Ecotoxicology and Environmental Safety 216 (2021) 112211

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

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

Are cadmium and lead levels linked to the development of anxiety and depression? - A systematic review of observational studies

Anna Maria Cybulska [a], Szymon Grochans [b], Magdalena Sylwia Kamińska [c,*], Mateusz Bosiacki [d], Karolina Skonieczna-Żydecka [e], Elżbieta Grochans [a]

[a] Department of Nursing, Faculty of Health Sciences, Pomeranian Medical University in Szczecin, 48 Żołnierska St., 71-210 Szczecin, Poland
[b] Department of Biochemistry and Medical Chemistry, Pomeranian Medical University in Szczecin, 72 Powstańców Wielkopolskich St., 70-111, Szczecin, Poland
[c] Subdepartment of Long-Term Care and Palliative Medicine, Department of Social Medicine, Faculty of Health Sciences, Pomeranian Medical University in Szczecin, 48 Żołnierska St., 71-210 Szczecin, Poland
[d] Department of Functional Diagnostics and Physical Medicine, Pomeranian Medical University in Szczecin, Żołnierska 54 Str., 71-210 Szczecin, Poland
[e] Department of Human Nutrition and Metabolomics, Pomeranian Medical University in Szczecin, 24 Broniewskiego St., 71-460 Szczecin, Poland

ARTICLE INFO

Edited by: Dr G Liu

Keywords:
Cadmium
Lead
Anxiety
Depression

ABSTRACT

The aim of this systematic review was to assess if cadmium and lead levels are linked to anxiety and depression. A systematic literature search was conducted to identify observational trials evaluating the impact of cadmium and lead on the incidence and phenotype of depression and anxiety. The search identified 1059 records. Overall eighteen studies comprising 28,304 participants with a female predominance (n = 19,483; 69%) were included. Cadmium and lead levels were analyzed in eight and thirteen studies, respectively. Five studies found an association between blood cadmium levels and depression, among them three trials which reported that individuals in the highest quartile of blood cadmium had higher odds of showing depressive symptoms. Sex and smoking status were found to be potential confounders of cadmium impact on the depressive phenotype. None of the studies found association between the level of anxiety and blood cadmium levels. Nine studies demonstrated association between depressive symptoms and blood lead concentration. High lead levels may be associated with anxiety and neurobehavioral deficits. There are many factors that influence both the levels of cadmium and lead, and the severity of depression and anxiety in the respondents. There is no clear evidence for the impact of cadmium and lead levels on the development of depressive symptoms but a lot of indirect evidence points to this.

1. Introduction

1.1. Cadmium

Cadmium (Cd) is a highly toxic heavy metal with a body half-life of 10–30 years. It is widely distributed in the environment as an agricultural and industrial pollutant (Järup and Akesson, 2009). The main source of Cd intake in the non-smoking population is food. Major sources of Cd exposure in the general smoking population are both smoking and diet, because tobacco (Faroon et al., 2012), potatoes, grains, and vegetables take up Cd from soil (Amzal et. al., 2009).

Cadmium has been recognized as an occupational health hazard for many decades (WHO, 2011). One of the most landmark moments was the infamous Itaiitai disease, caused by the consumption of cadmium-polluted rice (Nishijo et al., 2017).

The average Cd intake from food generally varies between 8 and 25 μg per day (Egan et al., 2007; Larsen et al., 2002; Llobet et al., 2003; Olsson et al., 2002; Sujka et al., 2019) but may be higher in Japan (Kikuchi et al., 2002; Zhong et al., 2015). In the whole European Union, limits have been set for the level of Cd in food products, and limitations on their emission have been imposed (EFSA, 2009, 2010; EC, 2006). Maximum levels for Cd in foodstuffs have been determined by the Commission Regulation No. 1881/2006, the framework EU legislation, which sets maximum levels for chemical contaminants in foodstuffs (EC, 1996). Regarding cadmium, the Scientific Committee on Food endorsed in its opinion of 2 June 1995 the provisional tolerable weekly intake of 7

Abbreviation: bCd, cadmium in blood; bPb, lead in blood; uCd, cadmium in urine.

* Corresponding author.
E-mail addresses: anna.cybulska@pum.edu.pl (A.M. Cybulska), grochans@pum.edu.pl (S. Grochans), magdalena.kaminska@pum.edu.pl (M.S. Kamińska), irena.bosiacka@pum.edu.pl (M. Bosiacki), karzyd@pum.edu.pl (K. Skonieczna-Żydecka), grochans@pum.edu.pl (E. Grochans).

https://doi.org/10.1016/j.ecoenv.2021.112211
Received 11 December 2020; Received in revised form 19 March 2021; Accepted 29 March 2021
Available online 13 April 2021

μg/kg bw (EC, 1994).

Cadmium may have a wide range of negative effects on human health. Cadmium toxic effect is related mainly to its occurrence in the form of free Cd ions that bind with atoms of sulphur, hydrogen and oxygen, thus disturbing various metabolic cycles (Genchi et al., 2020). Cadmium disturbs the metabolism of proteins and the transformation of vitamin B1. Cadmium is classified as an element having a carcinogenic and nephrotoxic effect, causing demineralisation of bones, and thus increasing their fragility (Åkesson et al., 2006; Nordberg et al., 2018). Furthermore, increased mortality in populations environmentally exposed to Cd and its embryotoxic and teratogenic effects have also been confirmed (Kippler et al., 2012). Nutritional status (for example low iron status) is one of factors that affect the bioavailability, retention, and toxicity of cadmium (Järup and Akesson, 2009).

Cd exposure has been linked to adverse neurobehavioral outcomes, for example lower intelligence quotients (Rodríguez-Barranco et al., 2014) and learning disabilities (Ciesielski et al., 2012). Cadmium may contribute to the etiology of depression through impairment of the monoaminergic neurotransmission system (Orisakwe, 2014; Scinicariello and Buser, 2015; Kim et al., 2016). Some researchers have reported a link between Cd levels in blood (bCd) and various psychiatric disorders, including schizophrenia and bipolar disorder. A positive relationship has been shown between elevated bCd and symptoms of depression. The relationship between urine Cd (uCd) levels and symptoms of depression is less obvious, possibly because bCd is more indicative of short-term mixed with long-term exposure, while uCd reflects rather lifetime exposure (Järup et al., 1998; Shiue, 2015).

Blood Cd level is a valid marker of both recent and cumulative exposure to Cd, since the half-life of this metal in blood displays a fast component of three to four months and a slow component of about ten years. This half-life is due to the influence of accumulation of Cd in the body on blood Cd levels (Rafati Rahimzadeh et al., 2017; Silver et al., 2013).

Normal reference bCd values for all ages are < 5.0 ng/mL, with most results ranging from 0.5 to 2.0 ng/mL. Acute toxicity is observed when the blood Cd level exceeds 50 ng/mL (Moreau et al., 1983; Strathmann and Blum, 2018). Cadmium levels in the blood of tobacco smokers can be up to four or five times higher, and in the kidneys—up to two or three times higher, compared to nonsmokers (Richter et al., 2017; Pappas, 2011; Nair et al., 2013).

1.2. Lead

Lead is a highly toxic heavy metal, whose half-life is about 40 days after which it deposits in bones for decades and is slowly released (De Souza et al., 2018). Lead exposure can come about from a variety of sources, for example: industrial pollution (air, water and soil) (Ren et al., 2006), traditional Chinese medicines (Karri et al., 2008), lead paint, imported ceramics, dust, imported toys, batteries, and occupational lead sources (Obeng-Gyasi, 2019).

The Center of Disease Control and the National Institute for Occupational Safety and Health (NIOSH) designated 5 μg/dL of whole blood as the reference blood lead level for adults (CDC, 2016). Advanced studies have shown that blood lead levels < 10 μg/dL have a negative impact on the nervous system (Jusko et al., 2008; Téllez-Rojo et al., 2006). Maximum levels for Pb in foodstuffs have been set by Commission Regulation No 1881/2006. Regarding lead, the Scientific Committee on Food endorsed in its opinion of 19 June 1992 the provisional tolerable weekly intake of 25 μg/kg bw proposed by the WHO in 1986 (EC, 2006).

Lead is highly toxic and its accumulation in the human body disturbs the activity of many enzymes and functions of structural proteins. Pb affects the enzymes of the respiratory chain, glycolysis pathway, and the synthesis of hem, which results in the disturbances in the metabolic transformation of cells, such as: regulation of energetic processes, and synthesis of proteins and nucleic acids (Mitra et al., 2017). Acute and chronic lead exposure causes many deleterious systemic effects, including anemia, hypertension, renal effects, cognitive deficits, infertility, immune imbalances, delayed skeletal and deciduous dental development, vitamin D deficiency, gastrointestinal effects, neurological and behavioral effects. Furthermore lead is a mutagenic element and can cause cancer, and disturbances of the central nervous system (CNS) (Mitra et al., 2017; Sanders et al., 2009). Research on neurotoxic effects of low Pb exposure has focused on early childhood and pregnancy. In adult populations, the neurotoxic effects of Pb have been studied mainly in the context of occupational exposures, especially in lead-exposed workers in foundries, battery plants, or lead smelter (Mitra et al., 2017; Sanders et al., 2009). Some studies present a link between Pb exposure and cognitive or neuromotor deficits, as well as mood disorders such as anxiety and depressive states. Lead-exposed workers with diagnosed mood disorders had an average bPb level as high as 40 μg/dL (Bouchard et al., 2009).

Heavy metals like Pb and Cd, even though they occur in small amounts, are a serious threat to the human organism, causing e.g. kidney failure, dementia, anaemia, neurological changes, mental disorders, and cancers (Sujka et al., 2019). Furthermore depression and anxiety disorders are common forms of psychiatric disorder in the general adult population, causing substantial morbidity. Based on existing literature we decided to assess: (1) whether the level of Cd is linked to depression and anxiety, (2) whether the level of Pb is linked to depression and anxiety.

1.3. Search strategy and selection criteria

This study was conducted according to the requirements included in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols. Two independent authors systematically searched PubMed/Medline/Embase from database inception until 23 October 2019.

The following search terms with medical subject headings (MeSH–bold font) for **PUBMED** ("cd"[All Fields] OR ("cadmium"[MeSH Terms] OR "cadmium"[All Fields]) OR "lead ion"[All Fields] OR "Pb"[All Fields] OR "lead 208"[All Fields]) AND level[All Fields] AND (("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) OR ("anxiety"[MeSH Terms] OR "anxiety"[All Fields])) for **EMBASE**: ('cadmium'/exp OR 'cadmium' OR 'cadmium ion' OR 'cadmium radioisotopes') AND ('depression'/exp OR 'central depression' OR 'clinical depression' OR 'depression' OR 'depressive disease' OR 'depressive disorder' OR 'depressive episode' OR 'depressive illness' OR 'depressive personality disorder' OR 'depressive state' OR 'depressive symptom' OR 'depressive syndrome' OR 'mental depression' OR 'parental depression' OR 'anxiety'/exp OR 'anxiety').

The electronic search was supplemented by a manual review of the reference lists from eligible publications and relevant reviews.

Inclusion criteria for studies were as follows:

- Human study;
- Anxiety and depression disorder;
- Language: Polish, English and German;
- Available data on Cd and Pb levels in serum/other tissues.

Exclusion criteria for studies were as follows:

- studies in animals;
- studies related to other disorders than anxiety and depression;
- language other than Polish, English and German;
- studies in children or pregnant women;
- no control group.

1.4. Data extraction and analysis

Two authors independently extracted information from each study, including details on study characteristics (e.g. study design, study type), group characteristics (e.g. age, sex, depression, Pb level, Cd level). When abstracting data from figures, WebPlot digitizer software was used (https://automeris.io/WebPlotDigitizer/).

1.5. Risk of bias assessment

The authors independently assessed the risk of bias using STROBE (Von Elm et al., 2008). If a discrepancy occurred a third author was involved. Indeed, a qualitative scoring in STROBE was arbitrarily introduced by ourselves. When the total number of points was below 16 (50%), we arbitrarily defined the quality of the study as low. When the results represented up to 75% of the maximum number of points (24 points), we treated the study as of moderate quality. Results with a strobe score over 75% (25–28 points) and 90% (> 29 points) were considered high and very high quality, respectively. When the total number of points was below 16 (50%), we arbitrarily defined the quality of the study as low. When the results represented up to 75% of the maximum number of points, we treated the study as of moderate quality. Results with a strobe score over 75% and 90% were considered high and very high quality, respectively.

2. Results

2.1. Search results

The search identified 1059 records; 1040 articles were excluded as duplicates or after evaluation at the title or abstract level. Out of 18 full-text articles that were reviewed, two were excluded as they did not meet the inclusion criteria. The reason for exclusion was language other than English and abstract exclusion due full text availably (Fig. 1).

