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CADMIUM AND HYPERTENSION IN EXPOSED WORKERS: A META-ANALYSIS

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Abstract
Objectives: In the general population, cadmium seems to be responsible for hypertension, atherosclerosis and an increase in acute coronary events. Therefore, the purpose of this meta-analysis was to analyze controlled studies conducted on cadmium and arterial pressure in occupationally-exposed workers. **Materials and Methods:** After analyzing all the relevant articles found in the literature, 6 publications were selected. **Results:** A higher prevalence of hypertension and higher values of systolic and diastolic blood pressure were recorded in the exposed subjects. **Conclusions:** Cadmium in occupationally-exposed individuals appears to induce an increase in systolic and diastolic blood pressure and an increase in the prevalence of hypertension.

Key words:
Cadmium, Hypertension, Cardiovascular disease, Workers, Meta-analysis

INTRODUCTION

Cadmium is a ubiquitous pollutant in the living environment. The three main sources of exposure to cadmium in the general population are diet (it is found in several food types such as shellfish and organs [1]), smoke (it is a source of on average 10–15 μg per day), and atmospheric pollution (personal average absorption of cadmium due to pollution has been estimated at 0.5 μg/m^3 for populations residing in areas with a high level of urbanization) [2]. Moreover, it is found in small quantities i.e. less than 0.1 μg/l, in drinking water [3].

Exposure to cadmium and its components (cadmium oxide, cadmium sulphate, cadmium sulphide, cadmium chloride and others) also occurs in the work environment, where it is used for many purposes. It is mainly used in production of nickel-cadmium alkaline batteries (80%) [4], in production of pigments for paints (10%) (Landrigan, 1982), in mining, cadmium forging [5], in the construction of certain semi-conductors, in electronics, in the field of plastics as a stabilizer (e.g. polyvinyl chloride – PVC), as well as in the production of fertilizers. Cadmium recycling

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is gaining importance as another potential source of poisoning from cadmium and it now represents 10–15% of total cadmium production [6]. Cadmium penetrates the human body through the principal routes of toxic matter absorption (i.e. through the lungs, gastro-intestinal tract and skin), however, in the case of professional exposure, the amount of cadmium absorption through ingestion and skin is considered to be much less important.

The effects of cadmium on the kidney and lungs are well known. However, the role of cadmium and its derivatives in the induction of cardiovascular diseases seems much more controversial. Over time, several studies have been conducted on the general population, on animals and on cells in vitro. However, the literature concerning professional exposure to cadmium and the onset of cardiovascular pathologies is very limited [7].

Cadmium seems to be the cause of an increased prevalence of peripheral arteriopathies [8], heart failure [9], myocardial infarction [10], hypertension [11] and atherogenic alterations [12]. In a study conducted by Shutte in 2009 [13] on persons residing in two areas of the country with high and low concentrations of cadmium, alterations in femoral compliance and in femoral distensibility were reported in persons with high levels of cadmiuria. In 1989, Hermann [14] did not register higher systolic and diastolic blood pressure values in a group characterized by high exposure to cadmium.

As regards studies on people with cardiovascular diseases (hypertension, coronopathies, myocardial infarction, atherosclerosis) [15], a high concentration of cadmium was found in blood [16], urine [17], scalp [18], hair and nails [19] of the patients suffering from these pathologies. Studies conducted on animals demonstrated specific electrocardiogram alterations (lengthening of the P-R interval) [20], increased prevalence of hypertension [21], atherosclerosis [22], and other cardiovascular pathologies [23], while studies conducted *in vitro* on human cells, demonstrated how cadmium can induce endothelial alterations [24], oxidative damage to the cardiac muscle [25] and reduction of coronary flow [26], as well as inhibition of the electron transfer chain within myocytes [27].

As previously mentioned, little research has been conducted in order to explain the role of cadmium and its components in the induction of cardiovascular pathologies in persons exposed as part of their occupation. So far, no meta-analysis on cadmium exposure and the cardiovascular risk in exposed workers has been developed, probably due to the scarcity of appropriate controlled studies. The majority of research conducted on workers in past decades was in fact focused on other types of pathologies, primarily respiratory and renal ones. Many of the studies conducted to clarify the role of cadmium in the development of cardiovascular pathologies did not analyze the workers at the time of exposure to the toxic agent but were post-mortem examinations of their tissues [28–30]. Other researchers, on the other hand, did not include a control group [31], had incomplete data [32] or conducted research of an epidemiological nature [33]. Although the occupational exposure of workers and its effect on their health have been studied [34–39], the influence of cadmium on the cardiovascular system has not been analyzed.

Therefore, the purpose of this study was to summarize and analyze all the controlled studies conducted on cadmium and cardiovascular risks in occupationally-exposed workers by the use of one of the instruments of Evidence Based Medicine, i.e. meta-analysis, in order to understand the effect of this metal on blood pressure.

MATERIALS AND METHODS

Search strategy

The meta-analysis was performed by carrying out a systemic search for all articles concerning an evaluation of chronic effects on the cardiovascular system of workers occupationally exposed to cadmium. An extensive search for “cadmium”, “cadmium urinary”, “blood cadmium”,

"nickel-cadmium battery workers" (or alkaline battery workers), "pigment workers" (or pigment manufacturing plant workers), "cadmium recovery plant", "cadmium electroplating workers" and "hypertension" was performed, using free text and MeSH terms. The papers suitable for inclusion were identified by systematic research on the MEDLINE/Pubmed, TOXNET/Toxline, Biomedcentral, Nioshtic-2, Scopus and EMBASE electronic databases.

