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Neuropsychological impairment from manganese at contemporary occupational exposure levels: a meta-analysis

Submitted by: Michael Pysklywec MD MSc CCFP (EM) DOHS

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Introduction

Manganese is associated with significant neurological effects such as a Parkinsonian-like disorder (17, 46, 58) and manganism (34, 58), particularly with high exposure to manganese. Contemporary exposures to manganese are unlikely to cause such disorders. However, it has been postulated that the low-level exposures are associated with more subtle neurological health consequences. Neuropsychological testing has been increasing used to examine for neurological impairment in manganese-exposed workers.

Manganese is a common alloying agent in most steels. Welding or burning of steel vaporizes heavy metal molecules allowing for increased inhalation and absorption of toxins, such as manganese. Given the millions of welders worldwide, the potential burden of disease is high given the shear numbers of exposed individuals.

Neuropsychological testing is being used increasingly in toxicology to assess for subtle neurological effects. Such testing uses relatively reliable techniques to assess a wide variety of functional domains including attention, memory, motor function, visuospatial function and language. However, the use of such tests results in methodological issues. There are a multitude of different test batteries and little consistency as to which battery is employed. Despite relative reliability, testing protocol may affect results. The high sensitivity of the testing is offset by lower specificity. Multiple confounders such as age and psychiatric disease may affect results.

Meta-analysis has recently and increasingly been used to examine numerous studies of neuropsychological outcomes. This technique is appealing given that the subtle abnormalities of testing may not demonstrate an apparent difference in one study. As well, one may look for consistency in impairment of specific domains across studies. This technique has summarized neurobehavioural impairment in head injury (6, 21), psychiatric disease (26, 53), substance abuse (24) and other medical conditions (2, 19, 48).

Beyond this, meta-analysis has been used for neuropsychological outcomes for toxin-exposed workers. As toxicological awareness and engineering improvements continue, exposure to toxins continues to decrease. It is less likely that the obvious health effects (e.g. manganism, asbestosis) of the past will be seen. Increasing reliance has been placed on more sensitive measures, such as neuropsychological assessment. The need to synthesize the results of neuropsychological studies suggests that meta-analyses of neuropsychological studies will be increasingly useful.

This has included meta-analyses of lead (23, 43, 54, 65), mercury (41, 42, 52), manganese (33) and styrene (5). In particular, numerous meta-analyses of lead have shown disparate findings indicating the limitations of this technique. Two recent meta-analyses have been published by the same group in the United States (24(a), 33). These reviews conclude that there is no clear neuropsychological effect from Mn. However methodologic limitations render their results questionable (see discussion). Despite these publications, there remains the need for an even-handed, contemporary meta-anlaysis on the neurocognitive effects of Mn.

Numerous studies have been published in the past 20 years examining the neuropsychological function of manganese workers. Results are conflicting. Most studies show impairment of some tests measures in exposed workers, but this may occur by chance. It is not clear that a specific cognitive domain is being targeted by manganese toxicity. The application of meta-analysis may address these issues.

Thus, the objective of this paper was two-fold. Firstly a meta-analysis was performed on the neuropsychological consequences of contemporary occupation manganese exposure. Secondly, the methodological issues of applying meta-analytic techniques to toxin-induced neuropsychological studies were discussed.

Methods

Medline, Embase and NIOSH-TIC databases were searched for any article with a keyword of "manganese" and ("neuropsychological" or "neurobehavioural" or "neurobehavioral"). The references of each article were scanned for additional studies. Science Citation Index was used to find further publications that had cited obtained studies.

For inclusion in meta-analysis, the studies had to meet the following criteria:

1. the study had to be published in a scientific journal,
2. the study group consisted of occupationally-exposed workers to manganese,
3. both a manganese-exposed group and a control group had to be considered,
4. exposure level had to be documented,
5. outcome of at least one objective neuropsychological measure (note: measures of symptom reporting were excluded) had to be documented, and
6. a mean outcome and a measure of its dispersion had to be included for each test result.