2.2. Characteristics of the study and study samples

Of the eighteen studies included, the majority were cross-sectional studies (N = 12) (Bouchard et al., 2009; Buser and Scinicariello, 2017; Eum et al., 2012; Golub et al., 2010; Han et al., 2016; Jurczak et al.,

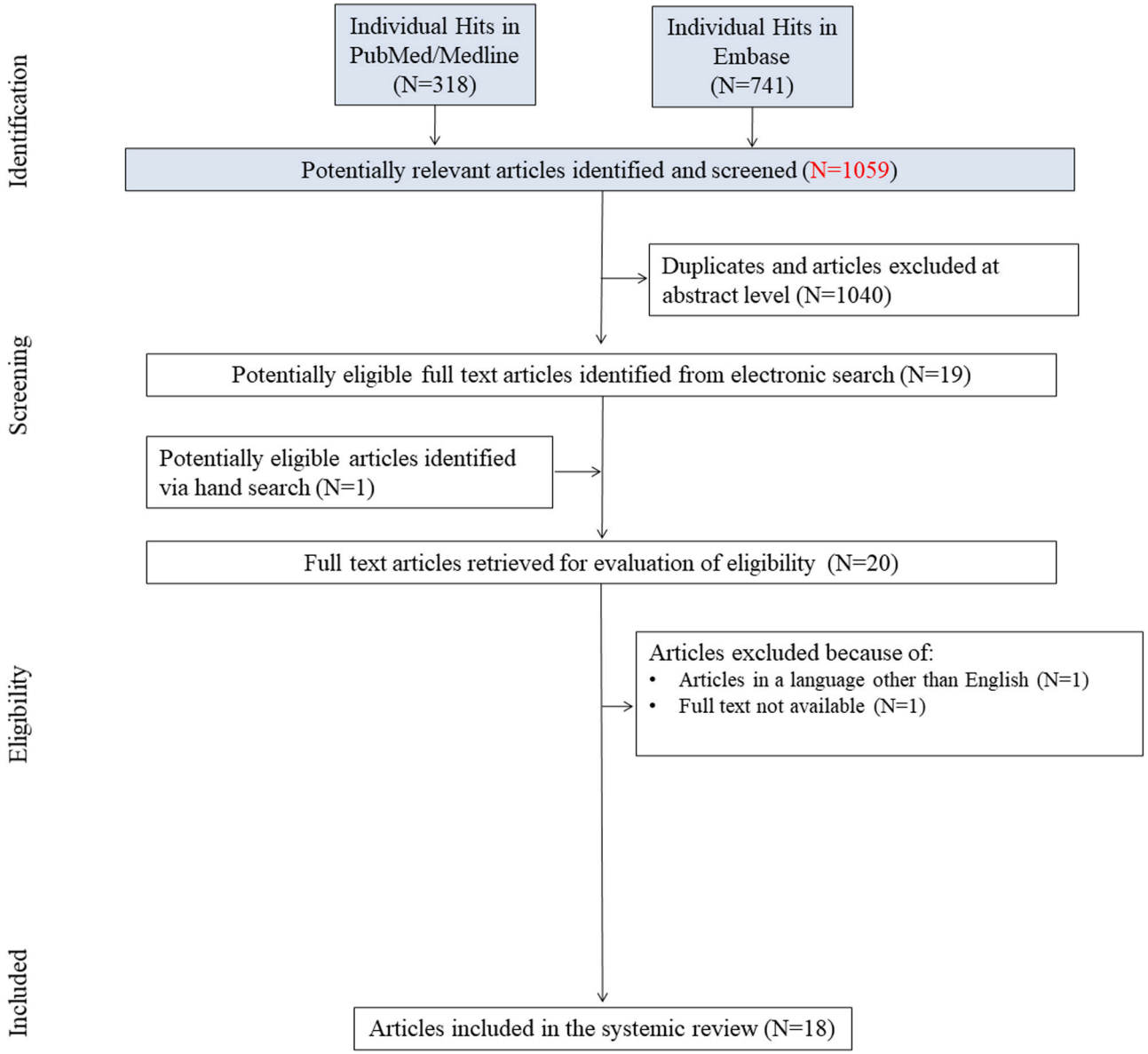

Fig. 1. A flow diagram of the included and excluded studies.

2018; Kim et al., 2016; Kostrubiak et al., 2017; Malekirad et al., 2013; Rhodes et al., 2003; Scinicariello and Buser, 2015; Wang et al., 2006). Thirteen studies analyzed Pb levels in the body: eleven studies in the blood (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Fenga et al., 2016; Golub et al., 2010; Jurczak et al., 2018; Lindgren et al., 1999; Malekirad et al., 2013; McFarlane et al., 2013; Wang et al., 2006) one in bones (Eum et al., 2012) and one in bones and blood (Rhodes et al., 2003). Eight studies analyzed Cd levels: seven included bCd levels (Buser et al., 2017; Han et al., 2016; Jurczak et al., 2018; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Wang et al., 2006) and one Cd levels in CNS tissues: Brodmann's area 6, 10 and 17 (Dean et al., 2019), (Fig. 2.).

Overall, eighteen studies were included, which comprised a total number of 28,304 subjects with a female predominance (n = 19,483; 69%). The respondents were of both sexes (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Dean et al., 2019; Han et al., 2016; Golub et al., 2010; McFarlane et al., 2013; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Wang et al., 2006) or women only (Eum et al., 2012; Jurczak et al., 2018) or men only (Fenga et al., 2016; Malekirad et al., 2013; Rhodes et al., 2003). In one article we did not find information about the respondents' sex (Lindgren et al., 1999). The range of the respondents' age was 18–80

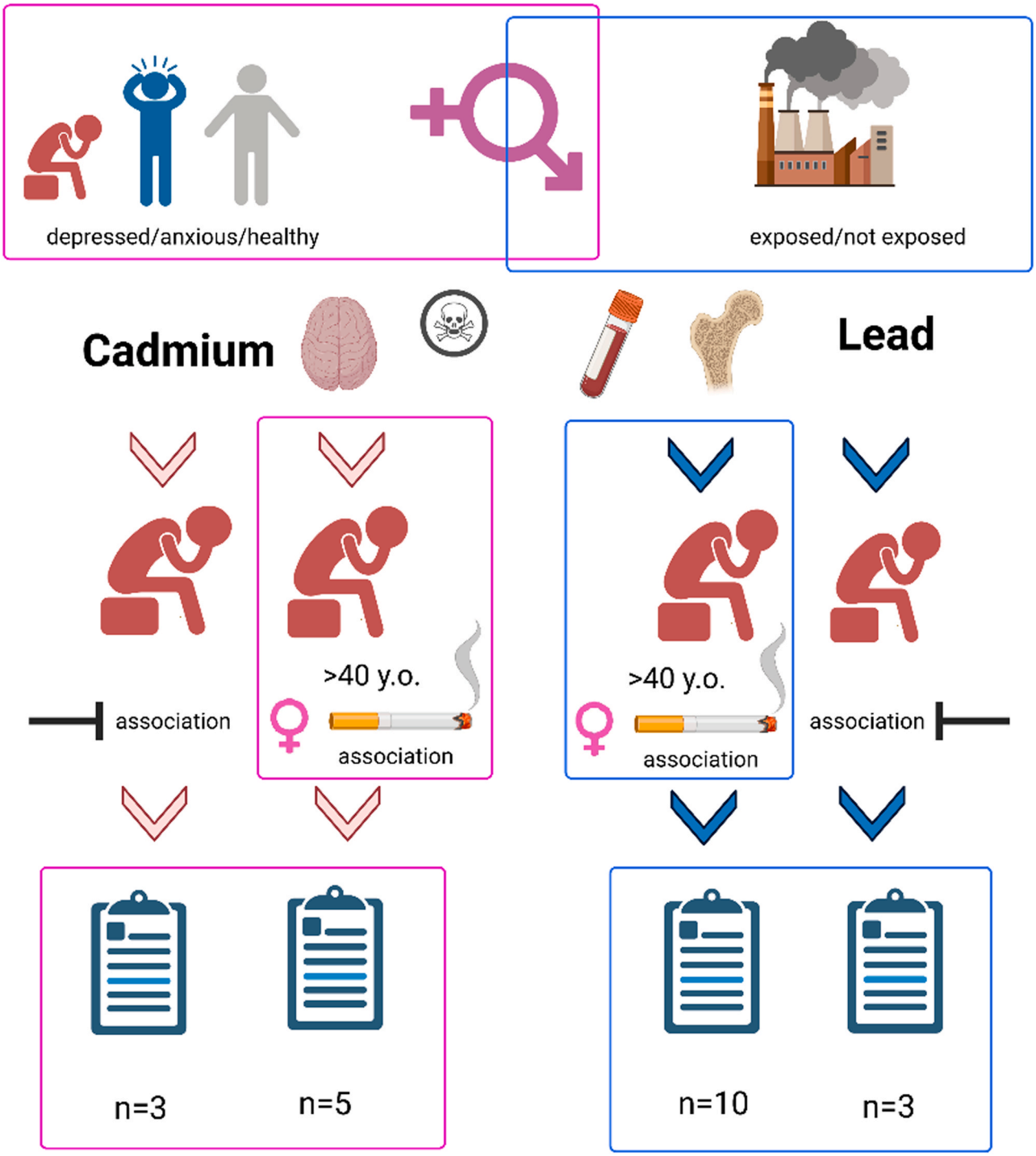

Fig. 2. Characteristics of the study and influence of Pb and Cd on depression and anxiety.

years. The details are given in Table 1.

Ten studies analyzed Cd or Pb levels in two groups: depressed and not depressed [Bouchard et al., 2009; Buser and Scinicariello, 2017; Dean et al., 2019; Golub et al., 2010; Han et al., 2016; Jurczak et al., 2018; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Rhodes et al., 2003]. Five studies included two groups: exposed and unexposed to heavy metals (Cd or Pb) [Baker et al., 1983, 1985; Fenga et al., 2016; Malekirad et al., 2013; Wang et al., 2006]. In participants designated as exposed worked directly with lead/cadmium (e.g. a battery recycling plant), and unexposed group consisted of persons working in the same factories but with no direct contact with heavy metals (e.g. welders, not operators). Three authors did not write anything about the division of the study samples [Eum et al., 2012; Lindgren et al., 1999; McFarlane et al., 2013] (Table 1).

The presence or absence of depressive symptoms was determined using standardized research tools. The most popular were: the Profile of Mood States (POMS) (Baker et al., 1983, 1985; Fenga et al., 2016; Lindgren et al., 1999), the Patient Health Questionnaire-9 (PHQ-9) (Buser and Scinicariello, 2017; Golub et al., 2010; Kostrubiak et al., 2017; Scinicariello and Buser, 2015) and the Composite International Diagnostic Interview (CIDI) (Bouchard et al., 2009; McFarlane et al., 2013). The details concerning the questionnaires are given in Table 2 and Table 4. Only Malekirad et al. (2013) and Dean et al., 2019 did not indicate the standardized research tools used to check depressive symptoms.

Assessment of the risk of bias by STROBE showed that one article was low quality (Malekirad et al., 2013), eleven was of moderate-quality (Baker et al., 1983, 1985; Dean et al., 2019; Eum et al., 2012; Fenga et al., 2016; Jurczak et al., 2018; Lindgren et al., 1999; McFarlane et al., 2013; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Wang et al., 2006) and six were of high quality (Bouchard et al., 2009; Buser and Scinicariello, 2017; Golub et al., 2010; Kim et al., 2016; Han et al., 2016; Rhodes et al., 2003).

2.3. Depression and anxiety-related outcomes following Cd exposure

Eight studies analyzed the influence of Cd exposure on the development of depression (Buser and Scinicariello, 2017; Dean et al., 2019; Han et al., 2016; Jurczak et al., 2018; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Wang et al., 2006). Only two investigations revealed a relationship between Cd levels and anxiety symptoms (Jurczak et al., 2018; Wang et al., 2006). Five studies found an association between bCd and depression (Buser and Scinicariello, 2017; Dean et al., 2019; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015). Many factors contributing to the severity of depression and Cd levels in blood have been found. Three studies reported that individuals in the highest quartile of bCd had higher odds of having depressive symptoms (Buser and Scinicariello, 2017; Kim et al., 2016; Scinicariello and Buser, 2015). Other risk factors were: sex (Buser and Scinicariello, 2017) and smoking cigarettes (Buser and Scinicariello, 2017; Kostrubiak et al., 2017) (Table 3). Three studies did not confirm a relationship between depressive symptoms and bCd levels in the population (Han et al., 2016; Jurczak et al., 2018; Wang et al., 2006). Jurczak et al. (2018) analyzed the correlation between the severity of depression and the level of bCd in the whole blood of patients after menopause. They did not find any statistically significant correlations ($R = -0.081$ $p > 0.05$) (Table 2).

Neither Jurczak et al. (2018) nor Wang et al. (2006) found any association between the severity of anxiety and the level of bCd, though they analyzed many factors (age, menopausal status, education level) (Table 3).

2.4. Depression and anxiety-related outcomes following Pb exposure

Thirteen studies analyzed the influence of Pb exposure on the development of depression (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Eum et al., 2012; Fenga et al., 2016; Golub et al., 2010; Jurczak et al., 2018; Lindgren et al., 1999; Malekirad et al., 2013; McFarlane et al., 2013; Rhodes et al., 2003; Wang et al., 2006). Eight studies investigated the influence of Pb levels on anxiety (Baker et al., 1983, 1985; Bouchard et al., 2009; Fenga et al., 2016; Jurczak et al., 2018; Lindgren et al., 1999; Rhodes et al., 2003; Wang et al., 2006) (Table 4).