The research included articles published between March 1950 and February 2011; unpublished data the authors were aware of, as well as papers from domestic and international conferences in accordance with the indications contained in the Cochrane Handbook for Systematic Reviews (http://www.cochrane-handbook.org). Section 4.7.1 of the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org) reports that any meta-analysis must take into consideration both published as well as unpublished works. This is to avoid errors in the process of selection and inclusion of data, since meta-analysis is acceptable only when it includes all the data available on the topic, whatever their nature or origin.

No restriction was applied with regard to the language or the type of publication.

Study selection and patients

The study included the following categories of workers: nickel-cadmium battery factory workers, paint/pigment industry workers, ceramic industry workers, metal workers, welders, plating industry workers, workers employed in the disposal of cadmium, as well as farmers.

A systematic search resulted in 454 publications, of which only 47 met the requirements of our study and only 11 were in compliance with the following inclusion criteria (Figure 1):

1. Case-control studies, where the studied group was composed of subjects occupationally exposed to cadmium and a control group of subjects who were not occupationally exposed to cadmium.
2. Studies in which the results were expressed in numerical terms of mean and standard difference or frequency.

Articles which were eliminated basing on the following exclusion criteria (Figure 1):

1. Studies conducted on persons not occupationally exposed to cadmium.
2. Studies conducted on persons with poisoning due to ingestion of cadmium.
3. Reviews, editorials or commentaries without original data.
4. Animal studies without data concerning humans.
5. *In vitro* studies.
6. Case reports with no control group.
7. No hypertension or blood pressure outcomes.
8. Studies conducted on the effects of environmental pollution with cadmium and with cigarette smoke.

Of the 11 selected works, the final study was excluded, since the control group comprised workers exposed to cadmium pollution [40]. In fact, in this study, a group of workers from an alkaline battery factory was divided into normotensive and hypertensive. Other parameters, such as urinary excretion of cadmium, average age and length of occupational exposure, were also investigated.

Authors of the publications where the full texts was not present were contacted in order to obtain all necessary data to perform the meta-analysis. However, the full texts of four more articles could not be found [41–44], and thus the articles in question were excluded (Figure 1). Finally, a total number of six works was included in the meta-analysis [45–50] (Table 1, Figure 1).

In these six articles, the exposed workers, identified by means of working medical histories, were nickel-cadmium battery factory workers, farmers, those working with pigments and cadmium resins, workers employed in the disposal of cadmium, steel industry workers, and workers in factories producing plastic materials. The control group,

Table 1. Characteristics of the studies included in the meta-analysis

References	Location	Characteristics of experimental groups	Characteristics of control groups	Cadmium biomarkers	Cadmium determination method	Cadmium exposure levels
Poręba et al., 2010 [45]	Steelworks in Legnica and Głogów (Poland)	17 workers in steelworks age (X±SD): 37.53±8.61 males: 100% BMI (X±SD): 24.82±2.79 smokers (n): 11 (64.71%) duration of employment (X±SD): 13.82±8.02 years systolic blood pressure (X±SD): 124.40±10.64 mmHg diastolic blood pressure (X±SD): 80.54±6.71 mmHg hypertension rate (n): 3[a] (17.65%)	19 workers in office of steelworks age (X±SD): 40.83±9.28 years males: 100% BMI (X±SD): 24.56±2.66 smokers (n): 13 (68.42%) duration of employment: n.a. systolic blood pressure (X±SD): 118.68±7.97 mmHg diastolic blood pressure (X±SD): 77.89±5.85 mmHg hypertension rate (n): 1[a] (5.26%)	blood cadmium	atomic absorption spectrometry with graphite furnace	2.98±3.29 µg/l (case) 1.41±2.08 µg/l (control)
Zhang et al., 1996 [48]	Nickel-cadmium battery factor in China	362 workers in nickel-cadmium battery factors age (X±SD): 31.5±10.5 years males: 55% BMI (X±SD): 21.3±3.2 smokers: n.a. duration of employment: n.a. systolic blood pressure (X±SD): 117.01±15.0 mmHg diastolic blood pressure (X±SD): 73.5±12.0 mmHg hypertension rate (n): 18[a] (5%)	526 workers / farmers age (X±SD): 33.2±8.7 years males: 53.42% BMI (X±SD): 23.2±2.8 smokers: n.a. duration of employment: n.a. systolic blood pressure (X±SD): 115.51±16.5 mmHg diastolic blood pressure (X±SD): 72.75±25.5 mmHg hypertension rate (n): 27[a] (5.1%)	urinary cadmium	atomic absorption spectrometry with carbon-rod	12.5±7.3 µg/g creatinine (case) 2.4±2.0 µg/g creatinine (control)

Table 1. Characteristics of the studies included in the meta-analysis – cont.