To look for the effects of contemporary manganese levels, only studies with a mean manganese exposure of *0.5 mg/m*^{3} were included in meta-analysis. This level was chosen as it approaches the ACGIH threshold limit value (TLV) of 0.2 mg/m^3 and represents a practical cut-off given literature reports.

Thirty potential studies were located in the literature. Of these, ten studies fulfilled the inclusion criteria (Table 1). In addition, three further studies were included in meta-regression analysis, as they fulfilled all inclusion criteria, aside from exposure limits. All study designs were cross-sectional. Table 2 indicates the reasons for exclusion for the additional 17 studies.

Geometric (as opposed to arithmetic) means of exposure was extracted as most studies reported only this measure. Average intensity of exposure (i.e. cumulative exposure divided by years worked) was used for exposure if available.

The Lucchini group published three studies (36, 37, 38) on the same population. Only the most recent of duplicated tests were included. For the Myers study (45), only exposure group 2 (exposure = 0.1 to 0.2 mg/m^3) was considered to best match the exposure scope of this report.

Quality Assessment

Quality assessment criteria were considered for this meta-analysis. However the application of a tool, such as the Newcastle-Ottawa Scale (60), did not significantly discriminate between any the studies. The constraints of the inclusion criteria seemed to minimize significant quality differences. Given the small number of included studies and the lack of discrimination, further analysis on study quality was not done.

For cohort designs and for neuropsychological studies in particular, comparability of the groups is essential and perhaps provides the best indication of quality of study. Table 3 indicates matching variables and comparative variables from the included studies. Four studies matched cohort and control by at least one variable. Most studies did not specifically match, but rather did a post-hoc reporting of the frequencies of important confounders in both groups. Age, education, alcohol and smoking were indicated for most studies. There was little indication of psychiatric conditions, head injuries or substance abuse amongst the groups, making it impossible to infer confounding by these important factors. A few studies demonstrated significant differences between cohort and control, notably the Myers study (education, smoking, alcohol) and Lucchini (education, vocabulary).

Consideration of outcomes

Outcomes were considered if they represented commonly used neuropsychological tests, suggesting a reasonable degree of objectivity and reliability. Symptom measures were excluded.

Some studies (15, 45, 62) reported "no difference" for parameters without providing means or standard deviations. In these cases the authors were contacted to provide missing information. None responded. Thus, effect sizes were assumed to be zero for such tests. When tests reported both dominant and non-dominant hand functioning, the average of the two was used. For multiple outcomes from the same test (e.g. multiple holes from tremormeter testing), the most commonly reported measure was used.

Given the inconsistency in tests across studies, individual tests are often aggregated into domains or constructs of neurobehavioural function. For example, tests such as finger tapping, thumb-finger sequencing and pegboard testing reflect a construct of motor function. This allows the meta-analyst to compress the number of outcomes from 50 to 100 specific tests to 5-15 cognitive domains.

Each test result was categorized as one of 6 neuropsychological constructs or domains as per the convention of Lezak (35). This convention was chosen given its relative frequency in the literature. The domains considered in this analysis and the tests assigned to each domain are indicated in Table 4. The limitations of this technique are acknowledged in that there is little agreement in defining domains of neuropsychological functioning and one test often measures numerous cognitive constructs.

Statistical methods

Effect size (Cohen's d) of each test in each study was calculated using Hedges g (25) as described in Appendix 1. Thus a standardized difference between exposed and controls for each test result. Effect sizes were determined such that a negative value indicated worse performance for exposed individuals.

The meta-analytic method of Hedges and Olkin (25) was used to determine a pooled effect size. The random effects model of DerSimonian and Laird (14) was used given the

heterogeneity of most studies and the conservative nature of this estimate. Heterogeneity was considered by the I^2 statistic (27, 28), a measure of the amount of variation between studies that is due to heterogeneity rather than chance. See Appendix 1 for a detailed description of the equations.

Sub-group analysis considered important confounders, such as education and occupation.

Dose-response relationships were investigated by plotting effect size versus average manganese exposure. Again, the effect sizes of tests from each domain within a study were averaged, so that there was only one effect size per domain per study. The use of each test from each study would violate the assumption of independence of regression analysis, as it is assumed that tests measuring the same domain within a study are dependent. Dose-response analysis considered additional studies (11, 49, 50) with exposures beyond that detailed in the exclusion criteria. One study was excluded (29) due to the extreme exposures in this group (> 62.5 mg/m^3). These manganese miners were felt to be significantly different from the workers of all other cohorts given their occupation and exposure.

