biological matrices at the cost for others. For example, we found that radiation caused increased antioxidant levels in sperm, resulting in a reduction of oxidative damage. This might indicate that, when exposed to chronic LDIR, males invest more in protection of sperm in order to limit reduction in fertility and so in the ability to successfully reproduce. Interestingly, previous studies of sperm motility in barn swallows showed that the relationship with individual oxidative status depended on environmental radiation, suggesting individuals prioritize protection of sperm when exposed to LDIR, at the expense of their

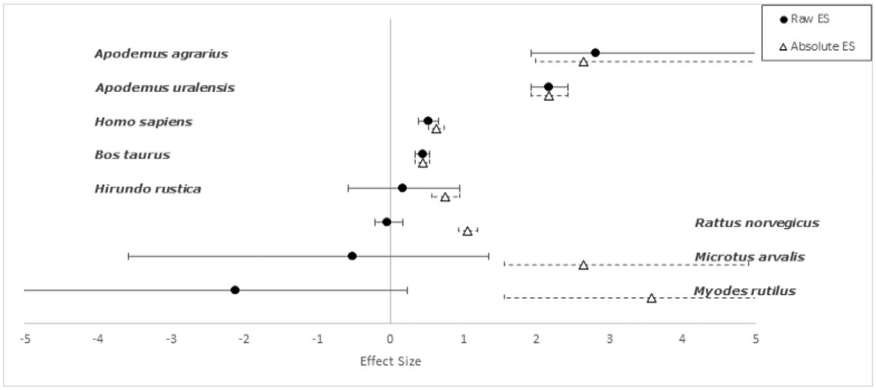

Fig. 4. Forest plots for mean and absolute effect sizes of oxidative damage for different species. Values are means and 95% bootstrap confidence intervals.

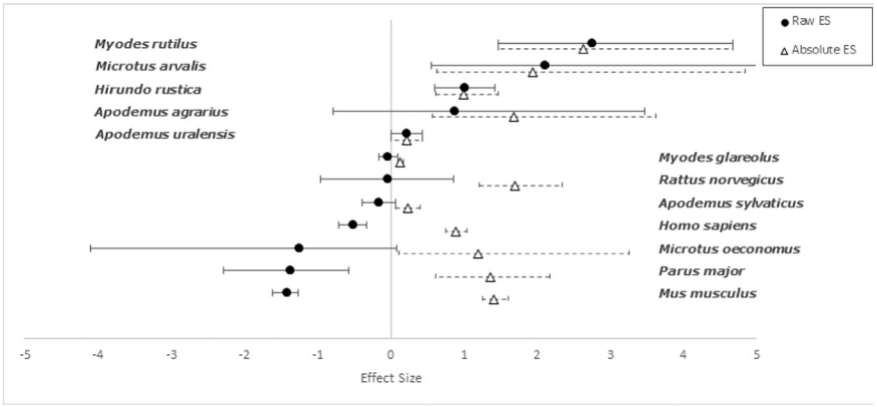

Fig. 5. Forest plots for mean and absolute levels of antioxidant response for different species. Values are means and 95% bootstrap confidence intervals.

plasma oxidative status (Bonisoli Alquati et al., 2011). The effect for eggs was opposite to that for sperm. It is possible that eggs and sperm differ in susceptibility to LDIR, and that this affects differences in the level of investment in antioxidant protection under LDIR.

Species varied significantly in level of antioxidant response and oxidative damage. Three species (*M. rutilus*, *M. arvalis* and *H. rustica*) showed an increase in antioxidant defenses after exposure to ionizing radiation, while three others (*M. musculus*, *P. major* and *H. sapiens*) showed a decrease. Of the seven species assessed for oxidative damage levels, the four species *Apodemus agrarius*, *A. uralensis*, *B. taurus* and *H. sapiens* showed an increase in oxidative markers, while *Rattus norvegicus*, *M. arvalis* and *M. rutilus* did not differ significantly from zero (Fig. 4). However, the analysis of absolute values demonstrated that mean effect size for *R. norvegicus* consisted of significant positive and significant negative effects of oxidative damage. This analysis also showed that *A. sylvaticus*, *A. uralensis* and *M. glareolus* had none to very weak effects (Fig. 4). Such heterogeneity may indicate that some species are negatively impacted by ionizing radiation while others are more resistant.

