Blood lead levels and cognitive functioning: A meta-analysis

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Accepted for publication at the journal *Science of the Total Environment*.

The final version is available at https://doi.org/10.1016/j.scitotenv.2019.03.052.

1. Introduction

Adverse effects of environmental and occupational heavy metal exposure are a constant public health concern. Particularly lead (Latin plumbum, Pb) and its biological effects have been a major research focus over the last decades. Due to their favorable physical properties, lead compounds are still used in various industrial processes (battery production, refining, smelting, etc.) resulting in environmental accumulation despite the already well-known health-related hazards. Lead is most commonly introduced into the human body through the respiratory and digestive systems, and, once in the bloodstream, has a biological half-life of approximately 30 days. In the circulation, lead is mainly bound to red blood cells, distributed into soft tissues and accumulates in bones, where it can remain for 20-30 years: during processes leading to bone matter turnover, the deposited lead is again released into the circulating blood (Mason et al., 2014). Thus, blood levels reflect not only recent and ongoing lead exposure but also mobilized lead from bones (Brito et al., 2005).

Human exposure to lead has been associated with increased mortality and dysfunction of various organ systems (e.g., anemia, renal disease, cardiovascular disease and hypertension) (Rosin, 2009). The nervous system is particularly sensitive to lead toxicity (Wani et al., 2015). The neurotoxicity of lead can be attributed to direct (e.g., disruption of neurotransmitter functions) and indirect (e.g., interference with supporting organ systems) effects on the nervous system (Mason et al., 2014). Neuropsychiatric disorders following severe lead poisoning are well described; however, even at lower exposure doses neurotoxic effects seem to occur, making a safe threshold for lead uncertain (Vorvolakos et al., 2016). Reduced cognitive abilities and neurobehavioral performance have been associated with occupational and environmental lead exposure (Meyer-Baron et al., 2000; Rosin, 2009). The adverse effects on cognitive performance might, however, be potentially reversible after prolonged abstinence from exposure (Winker et al., 2005). In this regard, blood lead levels are more suitable for direct biomonitoring and the detection of feasible effect thresholds in occupational exposure settings than, for example, bone lead.

A study in 2002 summarized two meta-analyses to identify adverse effects of elevated blood lead and found subtle neurocognitive deficits associated with blood levels between 37 and 52 µg/dl (Seeber et al., 2002). The study concluded that the results of both meta-analytical reviews support the

recommendations of the German Biological Exposure Index (BEI). It remained unclear, however, whether much lower concentrations of blood lead can also lead to cognitive neurobehavioral effects (Seeber et al., 2002). To our knowledge, no meta-analysis has recently summarized the current status quo in this area of research. Moreover, the importance of evaluating lead exposure and its impact on specific cognitive functions instead of general cognitive effects has been highlighted (Mason et al., 2014). Thus, the objectives of this paper were 1) to identify relationships between blood lead concentration and neurocognitive deficits, and 2) to evaluate whether recommendations regarding safe lead exposure levels can be derived from the current evidence.

2. Materials and methods

2.1. Search patterns online data base

We conducted a systematic literature search in PubMed, Medline, PsycINFO, PsycARTICLES and PsycNET, which were chosen for their great variety of clinical studies. We used the combinations "lead"[MeSH Terms] OR "lead"[All Fields] AND ("exposure"[MeSH Terms] OR "exposure"[All Fields]) AND ("cognition"[MeSH Terms] OR ("cognition"[All Fields] AND "health"[All Fields]) OR "cognitive health"[All Fields]). Also the combination ("lead"[MeSH Terms] OR "lead"[All Fields] AND ("exposure"[MeSH Terms] OR "exposure"[All Fields]) AND ("cognitive disorders"[MeSH Terms] OR ("cognitive"[All Fields] AND "disorders"[All Fields]) OR "cognition disorders"[All Fields] and the combination ("lead"[MeSH Terms] OR "lead"[All Fields] AND ("exposure"[MeSH Terms] OR "exposure"[All Fields]) AND ("neurocognition"[MeSH Terms] OR "neurocognition"[All Fields]) were used. The terms ("lead"[MeSH Terms] OR "lead"[All Fields] AND ("exposure"[MeSH Terms] OR "exposure"[All Fields]) AND ("neurocognitive"[MeSH Terms] OR ("neurocognitive"[All Fields] AND "disorders"[All Fields]) OR "neurocognitive disorders"[All Fields] OR ("cognitive"[All Fields] AND "functioning"[All Fields]) OR "cognitive functioning"[All Fields]) were also used.