Publication bias was assessed by consideration of funnel plot.

Results

Table 1 shows the characteristics of the ten included studies. The average manganese exposure was 0.18 mg/m^3 (range = 0.071 to 0.301 mg/m^3), just below the current ACGIH TLV of 0.2 mg/m^3. Most studies considered either manganese alloying or smelting facilities. In addition, there was one group of welders. These studies considered 39 different neuropsychological outcomes. Table 1 also indicates the number of tests performed in each

study (as judged by the criteria above) and the number of "positive" tests that were significant at a $p < 0.05$ significance level.

Meta-analysis of domains

The summary effect sizes for each domain are shown in Table 5. The forest plot for each domain is shown in Figure 1.

Manganese-exposed workers have slightly worse functioning for each of the six cognitive domains, compared with unexposed controls. All summary effect sizes are judged to be "small" as per the criteria put forth by Cohen (12). Only attention (E.S. = -0.14, 95% C.I. = -0.28 to 0), executive functioning (E.S. = -0.17, 95% C.I. = -0.33 to 0) and spatial ability (E.S. = -0.17, 95% C.I. = -0.31 to -0.03) were statistically significant at a 5% level.

Homogeneity was assessed by the I^2 statistic. Higgins et al (28) tentatively assigned adjectives of low, moderate and high heterogeneity to I^2 values of 25%, 50% and 75%, respectively. Looking at this data, there is considerable heterogeneity for most measures. Only language and spatial ability have heterogeneity that is less than moderate (both judged as 0%). This further justifies the use of random effects in meta-analysis.

Sub-group analysis

The study by Yuan et al (63) of manganese welders may contribute to heterogeneity in cognitive domains as this group examines a group of workers (welders) distinct from the other studies (alloying, smelting). It may be that welding develops hand-eye skills, leading to improved attention functioning, such as that of the reaction time test. To investigate the impact of this trade on results, a sub-group without the Yuan study was considered. Table 6 shows the

summary statistics of such. The magnitude of effect sizes has minimally changed. As would be expected, heterogeneity for attention and memory went down, although not appreciably. The I^2 statistic actually increased for motor and spatial domains. If one speculates that welding leads to improved skills, it would be expected that these domains would be similarly affected, but they clearly were not. Thus, it's not clear that the welding occupation of this group is responsible for heterogeneity.

There are many covariates that may potentially affect neuropsychological functioning. Examination of these cohorts showed educational disparities between exposed and controls in some studies, namely the Lucchini studies (36, 37, 38) and Myers study (45). Thus, these publications were excluded in a subgroup analysis. Table 7 shows the meta-analytic results of the remaining studies. There continues to be a small, albeit statistically insignificant, deficit in neuropsychological performance in manganese-exposed workers. Spatial functioning remains impaired without much change when excluding potentially-confounded studies. More significantly, both attention and motor performance have shifted considerably towards the null.

In removing the Myers and Lucchini studies, heterogeneity significantly decreased (Table 7 compared to Table 5). This was particularly true for the domains of attention (from I2 of 32.7% to 0%), executive function (44.7% to 26.4%), memory (70.7% to 0%) and motor function (64.4% to 20.4%). This suggests that these studies were measuring a slightly different effect.

Thus, it appears that the disparity in education levels between exposed and controls in these two groups is likely amplifying neuropsychological deficits in exposed workers.

Dose-response relationship

Figure 2 shows a plot of effect size versus average manganese exposure for all average effect sizes from all studies. This includes studies with exposure beyond that of the inclusion

cutoff of 0.5 mg/m3: Roels et al (50) with exposure of 0.94 mg/m^3, Roels et al (49) with exposure of 0.95 mg/m^3 and Chia et al (11) with exposure of 1.59 mg/m^3. Figure 3 shows similar plots for each domain separately and Table 8 shows the linear regression fit statistics for each of these plots.