Variation in effect among biological matrices within species can obscure the analysis of relationships, as seen in *R. norvegicus* and *H. rustica* (Fig. 4). While showing a non-significant level of signed oxidative effect, the average absolute effect size for these species was significantly large. Thus we suggest care when considering the particular marker analyzed and the predicted direction of effects when combining studies that are not homogeneous in the protocol used for analyses.

The literature sources that we used in the present study reported various measurements of LDIR on human or animal populations. For example, Souchkevitch et al. (1997) and Ovsyannikova et al. (2010) reported individual effective dose of exposure in milliSieverts (mSv), whereas Paranich et al. (1998), Drobinska and Moroz (1998) and Lyashenko (2000) used centiGray (cGy) as a unit of absorbed dose, and Verhoglyad et al. (1991) reported an older unit, millirem (mrem). Yet these units are cross-convertible with some minor assumptions (Thaul and O'Maonaigh, 1999), while others provide a vague estimate of individual radiation impact, reporting spatial contamination or rather the equivalent dose rate. Among such studies were those by Shishkina et al. (2005), with a commonly reported exposure rate in μSv/h. Likewise, Belov et al. (1997) estimated radionuclide intake in Bq/day, while other studies like Mirzoev et al. (1999) or Neyfakh et al. (1998) reported terrestrial contamination in kBq/m^2 or Ci/km^2, respectively. Thus, because of methodological inconsistencies in reporting radiation dosimetry among studies, we were unable to infer dose–response relationships to explain variation. Therefore, we call for the use of estimates of acquired dose of LDIR by individuals rather than reporting measurements of environmental contamination.

Young age classes are considered to be more susceptible to oxidative damage because juveniles produce large amounts of free radicals as a consequence of their development and growth process, whilst they have an enzymatic antioxidant machinery that takes time to become fully mature (Costantini, 2014; Surai, 2002). In addition, low levels of dietary antioxidants deposited by mothers into eggs or passed to the offspring through milk may result in embryos exposed to LDIR starting their development with low levels of antioxidants (Møller et al., 2005). Thus we expected that studies of early developmental stages would demonstrate greater sensitivity to increased oxidative damage. Levels of natural LDIR vary considerably with studies in high natural background radiation areas finding weak, but significant health effects associated with natural LDIR (Møller and Mousseau, 2013). This conclusion suggests that there is selection acting on the ability to sustain LDIR, and that there may be scope for adaptation to radiation. Indeed, studies of birds at Chernobyl and Fukushima have shown that species with carotenoid- and pheomelanin-based pigments in their plumage show stronger negative impact of LDIR on population density (Galván et al., 2011; Møller and Mousseau, 2007b, 2009; Møller et al., 2012). At the same time, Galván et al. (2014) showed that glutathione (an important intracellular antioxidant) levels and body condition increased, and oxidative damage and DNA damage decreased, with increasing background radiation in some species of birds. This effect was independent

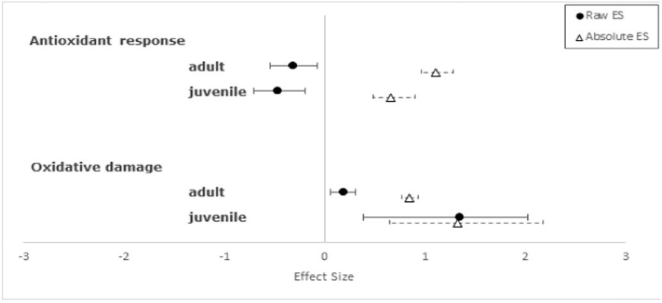

Fig. 6. Forest plots for levels of mean and absolute values of antioxidant response and oxidative damage for the two age classes. Values are means and 95% bootstrap confidence intervals.