2.2. Selection criteria

We considered all articles published before September 2018 that examined the effect of lead exposure on cognitive functioning and met the following conditions: (a) The study adopted either a quasi-experimental research design that compared participants exposed to high levels of lead in their daily lives to a control group, or a correlational design that reported the association between the degree

of lead exposure and cognitive abilities. (b) The study reported the sample size and appropriate statistics to calculate an effect size. (c) The study administered at least one of the following measures of cognitive performance:

- *Similarities* is a core *Verbal Comprehension* subtest of the Wechsler Adult Intelligence Scale (WAIS) test that measures verbal concept formation and verbal reasoning. Subjects are asked to indicate how apparently different words are in fact similar to each other. The number of correctly identified similarities is the response variable (Wechsler, 2008).
- *Block Design* for the assessment of visuospatial and visual-motor skills as well as nonverbal concept formation and reasoning is a core *Perceptual Reasoning* subtest of the WAIS. It requires subjects to arrange colored blocks in a certain pattern. The number of correctly reproduced patterns is the response variable (Wechsler, 2008).
- *Picture Completion* is a supplemental *Perceptual Reasoning* subtest of the WAIS and measures perceptual organisation. The subjects are presented with small pictures missing a vital detail that has to be identified. The number of correctly identified errors is the response variable (Wechsler, 2008).
- *Digit Span* is a core *Working Memory* subtest of the WAIS and consists of three versions: *Digit Span Forward, Digit Span Backward* and *Digit Span Sequencing*. *Digit Span Forward* measures memory, attention and encoding, whereas *Digit Span Backwards* and *Digit Span Sequencing* focus on working memory and mental manipulation. The subjects are read several pairs of number sequences, that are repeated by the participant in the same, reversed or ascending order, depending on the version of the test. The maximum number of correctly repeated numbers represents the subjects' response score (Wechsler, 2008).
- *Coding* is a core *Processing Speed* subtest of the WAIS measuring processing speed and additionally attention, perceptual speed, visual scanning as well as visuomotor speed. The subjects have to quickly match a sequence of numbers with a sequence of symbols on a page. The number of correctly matched pairs within a time-frame represents a subjects' response variable (Wechsler, 2008).

- *Simple Reaction Time Task* measures subjects' attention as indicated by their reaction times to various visual stimuli (e.g. a red light on a screen). The mean response time (in ms) to these stimuli represents the response variable (Cassito et al., 1990).
- The *Santa Ana* test measures manual dexterity by having subjects rotate pegs on a rectangular board. The number of correctly rotated pegs is noted as the response variable (Fleishman, 1954).

2.3. Study selection

After applying the word combination listed in section 2.1. a total of 3872 studies were identified via the systematic literature search of the online database. 3347 studies were excluded during the selection process due to the elimination of titles and abstracts that did not match the aim of the present meta-analysis. In addition, 503 studies needed to be excluded from further analysis, because they failed to meet the criteria cited in section 2.2. Overall a total of 22 studies were included in the meta-analytical procedure (see Fig. 1).