There appears to be a consistent negative association between average manganese exposure and effect size. That is, increasing manganese exposure is associated with poorer neuropsychological performance. The domain of spatial ability (Figure 3.f) is particularly illustrative of this relationship. The slope of this relationship is -0.58 (95% C.I. = -0.26 to -0.90), with an R^2 of 0.724 ($p = 0.004$). This strongly suggests worsening spatial ability with increasing manganese exposure.

However, it is apparent from the plot that one point (Chia) has considerable influence on the plot. Considering regression diagnostics, the Cook's D for this point is 3.4 indicating considerable influence on the plot (exceeding the tradition cut-off $4/n = 0.5$). This suggests that one must be cautious in interpreting this data point, particularly given that this study looked at only 34 total patients.

The plots emphasize the appropriateness of the exposure cut-off criteria used in meta-analysis. By considering studies below 0.5 mg/m^3, a cluster of similarly exposed workers was examined in meta-analysis, while excluding 3 cohorts with relatively higher exposures. These plots further suggest the homogeneity of the studies used in meta-analysis.

From sub-group analysis, there was suggestion that the Myers and Lucchini studies may have been confounded by educational differences between exposed and control. Omitting these two studies from regression analysis, slightly improves the fit of a number of these regressions, particularly the motor function-exposure and memory-exposure relationships (not shown).

Publication bias

Figure 4 shows a funnel plot of the average effect sizes. There is a clear lack of small, "negative" studies in the bottom right of the funnel. This suggests some element of publication bias, whereby small studies with "negative" results are not being published. Given the small pooled effect sizes, correction of this bias would most likely shift results to the null.

Discussion

There appears to be a slight impairment in neuropsychological performance in manganese workers compared to controls. All domains showed similar levels of effect, although only half of these were statistically significant. Cohen (12) considers such effect sizes to be "small", i.e. noticeably smaller than what is visible to the naked eye, but "not so small to be trivial". In quantitative terms, the typical effect of manganese on neuropsychological function is 15% of the standard deviation of means of the test.

There was impairment in all six functional domains. Such broad neurological toxicity is somewhat unusual, particularly at low levels. One might expect early neurological effects to be isolated to a few domains. However, spatial ability appeared to be most strongly affected in manganese workers. It had the largest, most statistically significant effect size and showed the strongest dose-response relationship. The tests that comprised this domain were most often specifically chosen or developed to test for manganese toxicity, including tremor and eye-hand coordination abilities. It may be suggested that this spatial domain most closely matches the hypothesized effects of manganese. This strengthens the validity of the observed effects.

The significance of such effects is difficult to interpret. Clearly manganese has neurological consequences at very high doses (17, 24, 58). The dose-response relationship in this paper suggests a continuum of this effect to lower exposures levels. Thus, these modest

effect sizes could logically represent the lower end of such a continuum. However, sub-group analysis identified possible confounding by education disparities in some studies and the funnel plot strongly suggests some degree of publication bias. Thus, the interpretation of these effect sizes is marred by these biases.

As with most toxicological matters, the issue becomes the "safe level" of manganese exposure. This meta-analysis considered only those workers exposed near the current TLV of 0.2 mg/m^3 so that one may examine the "safety" of the current level. It remains unclear if the mild neuropsychological impairment observed at manganese levels near the current TLV represents the low-end of the continuum of neurological impairment or some element of bias.

There is considerable heterogeneity of the effect sizes in a number of the domains. This may be due to within-study factors. Two such factors were explored: welding group versus others and education-controlled versus non-controlled studies. Heterogeneity was not substantially reduced by considering non-welders alone.

Education was found to account for heterogeneity amongst the studies. Two groups of manganese workers (36, 37, 38, 45) were significantly less educated than their corresponding controls. Subgroup analysis considered those studies that did not appear to have educational disparities between exposed and controls. It was found that attention and motor function were significantly altered by excluding these studies, whereas spatial functioning and executive functioning was minimally changed. Homogeneity considerably improved without these studies. This suggests that the effects observed in these workers may be partly due to their relative educational deficits. This emphasizes the potential for confounding of neuropsychological outcomes and the need to adequately control for these.