References	Location	Characteristics of experimental groups	Characteristics of control groups	Cadmium biomarkers	Cadmium determination method	Cadmium exposure levels
Schuhmacher et al., 1994 [47]	Cadmium pigment and resin factories in Barcelona (Spain)	40 workers in cadmium pigment and resin factories age (X±SD): 49.2±5.0 years males: 100% BMI: n.a. smokers (n): 29 (72.5%) duration of employment (X±SD): 12.3±8.7 years systolic blood pressure (X±SD): 125.9±13.2 mmHg diastolic blood pressure (X±SD): 77.6±8.15 mmHg hypertension rate: n.a.	40 males not exposed to cadmium age (X±SD): 46.3±3.2 years males: 100% BMI: n.a. smokers (n): 30 (75.0%) duration of employment: n.a. systolic blood pressure (X±SD): 128.2±19.5 mmHg diastolic blood pressure (X±SD): 79.8±11.9 mmHg hypertension rate: n.a.	urinary cadmium	atomic absorption spectrophotometry (varian spectrophotometer)	2.5±2.00 μg/g creatinine (case) 0.79±1.15 μg/g creatinine (control)
Thun et al., 1989 [49]	Metal recovery plant in Colorado (U.S.A.)	45 workers in metal recovery plant age (X±SD): 54.5±15.5 years males: 100% BMI: n.a. smokers (n): 17 (37.7%) duration of employment [X (range)]: 19 (1–38) years systolic blood pressure (X±SD): 133.9±1.14 mmHg diastolic blood pressure (X±SD): 80.0±1.13 mmHg hypertension rate (n): 17[a] (37.7%)	32 male workers employed at a hospital age (X±SD): 50.1±13.0 years males: 100% BMI: n.a. smokers (n): 14 (43.75%) duration of employment: n.a. systolic blood pressure (X±SD): 120.3±1.14 mmHg diastolic blood pressure (X±SD): 73.3±1.13 mmHg hypertension rate (n): 5[a] (15.62%)	urinary cadmium blood cadmium	modified method of Pruszowska atomic absorption spectrometry with graphite furnace	9.3±6.9 μg/g creatinine (case) 0.7±0.7 μg/g creatinine (control) 7.9±2.0 μg/l (case) 1.2±2.0 μg/l (control)

De Kort et al., 1989 [46]	U.S.A.	53 workers in plastics industry age (X±SD): 42.1±1.2 years males: 100% BMI: n.a. smokers: n.a. duration of employment (X±SD): 12.5±1.2 years systolic blood pressure (X±SD): 140.0±3.0 mmHg diastolic blood pressure (X±SD): 86.0±2.0 mmHg hypertension rate (n): 15[b] (28.3%)	52 workers in insulation materials industry age (X±SD): 38.2±1.1 years males: 100% BMI: n.a. smokers: n.a. duration of employment (X±SD): 8.6±0.8 years systolic blood pressure (X±SD): 131.0±3.0 mmHg diastolic blood pressure (X±SD): 80.0±2.0 mmHg hypertension rate (n): 8[b] (15.38%)	urinary cadmium blood cadmium	atomic absorption spectrophotometry	2.5±2.0 µg/g creatinine (case) 0.62±0.18 µg creatinine (control) 1.32±0.37 µg/l (case) 0.54±0.23 µg/l (control)
Sandifer et al., 1979 [50]	U.S.A.	31 green keepers age (X±SD): 41.68±9.82 years males: 100% BMI: n.a. smokers: n.a. duration of employment: n.a. systolic blood pressure (X±SD): 143.7±19.13 mmHg diastolic blood pressure (X±SD): 86.45±13.21 mmHg hypertension rate (n): 20[a] (64.5%)	10 employees and members of the Faculty of Medicine of South Caroline age (X±SD): 42.0±17.37 years males: 100% BMI: n.a. smokers: n.a. duration of employment: n.a. systolic blood pressure (X±SD): 129.9±10.7 mmHg diastolic blood pressure (X±SD): 80.7±6.1 mmHg hypertension rate (n): 4[a] (40.0%)	urinary cadmium	atomic absorption spectrophotometry	n.a.

X – mean; SD – standard deviation; n.a. – not available.

[a] Hypertension defined as PAS equal or higher to 140 mmHg and/or PAD equal or higher than 90 mmHg.

[b] Hypertension defined as PAS equal or higher to 160 mmHg and/or PAD equal or higher than 90 mmHg.

again identified by the use of working medical histories (workers not occupationally exposed to cadmium), was represented by insulation material plant worker, hospital employees, beer factory workers and workers involved in other fields of the industry.

The total number of participants included in the meta-analysis was 1227. The number of cases was 548, while the number of controls was 679. The average age of the study group was 42.4±7.18, while the average age of the control group was 41.77±5.43. The total number of male subjects in the study group was 386, while the total number of female subjects was 162; the total number of male subjects in the control group was 434, while the total number of female subjects was 245. The number of smokers, identified by medical questionnaires, was 57 out of 102 among those exposed to cadmium (55.88%) and 57 out of 91 among the controls (62.63%). Finally, the Body Mass Index (BMI), when data was available, was 23.06±1.76 kg/m^2 among the exposed workers and 23.88±0.68 kg/m^2 among the controls. In the examined studies no information concerning the length of service or lipid order was given.