2.4 Meta-analytic procedure

The unbiased standardized mean difference *g* was selected as the effect size for the meta-analysis. Compared to Cohen's *d* the estimator *g* is less biased, particularly in small samples, and leads to more precise estimates of the true effect (Hedges, 1981). For studies that did not report the appropriate sample statistics to compute *g*, we applied transformation formulas to transform correlation coefficients into *g* (Borenstein, 2009). Effect sizes were calculated in such a way that positive values indicate larger cognitive scores in the control group and negative values indicate larger scores in the lead exposure group. Moreover, the effect sizes for the reaction time tasks were reverse coded. As a consequence, for all cognitive measures positive values indicate better cognitive abilities in the control group. Corrections of the effect sizes with regard to unreliability could not be applied as none of the primary studies reported relevant information; hence, all of the effect sizes are uncorrected. Outliers in the effects sizes were identified using Cook's distance and discarded for the analyses (Viechtbauer and Cheung, 2010).

The average study effects were calculated with the software *metafor* using a random-effects model with a restricted maximum likelihood estimator (Viechtbauer, 2005; Viechtbauer, 2010). Because most studies provided more than one effect size (e.g., obtained for different cognitive

outcomes) the meta-analysis was formulated as a three-level model (Cheung, 2014). Three-level meta-analyses acknowledge dependencies between effect sizes stemming from the same sample by splitting the total random variance into two variance components. The random level-2 variance $\tau^2_{(2)}$ reflects the heterogeneity of effects within samples (e.g., due to different cognitive measures), whereas the random level-3 variance $\tau^2_{(3)}$ indicates the heterogeneity of effect sizes between samples. The heterogeneity in observed effect sizes was quantified with the I^2 index, which indicates the percentage of the total variance in observed effects due to random variance (Higgins et al., 2003). According to prevalent rules of thumb, I^2 of .25, .50, and .75 indicate low, medium and high heterogeneity, respectively. In addition, the homogeneity of effects was tested using the *Q* statistic (Cochran, 1954). Moderating effects on the pooled effect size were examined using weighted, mixed-effects regression analyses (López-López et al., 2014).

3. Results

We identified 22 articles (see Table 1) published between 1976 and 2014 that studied the effects of lead exposure on cognitive and sensorimotor parameters: verbal abilities, visuospatial abilities, memory, attention or psychomotor function. The studies included a total of 3,849 participants with a median sample size of *N*= 83 (*Min*= 28, *Max*= 938). The reported mean age of the samples was *M* = 39.94 (*SD* = 7.87) years. Due to missing information about lead exposure in the separated groups, only 13 out of the 22 studies (59.1%) were included when estimating the average lead exposure level in subjects. While the experimental group reported mean blood levels of 34.08 µg/dl (SD= 13.63, Mdn= 32.3), the control group showed an average of 12.18 µg/dl (SD= 7.19, Mdn= 11.9). On average, lead exposure was 21.09 µg/dl (*SD* = 6.44, *Min* = 0.70, *Max* = 33.00) higher in the experimental group than in the control group. Altogether, the studies reported 76 effect sizes. However, two effect sizes were identified as outliers and excluded from further analyses (Chia et al., 1997).

One effect (*g* = 10.19) was over seven times larger than the largest remaining effect size (*g* = 1.43), whereas the other was the largest negative effect in the database (*g* = -0.32). The random-effects three-level meta-analysis across the remaining effect sizes identified a significant ($p < .001$) pooled mean difference between the lead exposure group and the control group of $\Delta = 0.26$, *SE* = 0.05, 95% CI [0.17, 0.35]. However, there was significant heterogeneity between the effect sizes, $Q(df = 73)$

=177.43, $p < 001$. The respective random level 2 variance, $\tau^2_{(2)} = 0.02$ that reflects the heterogeneity in effect sizes within samples (i.e., stemming from different cognitive measures) was significant, $p = .01$, albeit rather small, $I^2_{(2)} = .22$.

Thus, the different cognitive outcomes did not exhibit markedly different effects. Similarly, the random level 3 variance, $\tau^2_{(2)} = 0.02$, $p = .01$, indicated only moderate heterogeneity in effect sizes between samples, $I^2_{(3)} = .33$. To study the observed heterogeneity in more detail we conducted two forms of sensitivity analyses. First, we repeated the meta-analysis and estimated different intercepts for each cognitive measure (see Table 2).