Heterogeneity was also likely due to the multiple tests that make up each domain. Thirty-nine distinct tests were generalized into six domains. There is no consensus in defining domains

nor in assigning tests to domains. Indeed a single test may measure aspects of numerous domains. The definition of Lezak (35) was chosen given its simplicity and relative frequency in the literature. However, it is evident that combining numerous tests into a composite outcome will increase the potential for heterogeneity.

The dose-response relationships demonstrated a negative association between manganese exposure and neuropsychological performance. This was particularly true for spatial and executive functioning. However the influence of a few studies (Chia in particular) was evident. A precise interpretation from the regression lines is elusive given the undue influence at this higher exposure level. More studies in the range of 0.4 mg/m^3 and 2 mg/m^3 would significantly enhance clarity of this dose-response relationship. The paucity of studies in this range may be indicative of organizational efforts to keep manganese exposures within range of the TLV. Given such limits, it is unlikely that there will be an abundance of studies in that range in the future, so a clarification of dose-response relationship will be difficult.

The results of this analysis may be compared to a recent meta-analysis of manganese workers (33). The authors found similar magnitudes of summary effect sizes for a slightly different domain structure. In particular, they found mild deficits for verbal comprehension (E.S. = -0.25, 95% C.I. = -0.09 to -0.41), attention (E.S. = -0.22, 95% C.I. = -0.09 to -0.35) and process speed (E.S. = -0.19, 95% C.I. = -0.07 to -0.31). The authors also found that there was an overall effect size of -0.17, suggesting that Mn-exposed workers have slightly worse overall neurocognitive function than controls. Despite this, they suggest that this effect size is undetectable given the confidence intervals of most neuropsychological measures and question the existence of clinically significant neurocognitive impairment from Mn.

However, this study has some significant limitations including the lack of 3 recent large cohorts, the use of symptom reporting as an outcome and the inclusion of very highly exposed

cohorts. In addition, the lead author has "consulted with attorneys representing current and former manufacturers of welding consumables".

The same authors published a similar meta-analysis in 2007 (24(a)). They come to the same conclusion. However the same criticism remain as the authors considered disparate groups and acknowledge their active association with the Mn consumable industry.

Meta-analysis is a technique that has unique methodological issues. This is particularly true for meta-analyses of neuropsychological outcomes. Such issues will be of ongoing importance given the increasing reliance of these sensitive tools in detecting sub-clinical health effects in toxicology. From the above analysis, a number of methodological issues were apparent. I will not discuss generic issues of meta-analysis, such as heterogeneity and publication bias, as these issues have been widely explored in the literature.

Meta-analyses of neuropsychological outcomes often assign individual tests into functional domains. The reasons for this are pragmatic: rather than doing meta-analysis on multiple individual tests, one may combine results into a small number of domains and do meta-analysis on a more manageable number of outcomes. In addition, such outcomes are more easily interpretable than individual tests. However, there are clearly methodological problems in generalizing tests into certain domains.

Meta-analyses of neuropsychological outcomes will have low reproducibility due to varying domain structures. This reflects the difficulty in making concise categorization of cognitive function. Indeed, a review of the neuropsychological literature indicates very little consistency in the choice of functional domains. Some studies have cited prior papers (21) or textbook references (19, 26) in justifying their choice of domains. Most studies give no justification for their domains (2, 24, 48, 53). Some studies have used factor analysis to justify their choice of domains (16). Given all these approaches, it's not surprising that basically no

study uses the same domain structure in presenting results. The difficulty in generalizing tests to domains could result in considerable heterogeneity in meta-analysis. There needs to be standardization of the cognitive domains that are used in reporting of meta-analyses of neuropsychological outcomes. This would contribute some generalizability between meta-analyses. However, it is unlikely that consensus would be achieved given the complexity of categorizing cognitive function. In addition, neuropsychological techniques are used by many disciplines (e.g. psychiatry, psychology, neurology, toxicology) and consensus across disciplines is unlikely.