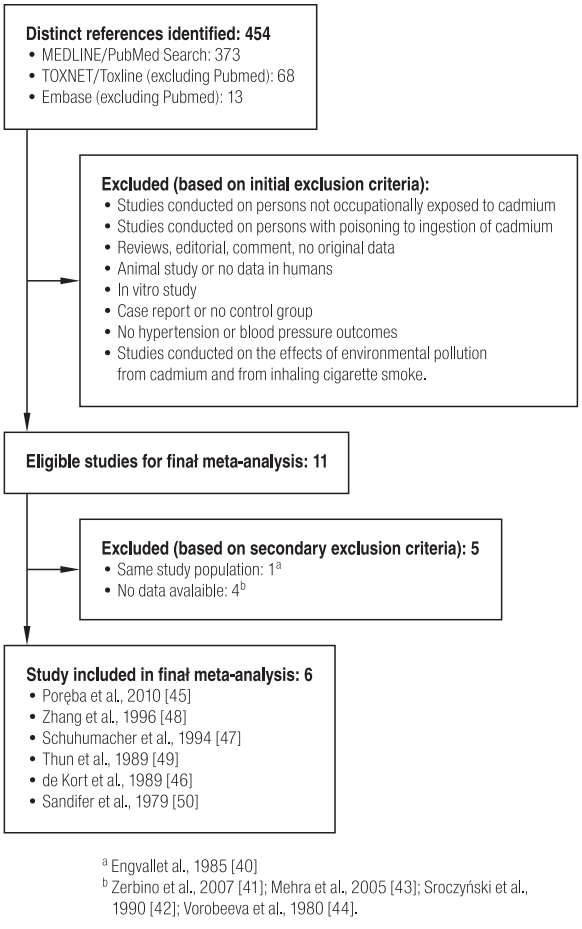


Fig. 1. Flow chart with included/excluded studies with specification of reasons

Based on the available data, the results were divided into 3 classes:

– Prevalence of hypertension.
– Values of systolic arterial pressure.
– Values of diastolic arterial pressure.

Measurement

Systolic and diastolic arterial pressure were measured in mmHg by the use of an ordinary sphygmomanometer, using respectively phase I and phase V of the Korotkov tones. Only in one study arterial pressure was measured in kilopascals (Kpa); transformation into mmHg was conducted in accordance with common methods (1 KPa: 7.5006151 mmHg).

In cases where prevalence of hypertension was not calculated, it was obtained by correlating the number of hypertensives with the total numbers of the group. A subject was considered hypertensive when his systolic arterial pressure was equal to or higher than 140 mmHg, or the diastolic arterial pressure was equal to or higher than 90 mmHg, according to the latest guidelines established by the World Health Organization (WHO) [50].

Cadmiemia, which was analyzed in four studies, and obtained by the use of atomic absorption spectrometry with graphite furnace [45–47,49] was expressed in μg/l. However, cadmiuria was expressed in μg/g of creatinine in three studies: by the use of atomic absorption spectroscopy [46], atomic absorption spectrometry using carbon rods [48] or the modified method of Pruszowska [49]. In the case of one study [50], the values of urinary cadmium were unknown. Ultimately, the available data did not

allow the limits of detection of cadmiemia and cadmiuria to be tested.

Quality assessment and data extraction

Two investigators (L.M. and M.F.), independently of each other, screened the titles and abstracts resulting from the search strategies. The articles with titles or abstracts clearly irrelevant were rejected during the first screening. The full texts of potentially relevant articles were reviewed to assess eligibility for the inclusion in the meta-analysis with any disagreement resolved by consensus. All discrepancies were rechecked and the consensus was reached by a third investigator (G.A.).

Statistical analysis

To express the result of our meta-analysis, the Effect Size (ES), a value which expresses the strength of association between two variables, was used. In addition, the confidence interval, which expresses the precision with which the Effect Size was estimated, was calculated.

Whenever the studies reported data expressed in mean and standard differences, the ES was expressed as Standardized Mean Difference (SMD), which expresses the relationship between the difference of the two means and the assessment of the standard difference within the same group.

The ES was evaluated using the Random Effects Model (REM) – a statistical model in which the confidence interval is influenced both by the error of internal sampling of the study as well as by the variability of the studies included in the meta-analysis. The REM is more reliable since the confidence interval it provides is broader than that provided by the Fixed Effects Model (FEM). As regards ES measurements based on differences, a difference equal to 0.0 indicated a lack of difference among the studied groups.

The Logarithmic Odds Ratio (Log OR) was also calculated between the study and control groups, using regression coefficients. Since the confidence interval corresponded (CI) to 95% of the observations, the p-value was regarded as $p < 0.05$, which expressed the significance of ES. Also in this case, the ES was evaluated using the Random Effects Model (REM). With respect to the ES measures based on relationships such as the OR, a ratio equal to 1.0 indicated the lack of differences among the studied groups.

If the studies reported data expressed in frequency, the ES was expressed as an Odds Ratio (OR). In addition, the ES was evaluated using the Random Effects Model (REM).

The Inconsistency Index (I^2) was used as an indication of heterogeneity. In systematic revisions, heterogeneity refers to the variability or differences among the studies in estimating the effect. I^2 allowed the percentage of variance to be calculated due to actual heterogeneity rather than chance. If the I^2 value is close to zero then the variance observed is due to chance but if the I^2 value is high, the variance is attributable to several factors requiring further investigation.

Publication bias was evaluated using funnel plots and by calculating standard errors.

All statistical measures mentioned above were calculated using "Comprehensive Meta-analysis 2.0" software.