The respective results are summarized in Fig. 2. These analyses showed that the confidence intervals that give the precision of the estimated population effects overlapped with the average mean effect for most cognitive measures. Thus, lead exposure did not result in markedly different effects across the examined outcomes. Only the digit symbol test exhibited a significantly ($p < .05$) smaller effect, $\Delta = 0.12$, $SE = 0.06$, 95% CI [0.01, 0.23]. However, the respective effect remained significantly ($p = .04$) greater than 0.

3.1. Verbal abilities

Significant differences were found in the context of the core subtest *Similarities* ($\Delta = 0.33$, $p < .001$). This result reflects that the control group achieved significantly higher scores than the experimental group in verbal concept formation as well as verbal reasoning, the cognitive components of verbal comprehension upon which the correct identification of similarities is based.

3.2. Visuospatial abilities

The results of the core subtest *Block Design* ($\Delta = 0.27$, $p < .05$) as well as the supplemental test *Picture Completion* ($\Delta = 0.30$, $p < .05$) showed significant differences between subjects with higher and lower blood lead levels. Therefore it can be stated that subjects with higher lead exposure performed less well in tasks based on visuospatial abilities than the control group.

3.3. Memory

Our meta-analytic results showed significant differences between the experimental and control group in the core subtest *Digit Span* ($\Delta = 0.34$, $p < .001$). This reveals that subjects with higher lead

exposure achieved a lower maximum of correctly repeated numbers than the control group with lower blood lead levels, implying reduced performance memory.

3.4. Attention

Although the core subtest *Coding* stated a significantly smaller effect size in comparison to the remaining ones, we found significant differences between the experimental and control groups. (Δ= 0.12, p= .037). Hence it can be pointed out that subjects with lower blood lead levels exhibited higher perfomance levels in processing speed, visual scanning and visomotor speed than the experimental group. In addition to the framework of processing speed, the results of the *Simple Reaction Time Test* (Δ= 0.35, p < .001) revealed significant performance differences between the experimental and control groups. Thus it can be demonstrated that subjects with higher lead exposure recorded higher reaction times during the task, reflecting lower scores in terms of vigilance and attentional capacity than their control group.

3.5. Psychomotor function

The *Santa Ana* (Δ= 0.32, p < .001) resulted in significant differences between the experimental and control groups regarding the number of correctly rotated pegs. Subjects with lower blood lead levels thus recorded higher psychomotor performance in tasks based on manual dexterity than subjects with higher blood lead levels.

3.6. Potential threshold

We tried to identify potential thresholds of lead exposure that might result in pronounced cognitive impairments, and therefore added the difference in lead exposure levels between the control and exposure groups to our model as a moderator. Because some studies neglected to report this information, these analyses are based on 49 effect sizes from 13 samples. This identified a marginally significant (p = .06) effect of exposure level, B = 0.01, SE = 0.00, 95% CI [-0.00, 0.02]. A difference of about 10 µg/dl in lead exposure translated into a decline in cognitive abilities of Δ= 0.09 (see Fig. 3).

4. Discussion

The results of our meta-analysis show that higher blood lead concentrations are associated with poorer neurocognitive performance with regard to verbal abilities, visuospatial abilities, memory,