Nine studies demonstrated associations between depressive symptoms and bPb levels (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Eum et al., 2012; Fenga et al., 2016; Lindgren et al., 1999; Malekirad et al., 2013; Rhodes et al., 2003). Many factors contributing to severity of depression and Pb levels in the body have been identified. Baker et al. (1983, 1984) reported that people with higher bPb levels scored higher on the Profile of Mood States (POMS). The same results were obtained by Bouchard et al. (2009), but they used another research instrument Composite International Diagnostic Interview (CIDI). In some studies, sex was as a factor contributing to the level of Pb and the severity of depression (Buser and Scinicariello, 2017; Eum et al., 2012). In two studies neurobehavioral symptoms were linked to Pb levels (Rhodes et al., 2003; Wang et al., 2006) (Table 5).

3. Discussion

To our knowledge, this is the only systematic review to examine the effect of Cd and Pb levels on the severity of depression and anxiety. It included 18 articles which involved a total number of 28.304 individuals. Our study shown that there are many factors that affect both Cd and Pb levels and the severity of depression and anxiety.

3.1. Main findings

Our systematic review reveals that exposure to Cd and Pb may be associated with an increased risk of depressive symptoms, however this is not unambiguous. The biological mechanisms by which exposure to Cd and Pb may increase the risk of depression and anxiety have not been fully explained. Cadmium, when penetrating the blood-brain barrier (Wang and Du, 2013), can accumulate in various regions of the mammalian brain (Lafuente et al., 2003). The intensity of Cd absorption is largely influenced by the physiological state of the organism. It has been shown that the deficiency of elements such as zinc and iron may cause, depending on age and sex, an increase in the absorption and accumulation of Cd (Reeves and Chaney, 2001; Horiguchi et al., 2004; Blazka and Shaikh, 1991; Satarug et al., 2003). There are different views on the biochemical mechanisms of the neurotoxic effects of Cd. Issues that have been described include disorders in the cellular antioxidant system (Labudda, 2011; Gutiérrez-Reyes et al., 1988), disturbances in energy production in metabolic pathways (Labudda, 2011; Kumar et al., 1994), changes in the metabolism of biogenic amines, neurotransmitters (Labudda, 2011; Lafuente et al., 2005a, 2005b), and calcium ions (Labudda, 2011; Vig and Nath, 1991) as well as enzymatic protein inhibition (Labudda, 2011; Carageorgiou et al., 2004). Various mechanisms leading to the development of depression have been described, in which an important role is attributed not only to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Rossi-George et al., 2009; Szymańska et al., 2009), an increased level of CRH and cortisol (Vreeburg et al., 2009), abnormalities in the serotonergic system (5-HT) (Cory-Slechta et al., 2004), but also Pb accumulation in the body (Cory-Slechta et al., 2008). The research by Lamtai et al. (2018) analysing the effect of chronic Cd administration on the severity of depression, anxiety, memory, and oxidative stress in male and female Wistar rats suggests that living in heavy metal polluted environments and continuous exposure to Cd may eventually lead to behavioral pathologies, such as affective and cognitive disorders. A meta-analysis by Taylor et al. (2014) demonstrated that quitting smoking is associated with a decrease in depression. Buser and Scinicariello (2017) suggest that depression can lead to behavioral changes that increase exposure to cadmium and lead.

Table 1
Study characteristics.

Reference/Year/Country/ Sponsorship	Focus of Study	Inclusion Criteria	Biological Material	Study Type	N Subjects Included/ Analyzed	Males (N/%)	Age (Mean±SD)	Groups Analyzed	STROBE score/ quality
Lead									
Baker et al. (1983)/USA/nd	neurobehavioral effects	Caucasian, English speaking natives, no history of prior lead poisoning, blood lead levels < 90 mcg/dl since beginning work at the plant, absence of excessive alcohol consumption or severe head trauma	blood	cohort	172/164	131/ 79.88%	32.38 range 18–62	exposed/ unexposed	20/ moderate
Baker et al. (1985)/ USA /government	nervous system symptoms in adults	workers with no history of heavy drinking or severe head injury	blood	cohort	171/160	129/ 80.6%	32.4 range 18–62	exposed/ unexposed	22/ moderate
Bouchard et al. (2009)/ USA /government	MDD and generalized anxiety disorder	adults aged ≥ 20 y.o., participants of NHANES 1999–2004	blood	cross-sectional	1987/1987	877/ 44.1%	nd/range 20–39	depressed/ nondepressed	26/ high
Buser et al., 2017/ USA /government	depressive symptoms	adults ages ≥ 20, participants of NHANES 2011–2012	blood	cross sectional	3905/3903	1955/ 50.08%	44.33 ± 61.2	depressed/ nondepressed	26/ high
Eum et al. (2012)/ USA /nd	depressive and anxiety symptoms	BMI < 29 kg/m^2, no history of major, chronic disease except mental disorders, female	bone	cross-sectional	621/488	0/0%	59.4 ± 7.3	na	24/ moderate
Fenga et al. (2016)/Italy/nd	mild cognitive impairment	living in mess in a metropolitan area, working in the battery storage plant for at least 5 h/day, ability to attend required study visits, no systemic disease	blood	cohort	80/80	80/ 100%	37.15 ± 8.09	exposed/ unexposed	17/ moderate
Golub et al. (2010)/ USA /government	depressive symptoms	adults aged ≥ 20, participants of NHANES 2005–2006	blood	cross-sectional	4979/4159	2013/ 48.41%	46.5 ± 47.1	depressed/ nondepressed	27/ high
Jurczak et al. (2018)/Poland /academia	severity of anxiety and depressive symptoms in postmenopausal women	postmenopausal women, no use of hormone therapy no history of psychiatric treatment, no addictions	blood	cross sectional	198/198	0/0%	56.26 ± 5.55	depressed/ nondepressed	21/ moderate
Lindgren et al. (1999)/ USA /nd	replicability of the POMS factor and its association with demographic variables	current or retired lead-smelter;	blood	cohort	467/340	nd	40.4 ± 8.96	na	19/ moderate
Malekirad et al. (2013)/Iran/academia and government	neurocognitive impairment	nd	blood	cross sectional	439/439	439/ 100%	33.13 ± 6.78	exposed/ unexposed	14/ low
McFarlane et al. (2013)/Australia/government	early childhood and adult mental health problems	complete data for lead exposure and covariates at the 7-year assessment,	blood	cohort	340/210	83/39%	26.3 ± nd	na	21/ moderate
Rhodes et al. (2003)/ USA /academia and government	scores on a psychiatric symptom scales	participants of the normative aging study, men aged 21–80 years, absence of past or present chronic medical conditions at the time of enrollment	bone and blood	cross-sectional	704/526	526/ 100%	67.2 ± 7.2	depressed/ nondepressed	25/ high
Wang et al. (2006)/China/nd	the central and peripheral nervous systems functions	workers welding longer than six months continuously by cluster (exposed of lead), no prior exposure to neurotoxic metals, organic solvent, hazardous gas, high temperature and heavy noise, no history of mental and neurological disorders, absence of chronic vascular and gastrointestinal diseases	blood	cross-sectional	133/133	96/ 72.18%	32.77 ± 7.59	exposed/ unexposed	17/ moderate
Cadmium									
Buser et al., 2017/ USA /government	depressive symptoms	adults aged ≥ 20 y.o., participants of NHANES 2011–2012	blood	cross sectional	3905/3903	1955/ 50.08%	44.33 ± 61.2	depressed/ nondepressed	26/ high
Dean et al. (2019)/ multicenter/government	MDD	postmortem study: persons with MDD or BD/suicide completers	CNS tissues: brodmann's area 6, 10, 17	cohort	45/38	19/ 48.7%	61.3 ± 4.1	depressed (with MDD or BD)/ nondepressed	21/ moderate
Han et al. (2016)/Korea/ government	depressive symptoms	adults aged ≥ 60 y.o.	blood	cross-sectional	560/395	106/ 26.8%	nd	depressed/ nondepressed	26/ high
Jurczak et al. (2018)/ Poland/academia	severity of anxiety and depressive	postmenopausal women, no hormone therapy, no history of psychiatric treatment, no addictions	blood	cross sectional	198/198	0/0	56.26 ± 5.55	depressed/ nondepressed	21/ moderate
	depressive symptoms	adults aged ≥ 60 y.o.	blood		1253/983		75.2 ± 6		26/ high

(*continued on next page*)

Table 1 (*continued*)

Reference/Year/Country/ Sponsorship	Focus of Study	Inclusion Criteria	Biological Material	Study Type	N Subjects Included/ Analyzed	Males (N/%)	Age (Mean±SD)	Groups Analyzed	STROBE score/ quality
Kim et al. (2016)/Korea/ government				cross-sectional		272/ 27.7%		depressed/ nondepressed	
Kostrubiak et al. (2017)/ USA /nd	depressive symptoms	adults aged ≥ 18 y.o., participants of NHANES 2005–2012	blood	cross-sectional	11,209/ 11,209	656/ 54.03%	46.5 ± 17.14	depressed/ nondepressed	24/ moderate
Scinicariello and Buser, 2015/USA/ government	depressive symptoms	adults aged ≥ 20 y.o., participants of NHANES 2007–2010	blood	cross-sectional	3169/2892	1439/ 51.38%	28.93 ± 18.3	depressed/ nondepressed	24/ moderate
Wang et al. (2006)/ China/nd	central and peripheral nervous systems functions	workers welding longer than six months continuously by cluster (exposed of cadmium), no prior exposure to neurotoxic metals, organic solvent, hazardous gas, high temperature and heavy noise, no history of mental and neurological disorders, absence of chronic vascular and gastrointestinal diseases	blood	cross-sectional	133/133	96/ 72.18%	32.77 ± 7.59	exposed/ unexposed	17/ moderate

BD – bipolar disorder; BMI- body mass index; CNS- central nervous system; MDD – major depressive disorder; NHANES - National Health and Nutrition Examination Survey; POMS- Profile of Mood States; SD- standard deviation; na- not analyzed; nd- no data; y.o. – years old.

Considering that both Cd and Pb are associated with the occurrence of chronic diseases (Faroon et al., 2012; Abadin et al., 2007), the benefits of quitting smoking include not only a reduction of the incidence of smoking-related diseases, but also diseases associated with the negative influence of Cd and Pb on the human body (cadmium-associated and lead-associated diseases) (Buser and Scinicariello, 2017).

It is worth noting that many studies confirm that it are women who are particularly at risk of developing depression at any time in their lives (Tang et al., 2019; Ngocho et al., 2019; Salehi-Pourmehr et al., 2019; Kessler et al., 2003). Our systematic review demonstrated that most of the researchers analyzed the effect of heavy metal concentration among both male and female respondents (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Dean et al., 2019; Han et al., 2016; Golub et al., 2010; McFarlane et al., 2013; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Wang et al., 2006). Only Eum et al. (2012) and Jurczak et al. (2018) recruited only women for their research, while Fenga et al. (2016), Malekirad et al. (2013), and Rhodes et al. (2003) - men. Only Buser and Scinicariello (2017) found that individuals in the highest quartile of bCd had higher odds of depressive symptoms (OR: 1.68; 95% CI: 1.12–2.51). This association was only observed in male respondents and, more specifically, in young male participants at the age of 20–47 years. Buser and Scinicariello (2017) also reported that bPb, cigarette smoking, and obesity were associated with depressive symptoms in young female adults. According to Eum et al. (2012), on the other hand, Pb exposure was linked to depression among older women. The remaining studies did not show any relationship between the levels of heavy metals (Pb and Cd) and depressive symptoms.

Our observations revealed that the vast majority of the studies analyzed assessed the levels of Pb and Cd in the material from living patients. Only Dean et al. (2019) obtained postmortem samples. The most popular biological material for research was blood, which was analyzed in fifteen studies (Baker et al., 1983, 1985; Bouchard et al., 2009; Buser and Scinicariello, 2017; Fenga et al., 2016; Golub et al., 2010; Jurczak et al., 2018; Lindgren et al., 1999; Malekirad et al., 2013; McFarlane et al., 2013; Wang et al., 2006; Han et al., 2016; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015). Only in three studies a different material was used: bones and blood (Rhodes et al., 2003), bones (Eum et al., 2012), and CNS tissues: Brodmann's area 6, 10 and 17 (Dean et al., 2019). Therefore, it is worth noting that whole blood is the key material for assessing the levels of Pb and Cd in the human body. However, due to the two main absorption routes (inhalation and alimentary tract) (Satarug and Moore, 2004) and the penetration of the blood-brain barrier (Murphy, 1997), heavy metals presented in the meta-analysis may accumulate in various regions of the body's brain (Ong et al., 2006). Hence, another marker of Pb exposure is the assessment of delta-aminolevulinic acid (ALA) concentration in the urine (Krzywy et al., 2010).

In our review, we found that most researchers divided their respondents into two groups: depressed and non-depressed (Bouchard et al., 2009; Buser and Scinicariello, 2017; Dean et al., 2019; Golub et al., 2010; Han et al., 2016; Jurczak et al., 2018; Kim et al., 2016; Kostrubiak et al., 2017; Scinicariello and Buser, 2015; Rhodes et al., 2003), and only four scientists divided respondents into: those exposed and those unexposed to heavy metals (Cd or Pb) (Baker et al., 1983, 1985; Fenga et al., 2016; Wang et al., 2006). The data show that only five researchers confirmed the contribution of Cd levels to the development of depressive symptoms, of whom Dean et al. (2019) analyzed the material obtained after the patient's death. Dean et al. (2019) suggest that changes in metal levels observed in bipolar and major depressive disorders may affect cortical oxidative balance in patients with mood disorders. These authors analyzed the levels of heavy metals in human postmortem CNS tissues. They reported that the levels of Cd in Brodmann's area 10 (BA 10) in patients with major depressive disorder were lower. This suggests that the levels of specific biometals in blood could be used as a biomarker for increased risk of suicide (Dean et al.,

Table 2
Depression-related outcomes following cadmium (Cd) exposure.