Table 3
Ordinary least squares model of effect size of oxidative damage weighted by sample size in relation to species, biological matrix and age. The model had the statistics $F = 2.413$, d.f. = 16, 252, $r^2 = 0.08$, $P = 0.0022$.

Term	d.f.	Sum of squares	*F*	*P*	Estimate	SE
Intercept			0.212	0.646	0.286	0.624
Species	6	2173.44	2.344	0.032		
Biological matrix	9	1377.95	0.991	0.448		
Age	1	843.14	5.46	0.020	−0.493	0.211
Error	252	38,947.77				

Table 4
Ordinary least squares model of effect size for antioxidant response weighted by sample size in relation to species, biological matrix and age. The model had the statistics $F = 3.9151$, d.f. = 18, 177, $r^2 = 0.17$, $P < 0.0001$.

Term	d.f.	Sum of squares	*F*	*P*	Estimate	SE
Intercept			7.182	0.008	−2.660	0.992
Species	10	3578.30	2.449	0.009		
Biological matrix	7	3552.67	3.484	0.0016		
Age	1	724.86	4.975	0.027	−0.269	0.121
Error	177	25,787.78				

of a number of potentially confounding variables including effects of similarity among taxa due to common phylogenetic descent. We only found a significant difference in the effect of LDIR on oxidative damage among species and age classes in a meta-regression accounting for the effects of other potentially confounding variables. In contrast, there was a significant effect of species and matrix on the level of antioxidant response. While some species showed a positive response for oxidative damage, other species did not. This dichotomy and the significant heterogeneity among species are consistent with adaptation to LDIR although alternative explanations may also account for such heterogeneity (Lademann et al., 2015).

In conclusion, we have found generally strong effects on oxidative status in response to low-dose ionizing radiation. We showed significant heterogeneity among biological matrices, species and age classes. These findings are consistent with some species apparently being negatively impacted by ionizing radiation while others are not, or even showing evidence consistent with adaptation to radiation by having positive antioxidant responses at high levels of radiation.

The results of our meta-analysis have important implications for studying the effects of LDIR in human populations and in the wild. For example, over the last few decades exposure of the average American to ionizing radiation has increased from 3.6 to 6.2 mSv/year (NCRP, 1987; NCRP, 2009). Generally, this low rate of exposure comes from natural sources in air, soil, rocks and cosmic rays (accounting for 2–2.5 mSv/year), while the remainder is acquired from man-made sources such as medical procedures (periodic X-ray, CT scans and others) and industrial activities such as those associated with mining and processing of ores, minerals, nuclear fuels and oil. Such trends as those revealed in the NCRP reports and elsewhere forecast an increase in exposure due to such artificial sources (Fazel et al., 2009; Pandey et al., 2010). In addition, the advent of the "Atomic age" has ushered in several nuclear accidents. Two of these, at Chernobyl NPP in 1986 and at Fukushima NPP in 2011, were classified at the highest level on the International Nuclear and Radiological Event Scale (INES) scale of nuclear hazards leading to global increases in radioactive contamination. Overall, man-made sources of LDIR appear to increase radioactive intake, which, as our analysis suggests, might be reflected in the metabolic sensitivity to LDIR.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.01.027.

Declaration of interest

The authors state that they have no conflicts of interest.

Acknowledgments

The authors would like to thank the anonymous reviewers for their insightful comments and suggestions. We also thank I. Kozeretska, the Library of the University of Kyiv and National Library of Ukraine for help in locating publications and finding scientific papers in the Ukrainian and Russian scientific literature. We thank M. Owens for editorial assistance. Funding was provided in part from the Samuel Freeman Charitable Trust, the US Fulbright Program, the CNRS (France), the American Council of Learned Societies, and the University of South Carolina College of Arts & Sciences.

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