attention and psychomotor function. We identified a significant ($p < .001$) difference in performance between subjects from lead exposed and control groups; thus, subjects with higher blood lead concentrations due to lead exposure achieved lower neurocognitive performance scores on average than controls. Meta-analytic results showed significant differences regarding performance in the *Block Design* test and the *Santa Ana* test due to blood lead levels (Meyer-Baron et al., 2000). The findings of our study are consistent with the significant differences in these two tests, clearly outlining lower visuospatial abilities as well as manual dexterity in subjects with higher blood lead levels. Schwartz et al. (2007) came to the same conclusion by linking former lead exposure to reduced cognitive function, especially to the fields of visuospatial abilities, processing speed and eye-hand-coordination. Additionally they found out that lower cognitive performance was associated with smaller volumes of the relevant brain areas. Visuospatial function was associated with decreased volumes in frontal-parietal-occipital regions, while processing speed was associated with reduced volumes in different regions, e.g. frontal, parietal, and occipital. Impaired psychomotor functioning was associated with reduced brain volumes in the insula and the corpus callosum. Hence lead may influence cognitive functioning by reducing the volume of relevant brain regions. The results of a meta-analytical summary of showed only slight but reproducible associations between lead exposure and impairments in memory function, attention, visuospatial information processing and psychomotoric functions (Seeber et al., 2002). Our meta-analytic findings provide further evidence for the negative effects of lead on these neurocognitive functions while also taking significantly impaired verbal abilities into account.

A recent study came to the same conclusion as we do by associating deficits in working memory and attention to lead exposure. Furthermore, they showed that impairment of working memory is connected to reduced activity in the prefrontal cortex, especially in terms of performance of the dorsolateral prefrontal cortex and the ventrolateral prefrontal cortex in lead-exposed workers. In addition, attention impairment was associated with decreased activity in the right hemisphere of the posterior parietal cortex. Lead exposure therefore seems to have a considerable impact on the frontoparietal brain network, resulting in impaired performance of working memory as well as reduced sustainability of attention (Seo et al., 2014).

As a potential underlying pathomechanism in brain, the toxic impact of metal ions interacting with NMDA receptor can be stated to cause neuronal damage to the hippocampus (Karri et al., 2016). Lead is seen to be a main disruptor of the mechanism of Ca^{+2} ion signaling, resulting in a dysregulation of Ca^{+2}-sensitive paths in the hippocampal region. On a synaptical basis, lead interacts with the NDMA receptor by blocking its function and therefore inhibiting Ca^{+2} dependent processes that are linked to reduced neuronal plasticity and long-term potentiation dysfunction. In contrast, in relation to the extra-synaptical pathway, lead enhances the expression of Ca^{+2} and phospholipase-C, followed by a higher production of reactive oxygen species and decreased expression of antioxidants. From this neurotransmatic imbalance, neuronal cell death is caused, which is linked to cognitive dysfunction (Karri et al., 2016). Our results are consistent with these findings, outlining a clear association of blood lead with neurocognitive performance.

Concerning a threshold for lead exposure resulting in cognitive impairments, we were methodologically limited due to the low number of eligible samples. The respective regression model therefore did not reach sufficient statistical power and a significant effect of exposure level could not be identified. Regarding the limited effect sizes given, we would therefore highly recommend the replication of the analyses when a larger body of effects is available. With regard to the recommendation of potential thresholds, it of course should be noted that there are a number of confounding variables which must be taken into account. For future studies it is essential, in order to define a concrete limit value for cognitive impairments due to lead, to include the following characteristics. The difference in lead exposure levels between the control and experimental groups should be mentioned. Regarding our own analysis, only 49 out of 76 (64.5%) effect sizes could be taken into account when estimating potential thresholds because of missing data. This lack of information may be caused by the usage of heterogenic measurements for lead exposure. Therefore we recommend the uniform utilization of a measurement with which lead exposure is estimated. In addition, we encountered a great variety of methods used for measuring specific neurocognitive abilities. Thus a more homogenous deployment of measurement methods is suggested.

Regarding the limitations of our study, the well-known publication bias has to be considered (Coburn and Vevea, 2015). Scientific investigations that do not find any significant results often fail to

be published. Our results can thus be affected in that we might inevitably be overestimating the effects of lead exposure on cognitive performance. Furthermore, the complex nature of the effects of lead on human beings has to be mentioned. The majority of studies use current blood levels, resulting in a mere determination of acute lead effects. Hence our findings do not allow a distinction to be drawn between acute and chronic effects of lead. As a consequence, the possible effects of reversibility have to be taken into consideration when interpreting our results.