Reference/Year/ Country/ Sponsorship	Cd Concentration (Study Group)	Questionnaires	Depression-related Outcomes in Study Group	Depression-related Outcomes in Control Group	Conclusion
Cadmium (Cd)					
Buser et al., 2017/ USA/government	Whole study group (n = 429): 0.33 μg/L	PHQ-9	Multivariate Logistic Regression OR (95% CL) of having depression in NHANES 2011–2012 adult participants **Model 7 (p < 0.05)** **All:** Q1 (< 0.18 μg/L): OR (1.0) Q2 (0.18–0.29 μg/L): OR (1.12), 95% CI (0.70;1.77) Q3 (0.30–0.54 μg/L): OR (1.12), 95% CI (0.67; 1.87) Q4 (> 0.54 μg/L): OR (1.68) 95%,CI (1.12;2.51) **Men:** Q1 (< 0.18 μg/L): OR (1.0) Q2 (0.18–0.29 μg/L): OR (0.83), 95% CI (0.46;1.52) Q3 (0.30–0.54 μg/L): OR (1.08), 95% CI (0.65;1.79) Q4 (> 0.54 μg/L): OR (2.59) 95%,CI (1.11;6.00) **Women:** Q1 (< 0.18 μg/L): OR (1.0) Q2 (0.18–0.29 μg/L): OR (1.66), 95% CI (0.72;3.85) Q3 (0.30–0.54 μg/L): OR (1.47), 95% CI (0.64;3.39) Q4 (> 0.54 μg/L): OR (1.58) 95%,CI (0.77;3.24)	na	Depressive symptoms are associated with bCd levels and modified by age and sex.
Dean et al. (2019)/ multicenter/ government	Depressed: Brodman area 6 (0–77.5 n.mol/l); Brodman area 10 (0–75.6 n.mol/l); Brodman area 17 (0–66.7 n.mol/l) Not depressed: Brodman area 6 (0–112 n.mol/l); Brodman area 10 (0–118 n.mol/l); Brodman area 17 (0–99 n.mol/l)	nd	na na		In MDD observed lower levels of cadmium in Brodmann's area 6, 10 and 17 than in the group without a depressive disorder.
Han et al. (2016)/Korea/ government	Depressed (n = 50) Q1 (< 0.85 μg/L) n = 6 Q2 (0.85 ≤ bCd < 1.15) n = 14 Q3 (1.15 ≤ bCd < 1.53) n = 14 Q4 1.53 ≤ bCd) n = 16 Not depressed (n = 345) Q1 (<0.85 μg/L) n = 93 Q2 (0.85 ≤ bCd < 1.15) n = 83 Q3 (1.15 ≤ bCd < 1.53) n = 86Q4 1.53 ≤ bCd) n = 83	SGDS-K	ORs and 95% CIs for depressive symptoms according to bCd levels, analysis by each visit **FIRST VISIT:** **Model 8: (p = 0.04)** Q1: OR (1.0) Q2: OR (2.43), 95% CI (0.87–6.80) Q3: OR (2.70), 95% CI (0.96–7.65) Q4: OR (3.14), 95% CI (1.12–8.82) **Model 9: (p = 0.03)** Q1: OR (1.0) Q2: OR (2.62), 95% CI (0.93–7.41) Q3: OR (2.92) 95% CI (1.02–8.40) Q4: OR (3.50) 95% CI (1.22–10.00) **SECOND VISIT:** **Model 8: (p = 0.60)** Q1: OR (1.0) Q2: OR (0.39) 95% CI (0.09–1.76) Q3: OR (0.31) 95% CI (0.05–1.80) Q4: OR (0.67) 95% CI (0.18–2.54) **Model 9: (p = 0.79)** Q1: OR (1.0) Q2: OR (0.4) 95% CI (0.08–1.9) Q3: OR (0.31) 95% CI (0.05–2.04) Q4: OR (0.78) 95% CI (0.19–3.14) **LAST VISIT:** **Model 8: (p = 0.35)** Q1: OR (1.0) Q2: OR (0.81) 95% CI (0.1–6.53) Q3: OR (0.38) 95% CI (0.03–4.78) Q4: OR (0.36) 95% CI (0.03–4.58) **Model 9: (p = 0.65)** Q1: OR (1.0) Q2: OR (1.45) 95% CI (0.15–14.53) Q3: OR (0.54) 95% CI (0.04–7.56)		The study did not confirm a relationship between depressive symptoms and bCd levels in the elderly population.

(*continued on next page*)

Table 2 (*continued*)

Reference/Year/ Country/ Sponsorship	Cd Concentration (Study Group)	Questionnaires	Depression-related Outcomes in Study Group	Depression-related Outcomes in Control Group	Conclusion
			Q4: OR (0.58) 95% CI (0.04–8.77) nd		
Jurczak et al. (2018)/ Poland/ academia	Depressed (n = 70): 0.75 ± 0.67 μg/L Mild depression (n = 39): 0.77 ± 0.73 μg/L Average (n = 21): 0.85 ± 0.67 μg/L Severe (n = 10): 0.48 ± 0.28 μg/L Not depressed (n = 128): 0.94 ± 1.11 μg/L	BDI	Analysis of correlation between severity of depression and concentration of bCd in whole blood of postmenopausal patients **Cd (μg/l): R = − 0.081 p > 0.05**		The study did not confirm a relationship between depressive symptoms and bCd levels.
Kim et al. (2016)/Korea, government	Whole study group: 1.24 ± 0.53 μg/L	SGDS-K	**Generalized linear models^: IQR increase in bCd > 0.645 μg/L and SGDS-K≥ 8:** Model 1: OR (1.28) 95% CI (1.07; 1.52) Model 2: OR (1.23) 95% CI (1.06; 1.46) Model 3: OR (1.26) 95% CI (1.06; 1.51) Model 4: OR (1.27) 95% CI (1.06; 1.52)		Blood cadmium concentrations is linked to depression.
Kostrubiak et al. (2017)/USA/nd	Depressed (n = 876): 0.79 ± 0.84 μg/L Not depressed (n = 10.333): 0.53 ± 0.62 ug/L	PHQ-9	Logistic regression of the association between blood cadmium and depressive symptoms **Unadjusted:** N (876) β (0.43) OR (1.53) 95% CI (1.37, 1.71) **Model 5:** N (876) β (0.31) OR (1.37) 95% CI (1.24, 1.51) **Model 6:** N (876) β (0.15) OR (1.16) 95% CI (1.04, 1.30) **Never smokers**: N (322) β (− 0.36) OR (0.70) 95% CI (0.33, 1.47) **Former smokers:** N (148) β (− 0.41) OR (0.67) 95% CI (0.28, 1.58) **Current smokers:** N (406) β (0.07) OR (1.08) 95% CI (0.95, 1.22) Blood cadmium levels in μg/L (mean±SD) stratified by smoking status and depressive symptoms (Present). All: 0.79 ± 0.84 Current smokers: 1.32 ± 0.96 Never smokers 0.29 ± 0.16 Former smokers:0.39 ± 0.28	Blood cadmium levels in μg/L (mean±SD) stratified by smoking status and depressive symptoms (absent):All: 0.53 ± 0.62 Current smokers: 1.16 ± 0.09 Never smokers 0.29 ± 0.21 Former smokers:0.40 ± 0.26	Depressive symptoms are associated with bCd levels in a crude model and with adjustment for pack years and cotinine. But not by stratification of smoking status.
Scinicariello and Buser, 2015/ USA, government	Depressed (n = 287) 0.31 ± 0.17 μg/L Q1 (0.20 μg/L< bCd) n = 53 Q2 (0.20 – 0.27 μg/L) n = 44 Q3 (0.28 – 0.54 μg/L) n = 61 Q4 (>0.54 μg/L) n = 129 Not depressed (n = 2605) 0.31 ± 0.17 μg/L Q1 (0.20 μg/L< bCd) n = 780 Q2 (0.20 – 0.27 μg/L) n = 596; Q3 (0.28 – 0.54 μg/L) n = 658; Q4 (>0.54 μg/L) n = 571	PHQ-9	Adjusted ORs (95% CIs) of depressive symptoms by bCd levels and smoking status **All Participants (p = 0.001)** Q1: OR (1.0) Q2: OR (1.04), 95% CI (0.58, 1.87) Q3: OR (1.11), 95% CI (0.70, 1.76) Q4: OR (2.79), 95% CI (1.84, 4.25) **Never smokers: (p = 0.28)** Q1: OR (1.0) Q2: OR (1.28), 95% CI (0.58, 1.87) Q3: OR (1.26), 95% CI (0.71, 2.25) Q4: OR (2.91), 95% CI (1.12, 7.58) **Current smokers:** (p < 0.001) Q1: OR (1.0)	nd	Depressive symptoms are associated with bCd levels in a nationally representative sample but its independent of smoking status.

(*continued on next page*)

Table 2 (*continued*)

Reference/Year/ Country/ Sponsorship	Cd Concentration (Study Group)	Questionnaires	Depression-related Outcomes in Study Group	Depression-related Outcomes in Control Group	Conclusion
			Q2: OR (0.63), 95% CI (0.27, 1.45) Q3: OR (1.02), 95% CI (0.36, 2.94) Q4: OR (2.69), 95% CI (1.13, 6.42)		
Wang et al. (2006)/ China/nd	Depressed: 3.54 (0.2–12.5*) μg/L Not depressed: 0.79 (0.1–4.8*) μg/L	NCTB	Covariate analysis (age, education level) of NCTB items Depression-dejection: n = 82; 48.12 ± 11.38; p = 0.049	Covariate analysis (age, education level) of NCTB items Depression-dejection: n = 51; 53.02 ± 7.53; p = 0.049	The study did not confirm a relationship between depressive symptoms and bCd levels.

*range; Model 1: Adjusted for age, sex, and city of residence; Model 2: Model 1 + monthly income and education level; Model 3: Model 2 + smoking status, pack-years of smoking, passive smoking status, alcohol drinking, and moderate physical activity; Model 4: Model 3 + weight, height, and comorbidity status; Model 5: Adjusted for age, sex, race, PIR, and alcohol use; Model 6: Also adjusted for blood cotinine and pack-years smoking; Model 7: Adjusted for sex, age, race/ethnicity, blood lead levels, obesity, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level (all participants); Model 8: Adjusted by age, sex, fasting glucose, urinary cotinine.; Model 9: †: adjusted by age, sex, fasting glucose, urinary cotinine, alcohol drinking, hypertension, regular exercise, β - beta level, OR (95% CI) - 95% confidence interval, Q - quartile, R - Spearman's rank correlation coefficient, t (N-2) - Test statistics to check significance of R correlation coefficient; BDI – Beck Depression Inventory; NCTB- Neurobehavioral Core Test Battery; NHANES- National Health and Nutrition Examination Survey; PHQ-9 - Patient Health Questionnaire-9; SGDS-K - Korean version of the Geriatric Depression Scale-Short Form; Cd – cadmium; bCd- blood cadmium; nd- no data.

Table 3
Anxiety-related outcomes following cadmium (Cd) exposure.

Reference/Year/Country/ Sponsorship	Cd Concentration (study group)	Questionnaires	Anxiety-related Outcomes in Study Group	Anxiety-related Outcomes in Control Group	Conclusion
Cadmium Jurczak et al. (2018)/Poland/academia	Anxious (n = 53):	STAI-X	STAI-1: p > 0.05	STAI-1: p > 0.05	There is no relationship between anxiety and bCd levels.
	0.75 ± 0.67 μg/L Not Anxious (n = 145): 0.94 ± 1.11 μg/L		Standard (n = 100): 0.90 ± 1.16 μg/L	No anxiety (n = 45): 0.98 ± 0.80 μg/L	
			Anxiety (n = 53): 0.88 ± 0.98 μg/L STAI-2: p > 0.05	STAI-2: p > 0.05 No anxiety (n = 50): 0.85 ± 0.75 μg/L	
			Standard (n = 99): 0.93 ± 1.20 μg/L Anxiety (n = 49): 0.79 ± 0.67 μg/L Correlation analysis between concentration of Cd in blood and intensity of anxiety as a STAI-1 state and anxiety as a STAI-2 characteristic STAI- 1 Cd (μg/L): r (−0.04) p > 0.05 STAI-2 Cd (μg/L): r (−0.0708) p > 0.05		
Wang et al. (2006)/ China/nd	Anxious:	POMS/ NCTB - neurobehavioral core test battery	Covariate analysis (age, education level) of NCTB items	Covariate analysis (age, education level) of NCTB items	There is no relationship between anxiety and bCd levels.
	3.54 (0.2–12.5*) μg/L Not Anxious: 0.79 (0.1–4.8*) μg/L		N = 82; 50.31 ± 8.10.24 μg/L	N = 51; 51.92 ± 8.80	

*range; NCTB- Neurobehavioral Core Test Battery, POMS- Profile of Mood States, STAI- State-Trait Anxiety Inventory; Cd – cadmium; bCd- blood cadmium.