RESULTS

The exposed group and the control group were found to be comparable in terms of age, sex, BMI, and smoking status. In fact, the number of males in the group of exposed workers was 386, while the number of females was 162. In the control group the number of males was 434, while the number of females was 245. The average age of cases was 42.4±7.18 years, while the average age of the controls was 41.77±5.43 years ($p > 0.05$). In the studies where it was specified i.e. [45,47,49], the percentage of smokers in the group of cases was 55.88%, while the percentage of smokers in the control group was 62.63%

($p > 0.05$). BMI, in the studies where it was specified [45,48], was lower among the cases than among the controls (23.06 ± 1.76 kg/m^2 vs. 23.88 ± 0.68 kg/m^2; $p < 0.05$).
As already indicated, the available data enabled a division into 3 classes:

– Prevalence of hypertension.
– Values of systolic arterial pressure.
– Values of diastolic arterial pressure.

Prevalence of hypertension

The prevalence of hypertension, evaluated in 5 studies (Table 2) on a total sample of 508 cases and 639 controls, was more significant in the subjects occupationally exposed to cadmium than in the control group (Log OR: 1.814; 95% CI: 1.030–3.196; $p = 0.039$, with a value of heterogeneity among the studies equal to I^2 0.00) (Figure 2).

Systolic arterial pressure

Systolic arterial pressure, evaluated in 6 studies (Table 2), on a total sample of 558 cases and 679 controls, was more significant in the subjects occupationally exposed to cadmium; the recorded mean systolic blood pressure was in fact higher than 2.325 mm Hg compared to the controls (95% CI: 0.948–3.702; $p = 0.001$, with a value of heterogeneity among the studies amounting to I^2 83.65) (Figure 3a). The standard error was 0.702. Log OR between the cases and controls was 4.217 (95% CI: 1.719–6.714; $p = 0.001$) (Figure 3b). The standard error was 1.274.

Diastolic arterial pressure

Diastolic arterial pressure, evaluated in 6 studies (Table 2), on a total sample of 558 cases and 679 controls, was more significant in the subjects occupationally exposed to cadmium; the recorded mean diastolic blood pressure was higher than 1.548 mm Hg in comparison with the controls (95% CI: 0.284–2.812; $p = 0.016$, with a value of heterogeneity among the studies amounting to I^2 55.501) (Figure 4a). The standard error was 0.645. Log OR between the cases and controls was 2.809 (95% CI: 0.516–5.101; $p = 0.016$) (Figure 4b). The standard error was 1.170.

DISCUSSION

Cadmium has been associated with cardiovascular disorders since 1950 [52]. Over the years, several studies have been conducted to clarify the role of this ubiquitous metal in the determination of cardio-circulatory disorders. Some studies in the past theorized that accumulation of cadmium in human body could produce an alteration in the metabolism of certain metabolites such as calcium, nickel, zinc [53], selenium and copper. More recently, other authors have demonstrated the influence of cadmium on kidney tissues resulting in the decrease of CYP4A11 and PPARs (peroxisome proliferator-activated receptors), with possible production of hypertension, sodium retention, glucose intolerance, dyslipidemia, and zinc depletion [54]. Other studies have shown that cadmium can cause a loss of molecules with vasodilating functions, such as nitric oxide [55], and it can also increase the effect of norepinephrine [56]. In conclusion, some other authors have demonstrated a cadmium-induced endothelial alteration, which would be mediated by an alteration in the functionality of the M1 acetylcholine receptors [57].
In fact, the endothelial-toxic role of cadmium, has been amply demonstrated by several studies which evidenced its marked role in the constitution of atherosclerotic plaques [58,59]. Atherosclerosis, therefore, could be an ulterior factor explaining the hypertensive potential of cadmium. Also determination of hypertension by cadmium in occupational environments could be explained by its accumulation in kidney tissues, which occurs more often in persons chronically exposed to the metal. In the exposed subjects, cadmium can, in fact, cause alterations in the tubular

Table 2. Distribution of the studies on prevalence of hypertension, systolic blood pressure, cadmiuria and cadmiemia

Grade	Studies (n)	References	Sample (n)	Result	Indices of meta-analysis		
					p	I^2(%)	ES (range)
Prevalence of hypertension	5	Poręba et al.,, 2010 [45]; Zhang et al., 1996 [48]; Thun et al., 1989 [49]; De Kort et al. 1987 [46]; Sandifer et al.,, 1979 [50]	GS: 508 GC: 639	increased in the exposed	0.039	0.00	OR = 1.814 (1.030–3.196)
Systolic pressure	6	Poręba et al., 2010 [45]; Zhang et al., 1996 [48]; Schuhmacher et al., 1994 [47]; Thun et al., 1989 [49]; De Kort et al., 1987 [46]; Sandifer et al., 1979 [50]	GS: 558 GC: 679	increased in the exposed	0.001	83.65	SMD = 2.325 (0.948–3.702)
Diastolic pressure	6	Poręba et al., 2010 [45]; Zhang et al., 1996 [48]; Schuhmacher et al., 1994 [47]; Thun et al., 1989 [49]; De Kort et al., 1987 [46]; Sandifer et al., 1979 [50]	GS: 558 GC: 679	increased in the exposed	0.016	55.501	SMD = 1.548 (0.248–2.812)
Cadmiuria	4	Zhang et al., 1996 [48]; Schuhmacher et al., 1994 [47]; Thun et al., 1989 [49]; De Kort et al., 1987 [46]	GS: 510 GC: 650	increased in the exposed	0.0001	15.98	SMD = 1.784 (1.281–2.286)
Cadmiemia	3	Poreba et al., 2010 [45]; Thun et al., 1989 [49]; De Kort et al., 1987 [46]	GS: 115 GC: 103	increased in the exposed	0.005	13.06	SMD = 2.153 (0.657–3.648)

GS – experimental group; GC – control group.
P – probability; I^2 – Index of inconsistency; ES – effect size.
SMD – standardized mean difference; OR – odds ratio.