The sensitivity of neuropsychological tests is exploited to detect subtle neurological effects from occupational toxins. However, these methods will also be sensitive in detecting other impairments, such as psychiatric disease, age-related cognitive impairment, alcohol and substance abuse, educational deficits and neurological disease. Thus the potential for confounding is particularly significant for neuropsychological outcomes. The nature of occupational research makes it difficult to control for potential confounders. Randomization is often impossible and even simple matching can be constrained by work-related factors. Primary studies of neuropsychological outcomes need to control for potential confounders or comprehensively report group characteristics.

Meta-analysis of highly sensitive tests may be summarizing clinically insignificant disease. As with all neuropsychological assessments, it is difficult to extrapolate subtle testing abnormalities to clinical impairment. Specifically considering toxicologic studies, there is no established literature that has followed mildly neuropsychologically-impaired workers over time to look for progression to overt disease. Thus it remains unclear if the effects will progress to a clinically-apparent entity. There is an obvious need for prospective, longitudinal examination of these workers.

Conclusion

In conclusion, contemporary occupational manganese exposure is associated with mild impairment in neuropsychological function, particularly spatial ability. This may have ramifications on the numerous workers exposed to this metal, particularly welders. However, this effect is likely exaggerated by publication bias and some confounding by education. There is an ongoing need to refine neuropsychological studies of these workers. Good quality, longitudinal assessments would be of benefit in clarifying the neurological effects from manganese.

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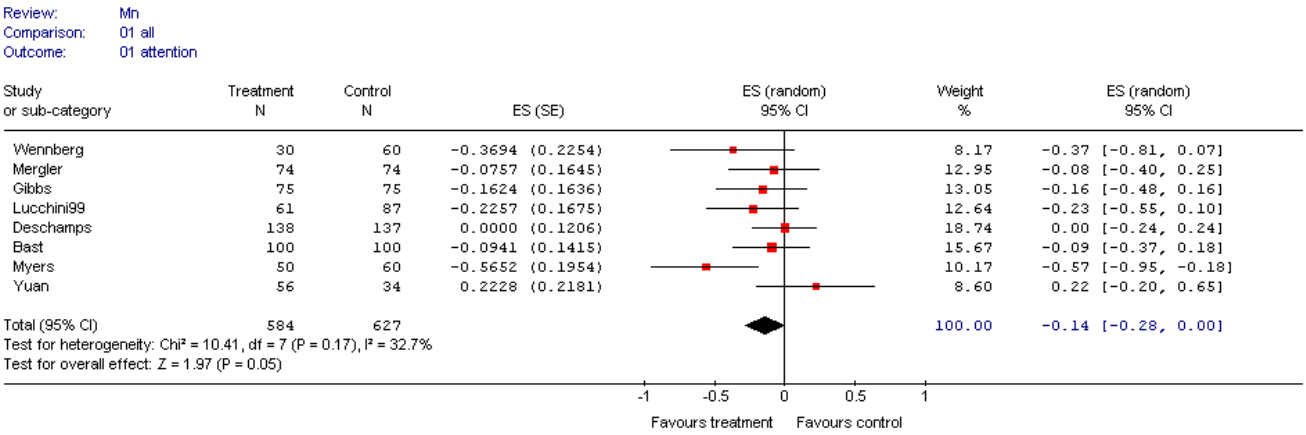
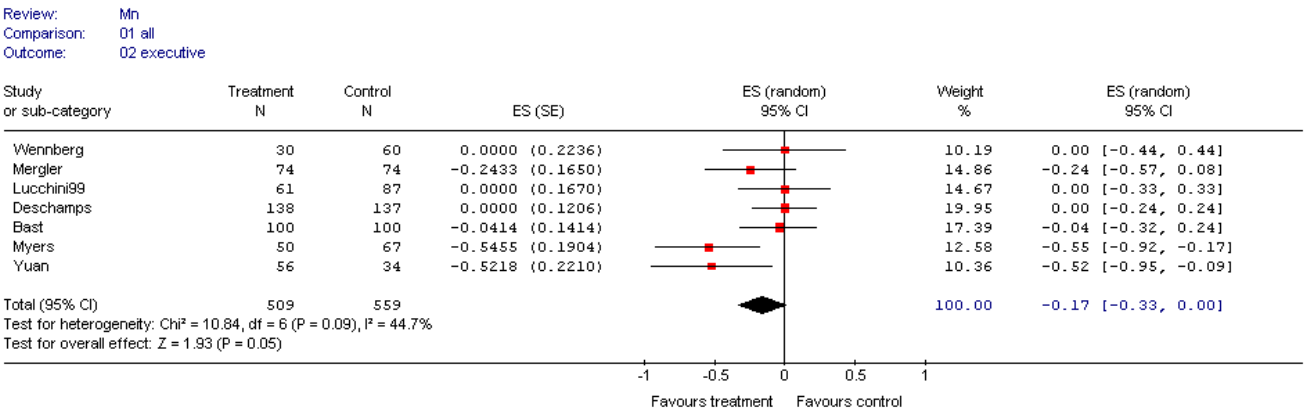
Figure 1: Forest plots of random effects summary effect sizes for each domain (a-f)