2019). Kim et al. (2016), on the other hand, reported that an interquartile-range increase in bCd levels (0.645 μg/L) was associated with depression defined as the SGDS-K score ≥ 8 (OR: 1.27, 95% CI: 1.06–1.52) and lower handgrip strength (right hand: β = − 0.40, 95% CI: − 0.75 to − 0.09; left hand: β = − 0.36, 95% CI: − 0.69 to − 0.04). The association between Cd levels and handgrip strength was robust after further adjustment for depressive status, although it attenuated by 14.7–18.0%. It was suggested that bCd levels were associated with depression and lower handgrip strength in an elderly population, and that there are potential confounders which should be analyzed. Different results were obtained by three researchers (Han et al., 2016; Jurczak et al., 2018; Wang et al., 2006), who did not confirm a relationship between depressive symptoms and bCd levels in cohort studies. Han et al. (2016) evaluated a total of 395 elderly Korean participants at three consecutive visits, obtaining demographic data and lifestyle information by a standardized questionnaire, and collecting blood samples for analysis. They found that bCd levels were associated with depressive symptoms in the first visit data analysis. On the first visit, the highest quartile bCd group (Q4) showed an increased risk for depressive symptoms compared to the lowest quartile group (Q1) (OR: 3.50, 95% CI: 1.22–10.00). However, at the other visits no relationship between bCd and depressive symptoms was observed (second visit data: Q4 vs Q1, OR: 0.78, 95% CI: 0.19–3.14; third visit data: Q4 vs Q1, OR: 0.58, 95% CI: 0.04–8.77). Jurczak et al. (2018) did not confirm a relationship

Table 4
Depression-related outcomes following lead (Pb) exposure.

Reference/ Year/Country/ Sponsorship	Pb Concentration (mean±SD)	Questionnaire	Depression-related Outcomes in Study Group	Depression-related Outcomes in Control Group	Conclusions
Lead (Pb)					
Baker et al. (1983)/USA/nd	Exposed (n = 103): 33.89 range 8–80 μg/dL Unexposed (n = 61): 18.6 range 3–36 μg/dL	POMS	**Blood lead levels of Pb (μg/dl)/POMS depression score:** 0–20 μg/dL/103.04 21–40 μg/dL/110.94 41–60 μg/dL/182.60		Blood lead level exceeding 40 mcg/dL is associated with increased rates of depression, confusion, anger, fatigue and tension along with other aspects of neurobehavioral function (verbal concept formation, memory, and visual/motor performance were also impaired).
Baker et al. (1985)/USA/government	Exposed (years:1980/1981/1982; μg/dL): -welters: 66.4 ± nd/49.3 ± nd/36.8 ± nd -grinders: 54.8 ± nd/38.3 ± nd/32.7 ± nd -maintenance: 46.1 ± nd/35.1 ± nd/31.7 ± nd -hunter operators: 36.8 ± nd/24.7 ± nd/24.3 ± nd -coremakers: 31.4 ± nd/24.6 ± nd/23.5 ± nd Unexposed workers (years: 1980/1981/1982 (μg/dL): 25.1 ± nd/22.9 ± nd/21.5 ± nd	POMS	**Effect of lead exposure reduction on mood scores** Initial blood lead concentration/mean annual blood lead concentration change/mean annual percentage change in POMS scores 1. 50–80 μg/dL; n = 10/ − 13.1/ − 25.6%[d] 2. 30–49 μg/dL; n = 22/ − 6.4; 6.1% 3. 10–29 μg/dL; n = 35/ − 1.1; 3.7%		The exposure is associated to scores on some of the POMS subtests.
Bouchard et al. (2009)/USA/government	Depressed (n = 134): 1.61 ± 1.72 μg/L Without depression nd±nd, n = 1853	CIDI	**Cases of MDD by blood lead quintile** Q1: 0.20 – 0.7 μg/dL; n = 30 (6.7%) O2: 0.71 – 1.0 μg/dL: n = 26 (6.7%) Q3: 1.01 – 1.4 μg/dL: n = 26 (6.4%) Q4: 1.41 – 2.1 μg/dL; n = 22 (5.9%) Q5: ≥ 2.11 μg/dL; n = 30 (8.1%) **Odds ratios (ORs) and 95% confidence intervals (CI) from logistic regressions for MDD by lead quantile** Q1: OR[c]= 1.0; n = 23 Q2: OR 1.26, 95% CI: 0.55 – 2.88; n = 16 Q3: OR: 1.50, 95% CI: 0.75 – 3.01; n = 12 Q4: OR: 1.47, 95% CI: 0.68– 3.17; n = 11 Q5: OR: 2.93, 95% CI: 1.243 – 6.92; n = 11 P for trend= 0.03		Elevated blood lead concentration increases odds of major depression and panic disorder.
Buser et al., 2017/USA/government	Depressed (n = 429): 1.09 ± nd μg/dL Healthy (without depression) (n = 3474): nd±nd	PHQ-9	**Multivariate logistic regression OR (95% CI) of having depression** Q1 (bPb <0.70 μg/l) 1 Q2 (0.70–1.06 μg/l) 1.19 (1.00,1.42) Q3 (1.07–1.76 μg/l) 1.26(0.93,1.71) Q4 (>1.76 μg/l) 0.94 (0.65,1.35) **Age quartile** (20–32 years) 1.00 (1.00, 1.00) (33–47 years) 1.19 (0.74, 1.90) (48–60 years) 1.55 (0.98, 2.46) (>60 years) 0.78 (0.42, 1.43) **Sex** Men 1.00 Women 1.78 (1.33, 2.37) P < 0.001 **Smoking status** Current smoker 1.79 (1.19, 2.69) P < 0.01 Former smoker 1.46 (0.94, 2.28) Never smoked 1.00		Blood Pb concentrations are associated with depressive symptoms and modified by age, sex and smoking status.
Eum et al. (2012)/USA/nd	Tibia: 10.3 ± 9.5 (μg/g)	MHI-5	**Adjusted[h] differences in MHI-5 score by bone lead tertile.** Tibia lead tertile (pg/g) and MHI-5 score T1) < 7.0 n = 202; score 81 ± 12; reference difference T2) 7.0–11.5 n = 159; score 79 ± 13; point difference (95% CI) − 1.70 (−3.75, 0.34)	**Adjusted[h] differences in MHI-5 score by bone lead tertile.** Patella lead tertile (pg/g) and MHI-5 score t1) < 8.5 n = 193; score 79 ± 12; reference difference t2) 8.5–14.5 n = 179; score 80 ± 13; point difference (95% CI) 1.02 (−1.06, 3.11)	Lead exposure corresponds to depression among older women.

(*continued on next page*)

Table 4 (*continued*)

Reference/ Year/Country/ Sponsorship	Pb Concentration (mean±SD)	Questionnaire	Depression-related Outcomes in Study Group	Depression-related Outcomes in Control Group	Conclusions
	Patella: 12.5 ± 11.2 (μg/g)		T3) > 11.5 n = 242; score 80 ± 13; Point difference (95% CI) − 1.06 (−3.05, 0.94) p-trend 0.33	t3) > 14.5 n = 230; score 80 ± 13; point difference (95% CI) 0.61 (−1.55, 2.78) p-trend 0.64	
Fenga et al. (2016)/Italy/nd	Exposed (n = 40): 56.4 ± 14.4 μg/dL Unexposed (n = 40): 15.4 ± 1.5 μg/dL	POMS	**Neurobehavioral score in exposed persons** 57 ± 10.6	**Neurobehavioral score in non-exposed persons** 48.3 ± 7.2	Lead exposure elevates the risk toward the impairment of certain cognitive abilities.
Golub et al. (2010)/USA/government	Depressed (n = 836): 1.73 ± 1.2 μg/dL Not depressed (n = 3323): 1.75 ± 2.9 μg/dL	PHQ-9	**Blood lead levels in relation to depression prevalence (poison regression)** Continuous lead % depressed:20.02, crude RR[a] 0.99 (0.94–1.04), adjusted[b] RR 1.04 (0.98–1.1); 0–0.88 μg/dL- 20.19% RR 1.00 (reference); 0.89–1.40 μg/dL-20.53% RR 1.02 (0.85–1.22); 1.41–2.17 μg/dL-19.93% RR 1.00 (0.90–1.11); 2.18–26.4 μg/dL-19.43% RR 0.97 (0.76–1.24)		No consistent evidence for an association between environmental lead exposure and depression.
Jurczak et al. (2018)/Poland/academia	Depressed (n-70): 18.16 ± 8.0 μg/L Healthy (without depression) (n-128): 9.38 ± 20.79 μg/L	BDI	Average concentration of Pb in whole blood of postmenopausal women **with characteristics of depression** Pb (μg/L) 18.16 ± 8.00	Average concentration of Pb in whole blood of postmenopausal women **without depression** Pb (μg/L) 20.79 ± 9.38	A correlation between the level of Pb and the depression does not exist.
Lindgren et al. (1999)/USA/nd	Current blood lead level (28 μg/dL; range, 4–62 μg/dL) Working-lifetime integrated blood lead level (711 micrograms-yr/dL; range, 1–1537 micrograms-yr/dL	POMS	**POMS subscale score for depression:** Median = 6 range 0–58 maximum possible score = 60		Integrated (cumulative) but not current blood lead level is significantly related to the POMS 'general distress' factor.
Malekirad et al. (2013)/Iran/ academia and government	Exposed (n = 316): 52.0 range 37–70 μg/dL, Unexposed (n = 123): 37.57 range 28.33–67.92 μg/dL	nd	**The correlation between blood lead level and clinical symptoms**, r = 0.131, p < 0.01		Blood lead level is associated with clinical disorders (depression, nocturia, urinary frequency, oedema, low deep tendon reflex, low concentration, agitation, headache, abdominal pain, palpitation, fatigue, and diminished sex drive) and poor haematological parameters.
McFarlane et al. (2013)/Australia/government	Whole group (n = 210): 17.2 ± 5.2 μg/dL	CIDI	**Odds reflecting the likelihood of a depression diagnosis for a 10 mg/dl increase in childhood average blood lead** Females[e] n = 127; OR (95% CI) 1.10 (0.35, 2.84); p > 0.10 AOR[f] (95% CI) 0.31 (0.07, 1.22); p > 0.10 Males[g] n = 83; OR (95% CI) 0.48 (0.06, 3.71); p > 0.10; AOR[c] (95% CI) 0.31 (0.02, 4.05); p > 0.10		Early childhood lead exposure may show small associations with adult emotional and behavioural functioning in females.
Rhodes et al. (2003)/USA/academia and government	Depressed (n = 85): 6.6 ± 4.6 (μg/dL) Without depression (n = 441): 6.2 ± 4.1 μg/dL	BSI	**Depression status by Pb level:** Blood Pb level: 6.6 ± 4.6 μg/dL Tibia bone Pb level: 23.4 ± 14.8 μg/g; Patella bone Pb level: 36.5 ± 24.0 μg/g *	**Nondepressed subjects by Pb levels** Blood Pb level: 6.2 ± 4.1 μg/dL Tibia bone Pb level: 21.6 ± 13.2 μg/g Patella bone Pb level: 31.3 ± 18.9 μg/g *	The exposure to lead is linked to prevalence of nervous system symptoms.
Wang et al. (2006)/China/nd	Study group (n = 82): 117.31 range 0.5–327.6 μg/L, Operators demographically matched to studied persons (n = 51): 69.92, range 0.6–234 μg/L	NCTB	**Depression-dejection** n = 82; 48.12 ± 11.38; p = 0.049	**Depression-dejection** n = 51; 53.02 ± 7.53;	The prevalence of complaint of neurobehavioral symptoms and neurobehavioral is linked to Pb level.

[a]RR –relative risk, [b]adjusted for age, gender, and ethnicity, [c]adjusted forage, sex, race/ethnicity, education, PIR and excluding current smokers, [d]anegative percent change represents an improvement in mood for all scores (thevigour scale was reversed to achieve a consistency of presentation), [e]regressionfor females adjusted for home, paternal occupation, and mothers' age at birth, [f]OR/AOR- odds ratio/adjusted odds ratio, reflecting the likelihood of a disorderdiagnosis for a 10 mg/dL increase in childhood average blood lead., [g]regressionfor males adjusted for paternal and maternal education, mothers' age at birth, [h]adjustedfor substudy group, age at bone lead at MHI-5 measurement, education, husband'seducation, alcohol consumption, pack-years of smoking, and employment status atMHI-5 measurement, lower scores indicate more depressive symptoms (lower MHI-5scores indicate worse symptoms), *p < 0.05;

BDI – Beck Depression Inventory; BSI - Brief Symptom Inventory; CIDI - Composite International Diagnostic Interview; MDD – major depressive disorder; MHI-5 -Mental Health Inventory-5, NCTB - Neurobehavioral Core Test Battery; PHQ-9 - Patient Health Questionnaire; POMS- Profile of Mood States; nd- no data; Pb; - lead; bPb; - blood lead.

between bCd levels and the severity of anxiety and depressive symptoms in healthy women ($R = -0.081$ $p > 0.05$). The mean level of bCd (0.87 ± 0.98 μg/l) was within normal ranges.