5. Conclusion

Our findings provide evidence that, occupational and environmental lead exposure significantly impairs cognitive performance and sensorimotor functioning in adults. However due to the previously discussed limitations of data, estimations of a distinct significant threshold of exposure level followed by a decline in neurocognitive abilities were restricted. Based on this, we recommend the homogenous use of measurement methods, not only for lead levels but also for neurocognitive performance. Additionally, further studies clearly outlining differences in blood lead levels, time since abstinence and information about chronic exposure to lead would be desirable for the deduction of feasible exposure thresholds in the field of occupational health and safety.

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Table 1.

Study Characteristics

Study	*N* (exposure)	*N* (control)	Age[a]	Research design	Exposure[b]	Number of effect sizes	Effect size[c]
1. Araki et al. (1986)	16	12	47	quasi-experimental	30.00	3	0.51
2. Asa-Mäkitaipale (2009)	20	48	54	quasi-experimental	-	5	0.12
3. Barth et al. (2002)	47	53	40	quasi-experimental	26.48	3	0.23
4. Bolla et al. (1995)	190	52	45	quasi-experimental	-	3	0.18
5. Braun et al. (1991)	41	37	36	quasi-experimental	-	1	0.46
6. Campara et al. (1984)	20	20	39	quasi-experimental	21.55	12	0.35
7. Chia et al. (1997)	50	97	35	quasi-experimental	31.00	3	3.47
8. Haenninen et al. (1978)	49	24	34	quasi-experimental	20.40	6	0.25
9. Hänninen et al. (1998)		54	42	correlational	-	4	0.54
10. Hogstedt et al. (1983)	49	27	48	quasi-experimental	-	3	0.29
11. Jeyaratnam et al. (1986)	49	36	27	quasi-experimental	-	4	0.63
12. Lindgren et al. (2003)	40	40	48	quasi-experimental	13.50	2	-0.01
13. Maizlish et al. (1995)	43	45	35	quasi-experimental	27.00	4	-0.06
14. Milburn et al. (1976)	16	15	43	quasi-experimental	33.00	1	-0.11
15. Parkinson et al. (1986)	288	181	36	quasi-experimental	32.90	5	-0.02
16. Payton et al. (1998)		141	67	correlational	-	1	0.19
17. Schwartz et al. (2001)	803	135	40	quasi-experimental	25.70	3	0.45
18. Seo et al. (2014)	31	65	60	quasi-experimental	-	1	0.47
19. Stokes et al. (1998)	257	276	24	quasi-experimental	1.30	3	0.14
20. Valciukas et al. (1978)	89	25	43	quasi-experimental	-	3	0.57
21. Winker et al. (2005)	48	276	40	quasi-experimental	0.70	3	0.10
22. Winker et al. (2006)	47	28	40	quasi-experimental	25.30	3	0.23

[a]Mean age in years

[b]Differences in lead exposure in µg/dl between exposure and control groups

[c]Average effect size within the sample

Table 2.

Meta-Analysis on the Effects of Lead Exposure on Cognitive Abilities. 74 effect sizes from 22 samples

	Δ	*SE*	*z*	95% CI
Similarities	0.33	0.09	3.48*	[0.14, 0.51]
Block Design	0.27	0.07	3.96*	[0.14, 0.41]
Picture Completion	0.30	0.06	4.74*	[0.18, 0.43]
Digit Span	0.34	0.07	4.86*	[0.20, 0.48]
Coding	0.12	0.06	2.09*	[0.01, 0.23]
Simple Reaction Time	0.35	0.10	3.68*	[0.16, 0.54]
Santa Ana	0.32	0.09	3.52*	[0.14, 0.49]

Δ Estimated parameter, *SE* Standard error of Δ; A positive effect size indicates larger values in the control group; a negative effect indicates a higher value in the lead exposure group; effects for simple reaction tasks were reverse coded.