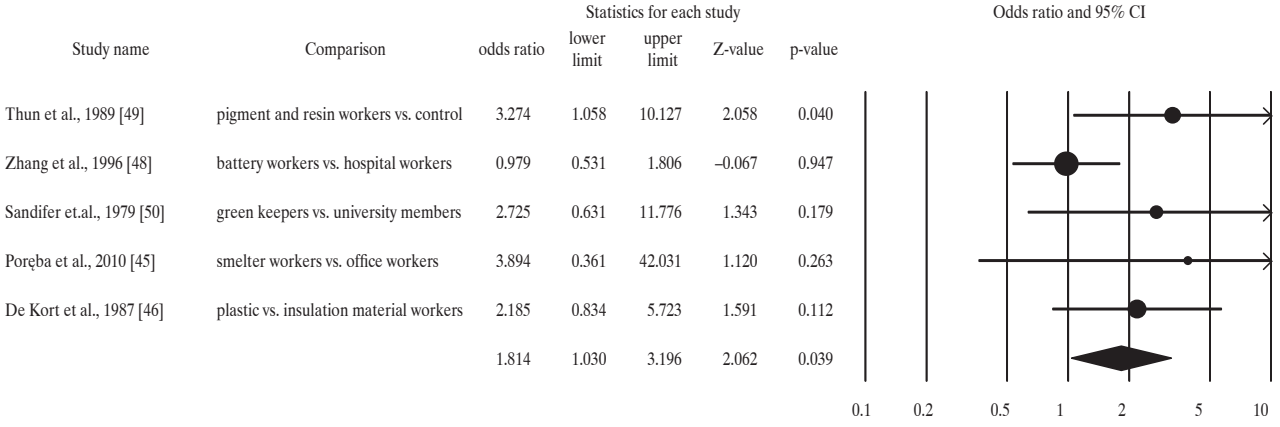
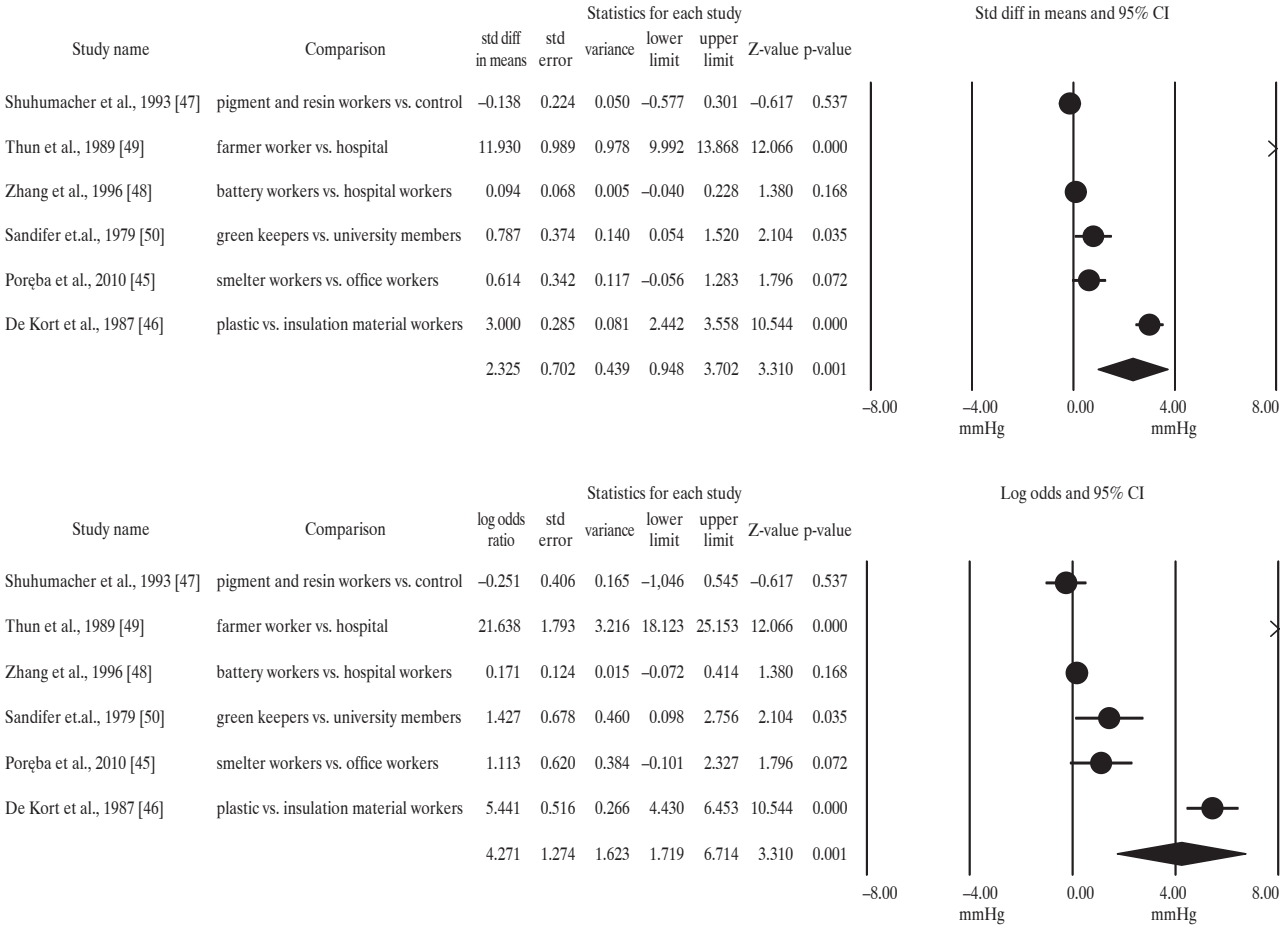