It seems important to divide the respondents into those particularly exposed to Pb and Cd and into a control group, because many people are exposed to Pb and Cd due to their professional work or smoking. Heavy metals are used in various industries, including metallurgy of non-ferrous metals and iron, machine, battery and ceramic industries, glass metallurgy, scrap storage and processing plants, printing industry, lead ore mines, in the production of plastics, dyes, alkaline nickel-cadmium batteries, fluorescent dyes, enamel, and rubber (Sańczuk-Przybyłowska et al., 2011). Many studies confirm the increased levels of Pb and Cd in the blood of smokers (Chlebda et al., 2004; Dynerowicz-Bal et al., 2005; Moździerz et al., 2014). In addition, there is a significant correlation between the number of cigarettes smoked, the time of tobacco smoke, and the level of Cd. With long-term smoking addiction, significantly higher Pb and Cd levels in the blood and kidneys are observed (Chlebda et al., 2004; Dynerowicz-Bal et al., 2005). In our review, several researchers confirmed the significant effect of cigarette smoking on elevated blood Pb levels, as well as on the occurrence of depressive symptoms in respondents. Buser and Scinicariello (2017) found that Pb levels and cigarette smoking were associated with depressive symptoms in young female adults. Moreover, Kostrubiak et al. (2017) identified that depressive symptoms were associated with bCd levels in a crude model and with adjustment for pack-years and cotinine. This association declined when the types of smokers (current, former, and never) were analyzed. Scinicariello and Buser (2015) reported that respondents in the highest bCd quartile had higher odds of having depressive symptoms [OR: 2.79, 95% CI: 1.84–4.25] than those in the lowest bCd quartile. Smoking status, but not bCd, was statistically significantly associated with depression.

Finally, we analyzed data concerning the standardized research instruments applied to measure depressive symptoms. It should be noted that the most popular of them was the POMS (Baker et al., 1983, 1985; Fenga et al., 2016; Lindgren et al., 1999), the PHQ-9 (Buser et al., 2017; Golub et al., 2010; Kostrubiak et al., 2017; Scinicariello and Buser, 2015), and the CIDI (Bouchard et al., 2009; McFarlane et al., 2013).

3.2. Strengths and limitations

The main advantage of our systematic review is that it is the first one concerning the effect of Cd and Pb levels on anxiety and depressive disorders, which gains particular importance in the context of modern populations, in which these disorders are epidemic (Hidaka, 2012). Moreover, this study was conducted in accordance with the requirements included in the Preferred Reporting Items for Systematic Review and Meta-Analysis (the STROBE) protocols.

However, several limitations of this systematic review require consideration. They include: (i) heterogeneous research objectives, (ii) heterogeneous groups of patients of different ages, (iii) objective assessment of depression and anxiety using various standardized tools, and (iv) various materials for testing Cd and Pb levels. The main disadvantage of the research is the lack of meta-analytic calculation as studied parameters (and biological samples) differed significantly.

3.3. Implications for current practice and future research

Environmental exposure to Cd increases total mortality in a continuous fashion, independently of kidney function and other classical factors associated with mortality, such as age, sex, smoking, and socioeconomic status. On the other hand, if Pb and Cd concentrations were independent risk factors for depression and anxiety, such effects would be more likely observed after longer periods of time. In complex diseases, such as emotional disorders, effects are typically more pronounced in the elderly, as the majority of other independent factors (such as eating habits, exposure at work) remain relatively unchanged. Thus, the age of the study participants should be considered as a covariate in such analyses, and other environmental factors (along with genetic background) as potential confounders.

Our results have important scientific, medical, and public health implications (Hidaka, 2012; Nawrot et al., 2010). Exposure to Pb in the environment is a global public health problem. Measures to control Pb transfer to the environment are implemented in most developed countries, however, due to the rapid industrialization and persistence of Pb in the environment, exposure to Pb is likely to remain a major public health problem in most developing countries for many years to come (Tong et al., 2000).

It seems important to conduct high-quality, well-designed studies to evaluate the effect of Cd and Pb exposure on the risk of developing anxiety and depression in order to fully understand their implications. Nevertheless, we hope that this study will help to better understand, prevent and treat anxiety and depression, as well as contribute to building a rational and science-based public health policy aimed at minimizing exposure to Pb and Cd that have adverse effects on the human body (Flora, 2002; Nogawa et al., 2004).

4. Conclusion

To sum up, on the basis of the results obtained, it is not possible to state clearly that the levels of cadmium and lead are linked to depression and anxiety in the respondents.

There is an urgent need to conduct more reliable observation studies in people exposed to high levels of cadmium and lead using similar parameters to evaluate pooled effect size.

It is pivotal to conduct high-quality, well-designed studies to evaluate the effect of cadmium and lead exposure on the risk of developing anxiety and depression in order to clarify their implications into these behavioral phenotypes.

Funding

The research was funded by the Pomeranian Medical University in Szczecin, Poland.

CRediT authorship contribution statement

Anna Maria Cybulska: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Visualization, Roles/Writing - original draft, Writing - review & editing.

Szymon Grochans: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Visualization, Roles/Writing - original draft.

Magdalena Sylwia Kamińska: Data curation, Validation, Visualization, Writing - review & editing.

Mateusz Bosiacki: Project administration, Supervision, Validation.

Karolina Skonieczna-Żydecka: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Roles/Writing - original draft.

Elżbieta Grochans: Methodology, Validation, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 5
Anxiety-related outcomes following lead (Pb) exposure.

Reference/Year/Country/ Sponsorship	Pb Concentration (mean±SD)	Questionnaire	Anxiety-related Outcomes in Study Group	Anxiety-related Outcomes in Control Group	Conclusions
Lead (Pb)					
Baker et al. (1983)/USA/nd	Exposed (n = 103): 33.89 range 8–80 μg/dL Unexposed (n = 61): 18.6 range 3–36 μg/dL	POMS	Tension scores from POMS by blood lead level. Blood lead levels of Pb (μg/dL); **POMS anxiety score**: 0–20 μg/dL: 98.17 21–40 μg/dL: 88.80 41–60 μg/dL: 99.40 > 60 μg/dL: 162.93		Blood lead level exceeding 40 mcg.dL is associated with increased rates of depression, confusion, anger, fatigue and tension along with other aspects of neurobehavioral function (verbal concept formation, memory, and visual/ motor performance were also impaired).
Baker et al. (1985)/USA/government	Whole group (n = 172): 32.8 range 10–80 μg/dL	POMS	**Neurobehavioral testing by blood lead concentration on day of testing, mean (SD)** 0–20 μg/dL (n = 26): 10.73 (SD = 7.44) 21–40 μg/dL (n = 97): 10.49 (SD = 5.81) 41–60 μg/dL (n = 28): 9.60 (SD = 5.24) 61–80 μg/dL (n = 9): 15.11 (SD = 5.40)		Lead exposure in adults causes dose dependent impairment of neurobehavioral function.
Bouchard et al. (2009)/USA/government	Depressed (n = 134): 1.61 ± 1.72 μg/L Without depression nd±nd, n = 1853	CIDI	**Cases of major GAD by blood lead quintile** Q1: 0.20 – 0.7 μg/dL, n = 6 O2: 0.71 – 1.0 μg/dL n = 6 Q3: 1.01 – 1.4 μg/dL n = 13 Q4: 1.41 – 2.1 μg/dL n = 13 Q5: ≥ 2.11 μg/dL n = 9 **Odds ratios (ORs)[a] and 95% confidence intervals (CI) from logistic regressions for major depressive disorder by lead quintile** Q1: ORa 1.0; n = 5 Q2: OR 1.17, 95% CI: 0.28–4.88; n = 4 Q3: OR: 1.29, 95% CI: 0.33–5.09; n = 4 Q4: OR: 3.18, 95% CI 0.96–10.49; n = 10 Q5: OR: 1.59, 95% CI 0.19–13.31; n = 3 P for trend = 0.44 **Gender** Women [1] 0.96 [2] 1.79 Men [1] 1.71 [2] 1.9 **Age** (20 – 24 y) [1] 1.14 [2] 1.89 (25 – 29 y) [1] 1.15 [2] 2.03 (30 – 34 y) [1] 1.27 [2] 2.02 (35 – 39 y) [1] 1.24 [2] 1.87 **Race/ethnicity** Non-Hispanic White[1] 1.07 [2] 1.87 Mexican American[1] 1.57 [2] 2.13 Non-Hispanic Black[1] 1.28 [2] 1.83 Other ethnic groups, multiracial [1] 1.23 [2] 1.84 **Education** Less than high school [1] 1.65 [2] 1.98 High school diploma[1] 1.28 [2] 1.97 More than high school [1] 1.06 [2] 1.85 **Poverty-income ratio** < 1.0 [1] 1.38 [2] 1.97 1.0 – 1.85 [1] 1.33 [2] 2.07 1.85 – 3.0 [1] 1.24 [2] 1.90 > 3.0 [1] 1.11 [2] 1.88		Increasing blood lead level was not associated with higher odds of generalized anxiety disorder (p for trend 0.75), after adjustment for sex, age, race/ethnicity, education, and poverty-income ratio.
Fenga et al. (2016)/Italy/nd	Exposed 56.4 ± 14.4 (μg/dL), n = 40 Unexposed 15.4 ± 1.5 (μg/dL), n = 40	POMS	**POMS score of Tension (as anxiety)** 58.3 ± 9.1	**POMS score of Tension (as anxiety)** 50.6 ± 6.7	

(*continued on next page*)

Table 5 (*continued*)

Reference/Year/Country/ Sponsorship	Pb Concentration (mean±SD)	Questionnaire	Anxiety-related Outcomes in Study Group	Anxiety-related Outcomes in Control Group	Conclusions
Jurczak et al. (2018)/multicenter/academia	Depressed (n = 70): 18.16 ± 8.0 μg/L Healthy (without depression) (n-128): 9.38 ± 20.79 μg/L	STAI	Lead (μg/L) Anxiety (n = 53); Mean = 17.20 ± 7.52; Min-Max: 5.00–40.00; Median: 15.00; Q1-Q3 12.00–22.00 ANOVA[b] test F = 49,848 p < 0.01	Lead (μg/L) No anxiety (n = 45); Mean= 22.84 ± 9.79 μg/l; Min-Max: 5.00–56.00; Median: 22.00; Q1–Q3 16.00–27.00 Standard anxiety (n = 100): 19.92 ± 8.98; Min-Max: 3.00–56.00; Median: 18.00; Q1-Q3 14.00–24.00 ANOVA test F = 4.9848 p < 0.01	There is a statistically significant negative correlation between the level of Pb and the severity of anxiety as a state.
Lindgren et al. (1999)/USA/nd	Current blood lead level (28 μg/dL; range, 4–62 μg/dL) Working-lifetime integrated blood lead level (711 micrograms-yr/dL; range, 1–1537 micrograms-yr/dL	POMS	**Tension (anxiety)** median = 9 range 0–31 maximum possible score = 36		
Rhodes et al. (2003)/USA/academia and government	Depressed 6.6 ± 4.6 (μg/dL), n = 85 Nondepressed 6.2 ± 4.1 (μg/dL), n = 441	BSI	**Characteristics by BSI Scale Status, the Normative Aging Study** Mean values ± SD Age 67.2 ± 8.8 Blood Pb level (μg/dL) 6.5 ± 4.3 Tibia bone Pb level (μg/g) 22.4 ± 14.2 Patella bone Pb level 35.6 ± 23.6[d]	**Characteristics by BSI Scale Status, the Normative Aging Study** Mean values (SD) N = 449; Age (years) 67.1 ± 6.9; Blood Pb level (μg/dL) 6.2 ± 4.1; Tibia bone Pb level (μg/g) 21.8 ± 13.4; Patella bone Pb level (μg/g) 31.5 ± 19.1[d]	
Wang et al. (2006)/China/nd	Study group (n = 82): 117.31 range 0.5–327.6 μg/L, Operators demographically matched to studied persons(n = 51): 69.92, range 0.6–234 μg/L	NCTB	Tension-anxiety[e] N = 82; 50.31 ± 10.24; p = 0.368	Tension-anxiety[e] N = 51; 51.92 ± 8.80; p = 0.368	Occupational exposure to Pb might cause neurobehavioral symptoms and neurobehavioral impairment in welders regarding quick memory and eye-hand coordination.

[a]Adjusted forage, sex, race/ethnicity, education, and PIR, excluding current smokers, [b]ANOVAanalysis of variance, [c]A negative percent change represents an improvement in mood for allscores. (The vigour scale was reversed to achieve a consistency ofpresentation.), [d]$p < 0.10$, [e]Covariant analysis of allitems of the NCTB and EMG between the two groups with the age and educationlevel as the covariates. All the scores of NCTB were standard-transformed fromthe original marks and had no unit; [1] Unweighted Geometric mean of Blood lead(μg/dL) [2] Unweighted Geometric Standard deviation of Blood lead (μg/dL);
BSI - Brief SymptomInventory; CIDI - Composite International Diagnostic Interview; GAD- *generalized anxiety disorder*; NCTB - Neurobehavioral Core Test Battery; POMS-Profile of mood states; STAI - State-Trait Anxiety Inventory; Pb; - lead; bPb; - blood lead.

References

Abadin, H., Ashizawa, A., Stevens, Y.W., Llados, F., Diamond, G., Sage, G., Citra, M., Quinones, A., Bosch, S.J., Swarts, S.G., 2007. Toxicological profile for lead. Agency for toxic substances and disease registry. Atlanta.