* $p < .05$

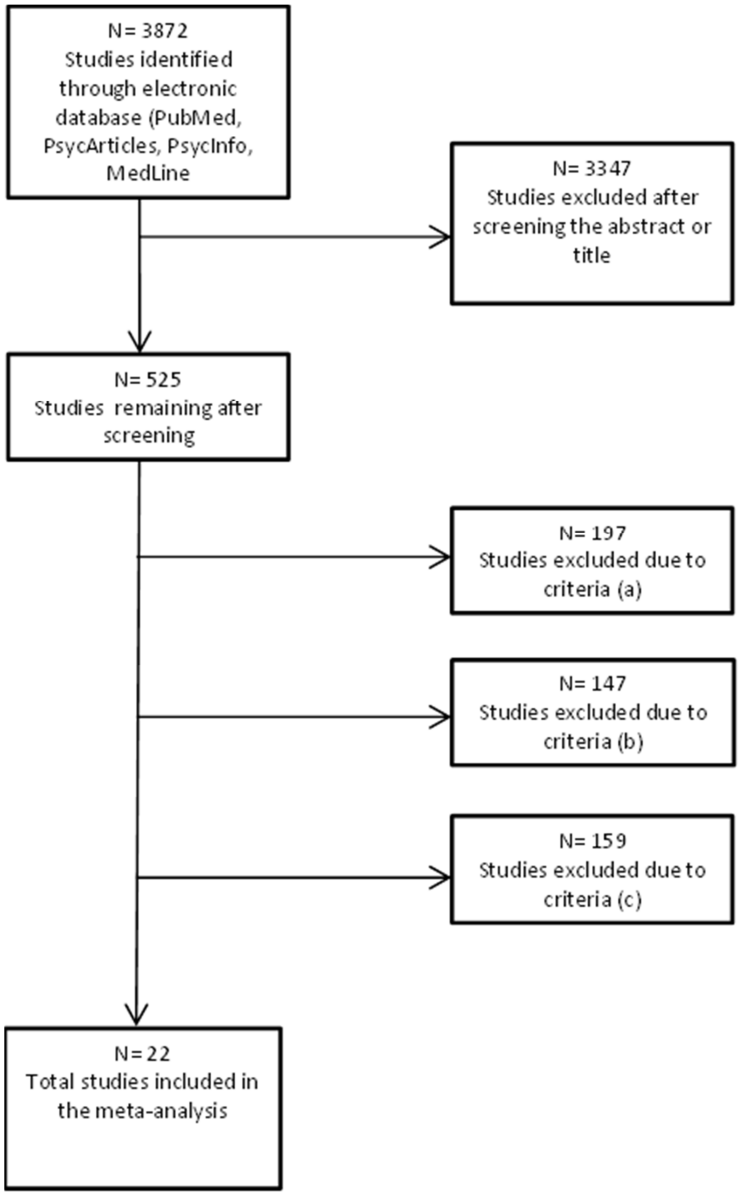

Figure 1. Study selection process

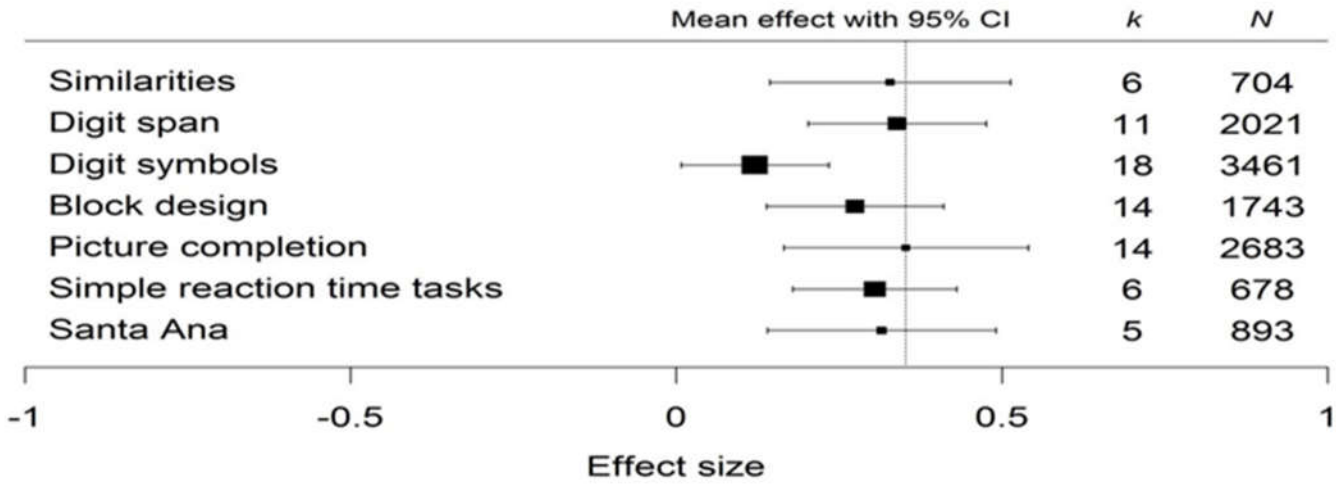

Figure 2. Pooled effects by cognitive abilities with confidence intervals (the