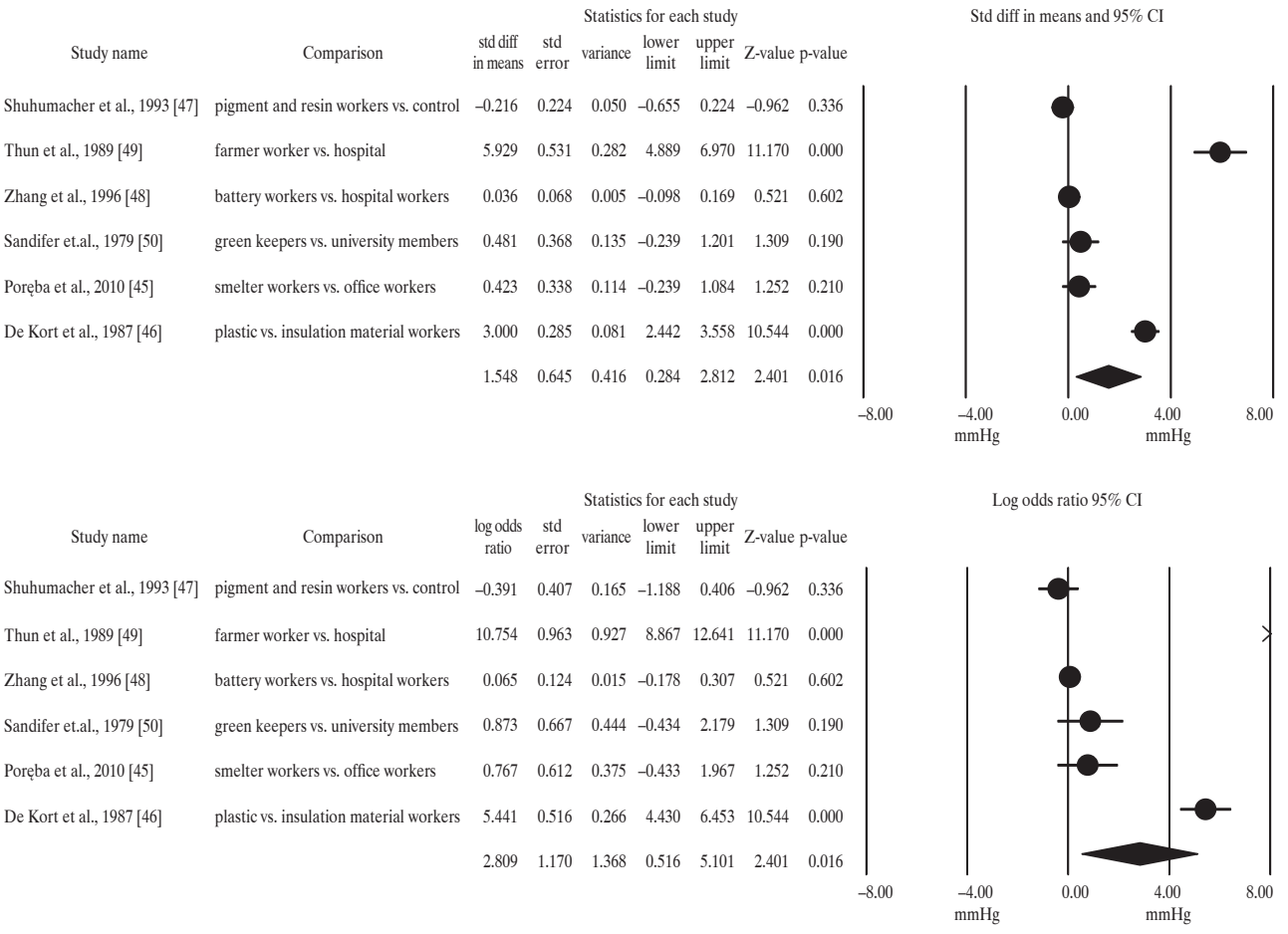