Åkesson, A., Bjellerup, P., Lundh, T., Lidfeldt, J., Nerbrand, C., Samsioe, G., Skerfving, S., Vahter, M., 2006. Cadmium-induced effects on bone in a population-based study of women. Environ. Health Perspect. 114 (6), 830–834. https://doi.org/10.1289/ehp.8763.

Amzal, B., Julin, B., Vahter, M., Wolk, A., Johanson, G., Akesson, A., 2009. Population toxicokinetic modeling of cadmium for health risk assessment. Environ. Health Perspect. 117 (8), 1293–1301. https://doi.org/10.1289/ehp.0800317.

Baker, E.L., Feldman, R.G., White, R.F., Harley, J.P., 1983. The role of occupational lead exposure in the genesis of psychiatric and behavioral disturbances. Acta Psychiatr. Scand. Suppl. 303, 38–48. https://doi.org/10.1111/j.1600-0447.1983.tb00940.x.

Baker, E.L., White, R.F., Pothier, L.J., Berkey, C.S., Dinse, G.E., Travers, P.H., Harley, J. P., Feldman, R.G., 1985. Occupational lead neurotoxicity: improvement in behavioural effects after red.uction of exposure. Br. J. Ind. Med. 42 (8), 507–516. https://doi.org/10.1136/oem.42.8.507.

Blazka, M.E., Shaikh, Z.A., 1991. Sex differences in hepatic and renal cadmium accumulation and metallothionein induction. Role of estradiol. Biochem. Pharmacol. 41 (5), 775–780 https://doi.org/10.1016/0006-2952(91)90080-o.

Bouchard, M.F., Bellinger, D.C., Weuve, J., Matthews-Bellinger, J., Gilman, S.E., Wright, R.O., Schwartz, J., Weisskopf, M.G., 2009. Blood lead levels and major depressive disorder, panic disorder, and generalized anxiety disorder in US young adults. Arch. Gen. Psychiatry 66 (12), 1313–1319. https://doi.org/10.1001/archgenpsychiatry.2009.164.

Buser, M.C., Scinicariello, F., 2017. Cadmium, lead, and depressive symptoms: analysis of national health and nutrition examination survey 2011–2012. J. Clin. Psychiatry 8 (5), e515–e521. https://doi.org/10.4088/JCP.15m10383.

Carageorgiou, H., Tzotzes, V., Pantos, C., Mourouzis, C., Zarros, A., Tsakiris, S., 2004. In vivo and in vitro effects of cadmium on adult rat brain total antioxidant status, acetylcholinesterase, (Na+, K+)-ATPase and Mg2+-ATPase activities: protection by L-cysteine. BCPT 94 (3), 112–118 https://doi.org/10.1111/j.1742-7843.2004.pto940303.x.

CDC (Center of Disease Control), 2016. Lead, Elevated Blood Levels. Case Definition Available from: ⟨https://www.cdc.gov/niosh/topics/ables/description.html⟩.

Chlebda, E., Antonowicz-Juchniewicz, J., Andrzejak, R., 2004. Wpływ ekspozycji zawodowej na ołów i arsen na stężenie karotenoidów w surowicy u pracowników huty miedzi. Med. Pracy 55 (5), 389–401.

Ciesielski, T., Weuve, J., Bellinger, D.C., Schwartz, J., Lanphear, B., Wright, R.O., 2012. Cadmium exposure and neurodevelopmental outcomes in U.S. children. Environ. Health Perspect. 120 (5), 758–763. https://doi.org/10.1289/ehp.1104152.

Cory-Slechta, D.A., Virgolini, M.B., Thiruchelvam, M., Weston, D.D., Bauter, M.R., 2004. Maternal stress modulates the effects of developmental lead exposure. Environ. Health Perspect. 112 (6), 717–730. https://doi.org/10.1289/ehp.6481.

Cory-Slechta, D.A., Virgolini, M.B., Rossi-George, A., Thiruchelvam, M., Lisek, R., Weston, D., 2008. Lifetime consequences of combined maternal lead and stress. Basic Clin. Pharmacol. Toxicol. 102 (2), 218–227. https://doi.org/10.1111/j.1742-7843.2007.00189.x.

De Souza, I.D., de Andrade, A.S., Dalmolin, R.J.S., 2018. Lead-interacting proteins and their implication in lead poisoning. Crit. Rev. Toxicol. 48 (5), 375–386 https://doi.org/10.1080/10408444.2018.1429387.

Dean, B., Lam, L.Q., Scarr, E., Duce, J.A., 2019. Cortical biometals: changed levels in suicide and with mood disorders. J. Affect. Disord. 243, 539–544. https://doi.org/10.1016/j.jad.2018.09.026.

Dynerowicz-Bal, E., Andrzejak, R., Antonowicz-Juchniewicz, J., Siewiński, M., Sujak, E., Smyk, B., 2005. Wpływ zawodowego narażenia na arsen i metale ciężkie na aktywność katepsyn i ich inhibitorów w surowicy krwi pracowników huty miedzi. Med. Pracy 56 (5), 347–361.

EC (European Commission). Directorate-General Industry. Food - Science and Techniques, 1994. Reports of the Scientific Committee for Food (32nd series). Office for Official Publications of the European Communities. Luxembourg. Available from: ⟨http://aei.pitt.edu/40841/1/32nd_food.pdf⟩.

EC (European Commission). Directorate-General Industry. Food - Science and Techniques, 1996. Reports of the Scientific Committee for Food (35th series). Office for Official Publications of the European Communities. Luxembourg. Available from: ⟨http://aei.pitt.edu/40844/1/35th_food.pdf⟩.

EC (Commission Regulation), 2006. No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. Off. J. Eur. Union (Available from). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02006R1881-20150521.

EFSA (European Food Safety Authority), 2009. Scientific opinion of the panel on contaminants in the food chain: cadmium in food. EFSA J. 980, 1–139 (Available from). https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.980.

EFSA (European Food Safety Authority), 2010. Scientific opinion of the panel on contaminants in the food chain: lead in food. EFSA J. 8, 1570 (Available from). https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2010.1570.

Egan, S.K., Bolger, P.M., Carrington, C.D., 2007. Update of US FDA's total diet study food list and diets. J. Expo. Sci. Environ. Epidemiol. 17 (6), 573–582. https://doi.org/10.1038/sj.jes.7500554.

Eum, K.D., Korrick, S.A., Weuve, J., Okereke, O., Kubzansky, L.D., Hu, H., Weisskopf, M. G., 2012. Relation of cumulative low-level lead exposure to depressive and phobic anxiety symptom scores in middle-age and elderly women. Environ. Health Perspect. 120 (6), 817–823. https://doi.org/10.1289/ehp.1104395.

Faroon, O., Ashizawa, A., Wright, S., Tucker, P., Jenkins, K., Ingerman, L., Rudisill, C., 2012. Toxicological profile for cadmium. Agency for toxic substances and disease registry. Atlanta.

Fenga, C., Gangemi, S., Alibrandi, A., Costa, C., Micali, E., 2016. Relationship between lead exposure and mild cognitive impairment. JPMH 57 (4), E205–E210.

Flora, S.J., 2002. Lead exposure: health effects, prevention and treatment. J. Environ. Biol. 23 (1), 25–41.

Genchi, G., Sinicropi, M.S., Lauria, G., Carocci, A., Catalano, A., 2020. The effects of cadmium toxicity. IJERPH 17 (11), 3782. https://doi.org/10.3390/ijerph17113782.

Golub, N.I., Winters, P.C., van Wijngaarden, E., 2010. A population-based study of blood lead levels in relation to depression in the United States. Int. Arch. Occup. Environ. Health 83 (7), 771–777 https://doi.org/10.1007/s00420-009-0497-3.

Gutiérrez-Reyes, E.Y., Albores, A., Ríos, C., 1988. Increase of striatal dopamine release by cadmium in nursing rats and its prevention by dexamethasone-induced metallothionein. Toxicology 131 (2–3), 145–154 https://doi.org/10.1016/s0300-483x(98)00126-7.

Han, C., Lim, Y.H., Hong, Y.C., 2016. Does cadmium exposure contribute to depressive symptoms in the elderly population? J. Occup. Environ. Med. 73 (4), 269–274. https://doi.org/10.1136/oemed-2015-102900.

Hidaka, B.H., 2012. Depression as a disease of modernity: explanations for increasing prevalence. J. Affect. Disord. 140 (3), 205–214. https://doi.org/10.1016/j.jad.2011.12.036.

Horiguchi, H., Oguma, E., Sasaki, S., Miyamoto, K., Ikeda, Y., Machida, M., Kayama, F., 2004. Comprehensive study of the effects of age, iron deficiency, diabetes mellitus, and cadmium burden on dietary cadmium absorption in cadmium-exposed female Japanese farmers. Toxicol. Appl. Pharmacol. 196 (1), 114–123. https://doi.org/10.1016/j.taap.2003.11.024.

Järup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol. Appl. Pharmacol. 238 (3), 201–208. https://doi.org/10.1016/j.taap.2009.04.020.

Järup, L., Berglund, M., Elinder, C.G., Nordberg, G., Vahter, M., 1998. Health effects of cadmium exposure–a review of the literature and a risk estimate. Scand. J. Work Environ. Health 24 (1), 1–51.

Jurczak, A., Brodowska, A., Szkup, M., Prokopowicz, A., Karakiewicz, B., Łój, B., Kotwas, A., Brodowska, A., Grochans, G., 2018. Influence of Pb and Cd levels in whole blood of postmenopausal women on the incidence of anxiety and depressive symptoms. Ann. Agric. Environ. Med. 25 (2), 219–223. https://doi.org/10.26444/aaem/85929.

Jusko, T.A., Henderson, C.R., Lanphear, B.P., Cory-Slechta, D.A., Parsons, P.J., Canfield, R.L., 2008. Blood lead concentrations < 10 microg/dL and child intelligence at 6 years of age. Environ. Health Perspect. 116 (2), 243–248. https://doi.org/10.1289/ehp.10424.

Karri, S.K., Saper, R.B., Kales, S.N., 2008. Lead encephalopathy due to traditional medicines. Curr. Drug. Saf. 3 (1), 54–59 https://doi.org/2174/157488608783333907.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289 (23), 3095–3105. https://doi.org/10.1001/jama.289.23.3095.289/23/3095.

Kikuchi, Y., Nomiyama, T., Kumagai, N., Uemura, T., Omae, K., 2002. Cadmium concentration in current Japanese foods and beverages. J. Occup. Health 44, 240–247. https://doi.org/10.1539/joh.44.240.

Kim, K.N., Lee, M.R., Choi, Y.H., Lee, B.E., Hong, Y.C., 2016. Associations of blood cadmium levels with depression and lower handgrip strength in a community-dwelling elderly population: a repeated-measures panel study. J. Gerontol. A Biol. Sci. Med. Sci. 71 (11), 1525–1530. https://doi.org/10.1093/gerona/glw119.

Kippler, M., Tofail, F., Gardner, R., Rahman, A., Hamadani, J.D., Bottai, M., Vahter, M., 2012. Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study. Environ. Health Perspect. 120 (2), 284–289. https://doi.org/10.1289/ehp.1103711.

Kostrubiak, D.E., Vacchi-Suzzi, C., Smith, D.M., Meliker, J.R., 2017. Blood cadmium and depressive symptoms: confounded by cigarette smoking. Psychiatry Res. 256, 444–447. https://doi.org/10.1016/j.psychres.2017.07.019.

Krzywy, I., Krzywy, E., Pastuszak-Gabinowska, M., Brodkiewicz, A., 2010. Ołów – czy jest się czego obawiać? Ann. Acad. Med. Stetin. 56 (2), 118–128.

Kumar, L.C.A., Vincent, S., Ambrose, T., 1994. Uptake and peristence of the heavy metal cadmium in tissues of the fresh water fish Cyprinus carpio. Poll. Res. 13, 361–364.

Labudda, M., 2011. Biochemiczne mechanizmy neurotoksyczności kadmu. Rocz. PZH 62 (4), 357–363.

Lafuente, A., González-Carracedo, A., Romero, A., Esquifino, A.I., 2003. Effect of cadmium on 24 h variations in hypothalamic dopamine and serotonin metabolism in adult male rats. Exp. Brain Res. 149 (2), 200–206 https://doi.org/10.1007/s00221-002-1356-6.

Lafuente, A., González-Carracedo, A., Cabaleiro, T., Romero, A., Esquifino, A.I., 2005a. Toxic effects of cadmium on GABA and taurine content in different brain areas of adult male rats. J. Physiol. Biochem. Pharmacol. 61 (3), 439–446 https://doi.org/10.1007/bf03168450.

Lafuente, A., González-Carracedo, A., Romero, A., Cabaleiro, T., Esquifino, A.I., 2005b. Toxic effects of cadmium on the regulatory mechanism of dopamine and serotonin on prolactin secretion in adult male rats. Toxicol. Lett. 155 (1), 87–96. https://doi.org/10.1016/j.toxlet.2004.08.011.

Lamtai, M., Chaibat, J., Ouakki, S., Berkiks, I., Rifi, E., El Hessni, A., Mesfioui, A., Tadlaoui Hbibi, A., Ahyayauch, H., Essamri, A., Ouichou, A., 2018. Effect of chronic administration of cadmium on anxiety-like, depression-like and memory deficits in male and female rats: possible involvement of oxidative stress mechanism. J. Behav. Brain Sci. 8, 240–268. https://doi.org/10.4236/jbbs.2018.85016.