size of the symbols are proportional to the precision). k = number of effect sizes N = sample size.

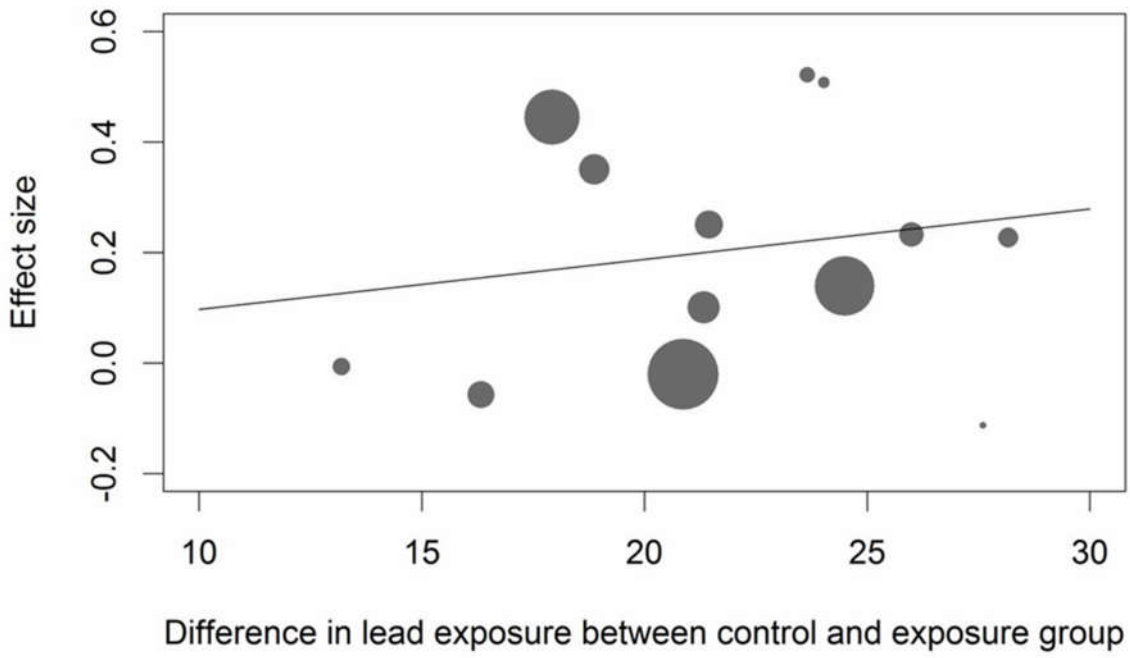

Figure 3. Difference in lead exposure between control and exposure group