Fig. 2. Forest plot of hypertension Rate



a – standard difference in means.
b – Log odds ratio.

Fig. 3. Forest plot of systolic pressure



Abbreviations as in Figure 3.

Fig. 4. Forest plot of diastolic pressure

function, salt retention and volume overload [60]: all factors that could cause an increase in blood pressure.

Our study seems to confirm the observations previously expressed in many articles and studies conducted mainly on the general population. In occupationally exposed individuals, cadmium seems to induce an increase in systolic, diastolic and mean blood pressure, and an increase in the prevalence of hypertension.

In particular, a significant increase in systolic arterial pressure was reported in the workers with an ES of 2.325. Less marked, but still valid and statistically significant, is the increase in diastolic blood pressure in the exposed workers with an ES of 1.548. The Logarithmic Odds Ratio values (Log OR) confirmed and supported these findings, both for systolic blood pressure (4.217), as well as for diastolic blood pressure (2.809).

The prevalence of hypertension was stronger in the exposed individuals, with an OR of 1.825.

Cadmiuria and cadmiemia are surely excellent indexes of exposure, with an ES of 1.784 and of 2.153 respectively, and with an index of heterogeneity of 13.38 and of 13.06 respectively (Table 2). Both these two markers seem to be useful in the determination of exposure to cadmium, since they play different and complementary roles: cadmiuria is, in fact, an indicator of exposure when it is high and prolonged in time and it is an indicator of accumulation when the exposure is

modest [61]. Cadmiuria also increases in the presence of cadmium-induced nephropathy [61]. Cadmiemia, on the other hand, is an indicator of recent exposure (2–3 months), and is more sensitive in smokers [62]. Statistically significant increases, both in cadmiuria (1.12±0.24±0.15 vs. 0.62 μg/mg creatinine, $p = 0.01$) [46] (9.3±6.9 vs. 0.7±0.7 μg/g creatinine, $p < 0.0001$) [49] and in cadmiemia (1.32±0.32 vs. 0.54±0.17 μg/l, $p = 0.001$) [46] (7.9±2.0 vs. 1.2±2.0 μg/l, $p < 0.0001$) [49] were reported in the two studies in which the two markers were measured [46,49].

Potential limitations of this study should be obviously sought in the lack of the controlled studies concerning the evaluation of chronic effects on the cardio-circulatory apparatus in the subjects occupationally exposed to cadmium and in the lack of systematic reviews on the topic. The poor number of articles concerning this subject necessitated the inclusion of a study that did not present sufficient data on the levels of cadmium. Nevertheless, the groups analyzed had been strictly selected according to their work history (greenkeepers vs. employees and members of the Faculty of Medicine of South Caroline).

For the same reason, a study that analyzed groups of workers who were exposed to heavy metals including cadmium, manganese and lead, another element known for its capacity to increase blood pressure, was included in the meta analysis. In this study, however, the group of 171 exposed workers was divided into subgroups according to the levels of metal found in their blood. For the meta-analysis, only the subgroup of workers who had blood cadmium levels above the median (1.93 mg/l) and levels of lead and manganese below the median were selected. In this subgroup the values of ALA-U (urine concentration or delta-Aminolevulenic acid) and FEP-E (protoporpyrin free erythrocyte concentration) were low, showing that the exposure of these subjects to lead and manganese was less relevant.

The heterogeneity shown in the studies is another possible limitation of our study. The I^2 turned out to be very high with respect to the "systolic blood pressure" variables (I^2: 83.65). The heterogeneity probably results from the lack of homogeneity in the number of cases and controls in some of the analyzed studies. Another possible cause of the high heterogeneity found in the "systolic blood pressure" classes is probably the highly significant difference in the number of the studied subjects. The studies involving a greater number of case and control groups could play a more important role in the final statistical analysis than the studies with fewer groups. Adopting the "random" method in the evaluation of SMD, has, however, partially corrected this issue, balancing the weight given to each study. In fact, the index of inconsistency in the analysis of the prevalence of hypertension and in the analysis of cadmiemia was found to be zero (I^2: 0.00).

The final, possible limitation of our research is the fact that some of the studies did not include important variables such as smoking status, BMI, cadmiuria and cadmiemia. Therefore, it was not possible to include this data in the statistical analysis and to assess how these variables could have influenced blood pressure in the groups of cases and controls. However, it's possible to imagine how, even a minimal smoking habit may have influenced blood pressure; the case and control groups have in fact similar percentages of smokers. Additionally, it was not possible to operate the stratification based on the values of cadmiuria or cadmiemia, since the analyzed studies did not provide such analyses.

The groups selected for the studies were substantially comparable in terms of age (42.4±7.18 in the cases and 41.77±5.43 in the controls), percentage of smokers (57 out of 102 in the cases: 55.88%; 57 out of 91 in the controls: 62.63%), and sex. All this contributes to the validity of the study by eliminating potential misleading factors. Another positive aspect is the low standard error reported in the available studies.

Our meta-analysis, therefore, is useful for establishing the role of cadmium in the determination of hypertension in the occupationally exposed subjects. As regards the exact physiopathology of the metal in hypertension induction, there is still a lot to be clarified.

CONCLUSION

Cadmium causes a distinct increase in systolic pressure and a more modest increase in diastolic blood pressure in subjects exposed as part of their occupation. Moreover, it causes an increase in the prevalence of hypertension.

Cadmiuria would seem to be an excellent index of chronic exposure to cadmium, while cadmiemia is less reliable for mid-long term exposure.

However, once again, it should be emphasized that cardiovascular disorders associated with exposure to cadmium in the workplace have not been extensively studied. Many studies have been conducted on the general population and the few studies available have different types of limitations such as small control groups. Consequently, it would be advisable to conduct a more extensive case-control study on this topic, also taking into account other cardiovascular parameters such as electrocardiogram – ECG, heart rate, eco-cardiographic parameters and other instrument tests, in order to more carefully analyze the effect of cadmium on cardio-circulatory functions in occupationally-exposed subjects.

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