Larsen, E.H., Andersen, N.L., Møller, A., Petersen, A., Mortensen, G.K., Petersen, J., 2002. Monitoring the content and intake of trace elements from food in Denmark. Food Addit. Contam. 19 (1), 33–46. https://doi.org/10.1080/02652030110087447.

Lindgren, K.N., Masten, V.L., Tiburzi, M.J., Ford, D.P., Bleecker, M.L., 1999. The factor structure of the Profile of Mood States (POMS) and its relationship to occupational lead exposure. J. Occup. Environ. Med. 41 (1), 3–10. https://doi.org/10.1097/00043764-199901000-00002.

Llobet, J.M., Falcó, G., Casas, C., Teixidó, A., Domingo, J.L., 2003. Concentrations of arsenic, cadmium, mercury, and lead in common foods and estimated daily intake by children, adolescents, adults, and seniors of Catalonia, Spain. J. Agric. Food Chem. 51 (3), 838–842. https://doi.org/10.1021/jf020734q.

Malekirad, A.A., Kalantari-Dehaghi, R., Abdollahi, M., 2013. Clinical, haematological, and neurocognitive findings in lead-exposed workers of a battery plant in Iran. Arh. Hig. Rada Toksikol. 64 (4), 497–503 https://doi.org/10.2478/10004-1254-64-2013-2385.

McFarlane, A.C., Searle, A.K., Van Hooff, M., Baghurst, P.A., Sawyer, M.G., Galletly, C., Sim, M.R., Clark, L.S., 2013. Prospective associations between childhood low-level lead exposure and adult mental health problems: the Port Pirie cohort study. Neurotoxicology 39, 11–17. https://doi.org/10.1016/j.neuro.2013.08.003.

Mitra, P., Sharma, S., Purohit, P., Sharma, P., 2017. Clinical and molecular aspects of lead toxicity: an update. Crit. Rev. Clin. Lab. Sci. 54 (7–8), 506–528 https://doi.org/10.1080/10408363.2017.1408562.

Moreau, T., Orssaud, G., Lellouch, J., Claude, J.R., Juguet, B., Festy, B., 1983. Blood cadmium levels in a general male population with special reference to smoking. Arch. Environ. Health 38, 163–167, 10.1080/00039896.1983.10543998.

Moździerz, A., Juszko-Piekut, M., Stojko, J., 2014. Zanieczyszczenie kadmem powietrza atmosferycznego miast śląskich. Med. Środ. 17 (1), 25–33.

Murphy, V.A., 1997. Cadmium: acute and chronic neurological disorders. Miner. Met. Neurotoxicol. 229–240.

Nair, A.R., Degheselle, O., Smeets, K., Van Kerkhove, E., Cuypers, A., 2013. Cadmium-induced pathologies: where is the oxidative balance lost (or not)? Int. J. Mol. Sci. 14 (3), 6116–6143. https://doi.org/10.3390/ijms14036116.

Nawrot, T.S., Staessen, J.A., Roels, H.A., Munters, E., Cuypers, A., Richart, T., Ruttens, A., Smeets, K., Clijsters, H., Vangronsveld, J., 2010. Cadmium exposure in the population: from health risks to strategies of prevention. Biometals 23 (5), 769–782. https://doi.org/10.1007/s10534-010-9343-z.

Ngocho, J.S., Watt, M.H., Minja, L., Knettel, B.A., Mmbaga, B.T., Williams, P.P., Sorsdahl, K., 2019. Depression and anxiety among pregnant women living with HIV in Kilimanjaro region, Tanzania. PLoS One 14 (10), e0224515. https://doi.org/10.1371/journal.pone.0224515.

Nishijo, M., Nakagawa, H., Suwazono, Y., Nogawa, K., Kido, T., 2017. Causes of death in patients with Itai-itai disease suffering from severe chronic cadmium poisoning: a nested case-control analysis of a follow-up study in Japan. BMJ Open 7 (7), e015694. https://doi.org/10.1136/bmjopen-2016-015694.

Nogawa, K., Kobayashi, E., Okubo, Y., Suwazono, Y., 2004. Environmental cadmium exposure, adverse effects and preventive measures in Japan. Biometals 17 (5), 581–587. https://doi.org/10.1023/b:biom.0000045742.81440.9c.

Nordberg, G.F., Bernard, A., Diamond, G.L., Duffus, J.H., Illing, P., Nordberg, M., Bergdahl, I.A., Jin, T., Skerfving, S., 2018. Risk assessment of effects of cadmium on human health (IUPAC Technical Report). Pure Appl. Chem. 90 (4), 755–808. https://doi.org/10.1515/pac-2016-0910.

Obeng-Gyasi, E., 2019. Sources of lead exposure in various countries. Rev. Environ. Health 34, 25–34. https://doi.org/10.1515/reveh-2018-0037.

Olsson, I.M., Bensryd, I., Lundh, T., Ottosson, H., Skerfving, S., Oskarsson, A., 2002. Cadmium in blood and urine–impact of sex, age, dietary intake, iron status, and former smoking–association of renal effects. Environ. Health Perspect. 110 (12), 1185–1190. https://doi.org/10.1289/ehp.021101185.

Ong, W.Y., He, X., Chua, L.H., Ong, C.N., 2006. Increased uptake of divalent metals lead and cadmium into the brain after kainite-induced neuronal injury. Exp. Brain Res. 173 (3), 468–474. https://doi.org/10.1007/s00221-006-0390-1.

Orisakwe, O.E., 2014. The role of lead and cadmium in psychiatry. N. Am. J. Med. Sci. 6 (8), 370–376 https://doi.org/10.4103/1947-2714.139283.

Pappas, R.S., 2011. Toxic elements in tobacco and in cigarette smoke: inflammation and sensitization. Metallomics 3 (11), 1181–1198. https://doi.org/10.1039/c1mt00066g.

Rafati Rahimzadeh, M., Rafati Rahimzadeh, M., Kazemi, S., Moghadamnia, A.A., 2017. Cadmium toxicity and treatment: an update. Casp. J. Intern. Med. 8 (3), 135–145. https://doi.org/10.22088/cjim.8.3.135.

Reeves, P.G., Chaney, R.L., 2001. Mineral status of female rats affect the absorption and organ distribution of dietary cadmium derived from edible sunflower kernels (Helianthus annuus L.). Environ. Res. 85, 215–225. https://doi.org/10.1006/enrs.2000.4236.

Ren, H.M., Wang, J.D., Zhang, X.L., 2006. Assessment of soil lead exposure in children in Shenyang, China. Environ. Pollut. 144, 327–335. https://doi.org/10.1016/j.envpol.2005.11.011.

Rhodes, D., Spiro 3rd, A., Aro, A., Hu, H., 2003. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. J. Occup. Environ. Med. 45 (11), 1144–1151. https://doi.org/10.1097/01.jom.0000094995.23808.7b.

Richter, P., Faroon, O., Pappas, R.S., 2017. Cadmium and cadmium/zinc ratios and tobacco-related morbidities. IJERPH 14 (10), 1154. https://doi.org/10.3390/ijerph14101154.

Rodríguez-Barranco, M., Lacasña, M., Gil, F., Lorca, A., Alguacil, J., Rohlman, D.S., González-Alzaga, B., Molina-Villalba, I., Mendoza, R., Aguilar-Garduño, C., 2014. Cadmium exposure and neuropsychological development in school children in southwestern Spain. Environ. Res. 134, 66–73. https://doi.org/10.1016/j.envres.2014.06.026.

Rossi-George, A., Virgolini, M.B., Weston, D., Cory-Slechta, D.A., 2009. Alterations in glucocorticoid negative feedback following maternal Pb, prenatal stress and the combination: a potential biological unifying mechanism for their corresponding disease profiles. Toxicol. Appl. Pharmacol. 234 (1), 117–127. https://doi.org/10.1016/j.taap.2008.10.003.

Salehi-Pourmehr, H., Dolatkhah, N., Gassab-Abdollahi, N., Farrin, N., Mojtahedi, M., Farshbaf-Khalili, A., 2019. Screening of depression in overweight and obese pregnant women and its predictors. J. Obstet. Gynaecol. Res. 45 (11), 2169–2177. https://doi.org/10.1111/jog.14100.

Sanders, T., Liu, Y., Buchner, V., Tchounwou, P.B., 2009. Neurotoxic effects and biomarkers of lead exposure: a review. Rev. Environ. Health 24 (1), 15–45. https://doi.org/10.1515/reveh.2009.24.1.15.

Satarug, S., Moore, M.R., 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ. Health Perspect. 112 (10), 1099–1103. https://doi.org/10.1289/ehp.6751.

Satarug, S., Baker, J.R., Urbenjapol, S., Haswell-Elkins, M., Reilly, P.E.B., Wiliams, D.J., Moore, M.R., 2003. A global perspective on cadmium pollution and toxicity in non--occupationally exposed population. Toxicol. Lett. 137, 65–83.

Scinicariello, F., Buser, M.C., 2015. Blood cadmium and depressive symptoms in young adults (aged 20–39 years). Psychol. Med. 45 (4), 807–815 https://doi.org/10.1017/S0033291714001883.

Sańczuk-Przybyłowska, M., Śmigielska, S., Woźniak, A., Przybyłowicz, A., Szyfter, W., Szyfter, K., Piekoszewski, W., Staniek, H., Gawęcki, W., Herman, M., Kulza, M., Florek, E., 2011. Ocena poziomu kadmu i ołowiu u pacjentów z nowotworami głowy i szyi. Prz. Lek. 68 (10), 794–802.

Shiue, I., 2015. Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011–2012. Environ. Sci. Pollut. Res. Int. 22 (21), 17095–17103 https://doi.org/10.1007/s11356-015-4944-2.

Silver, M.K., Lozoff, B., Meeker, J.D., 2013. Blood cadmium is elevated in iron deficient U.S. children: a cross- sectional study. Environ. Health 12, 117.

Strathmann, F.G., Blum, L.M., 2018. Toxic elements. In: Rafai, N., Horwath, A.R., Wittwer, C.T. (Eds.), Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 6th ed. Elsevier, p. 42.

Sujka, M., Pankiewicz, U., Kowalski, R., Mazurek, A., Ślepecka, K., Góral, M., 2019. Determination of the content of Pb, Cd, Cu, Zn in dairy products from various regions of Poland. Open Chem. 17 (1), 694–702. https://doi.org/10.1515/chem-2019-0072.

Szymańska, M., Budziszewska, B., Jaworska – Feil, L., Basta – Kaim, A., Kubera, M., Leśkiewicz, M., Regulska, M., Lasoń, W., 2009. The effect of antidepressant drugs on the HPA axis activity, glucocorticoid receptor level and FKBP51 concentration in prenatally stressed rats. Psychomeuroendocrinology 34, 822–832.

Tang, R., Luo, M., Li, J., Peng, Y., Wang, Y., Liu, B., Liu, G., Wang, Y., Lin, S., Chen, R., 2019. Symptoms of anxiety and depression among Chinese women transitioning through menopause: findings from a prospective community-based cohort study. Fertil. Steril. 112 (6), 1160–1171. https://doi.org/10.1016/j.fertnstert.2019.08.005.

Taylor, G., McNeill, A., Girling, A., Farley, A., Lindson-Hawley, N., Aveyard, P., 2014. Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ 348, g1151. https://doi.org/10.1136/bmj.g1151.

Téllez-Rojo, M.M., Bellinger, D.C., Arroyo-Quiroz, C., Lamadrid-Figueroa, H., Mercado-García, A., Schnaas-Arrieta, L., Wright, R.O., Hernández-Avila, M., Hu, H., 2006. Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 118 (2), e323–e330. https://doi.org/10.1542/peds.2005-3123.

Tong, S., von Schirnding, Y.E., Prapamontol, T., 2000. Environmental lead exposure: a public health problem of global dimensions. Bull. World Health Organ. 78 (9), 1068–1077.

Vig, P.J., Nath, R., 1991. In vivo effects of cadmium on calmodulin and calmodulin regulated enzymes in rat brain. Biochem. Int. 23 (5), 927–934.

Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2008. STROBE initiative, 2008. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61 (4), 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008.

Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch. Gen. Psychiatry 66 (6), 617–626. https://doi.org/10.1001/archgenpsychiatry.2009.50.

Wang, B., Du, Y., 2013. Cadmium and its neurotoxic effects. Oxid. Med. Cell. Longev., 898034 https://doi.org/10.1155/2013/898034.

Wang, X., Yang, Y., Wang, X., Xu, S., 2006. The effect of occupational exposure to metals on the nervous system function in welders. J. Occup. Health 48 (2), 100–106 https://doi.org/10.1539/joh.48.100.

World Health Organization (WHO), 2011. Safety evaluation of certain food additives and contaminants in food. Prepared by the Seventy-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization (WHO Food Additives Series, No. 64); pp 305–380. Available from: ⟨http://www.inchem.org/documents/jecfa/jecmono/v64je01.pdf⟩).

Zhong, M.S., Jiang, L., Han, D., Xia, T.X., Yao, J.J., Jia, X.Y., Peng, Ch, 2015. Cadmium exposure via diet and its implication on the derivation of health-based soil screening values in China. JESEE 25 (4), 433–442. https://doi.org/10.1038/jes.2015.5.