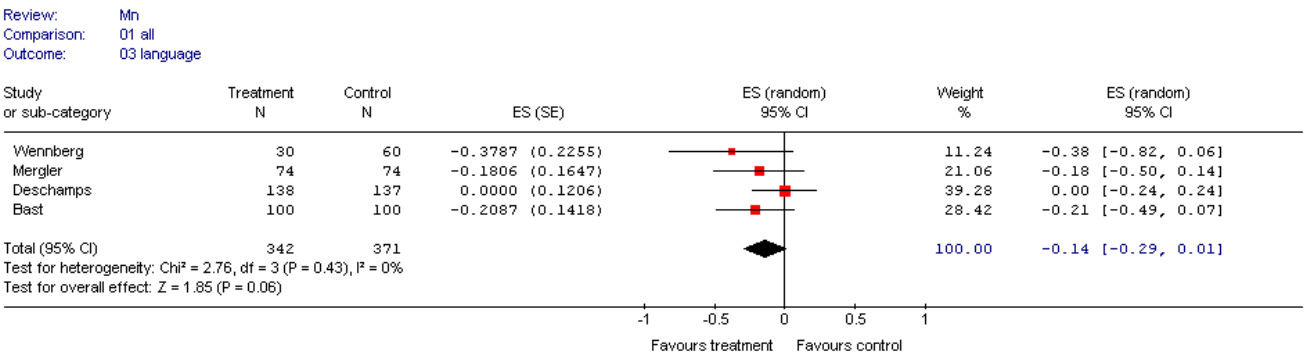
a) Attention domain



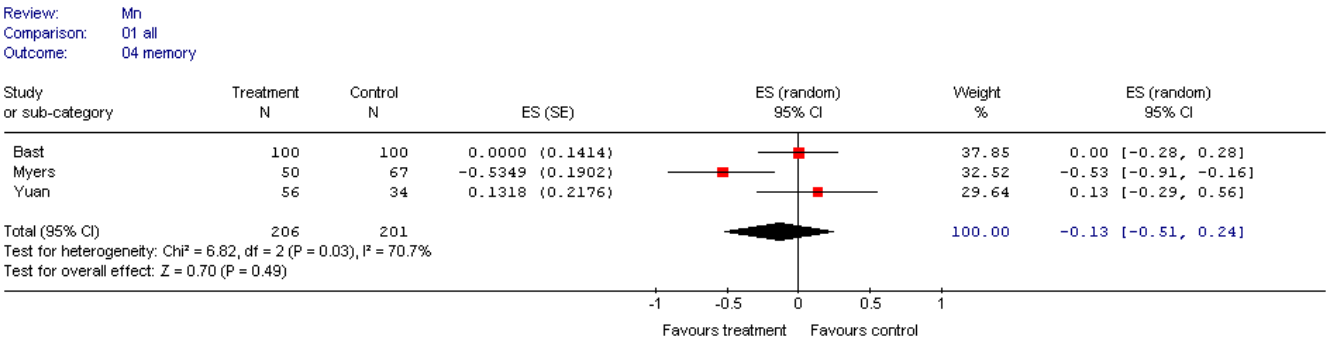
b) Executive domain



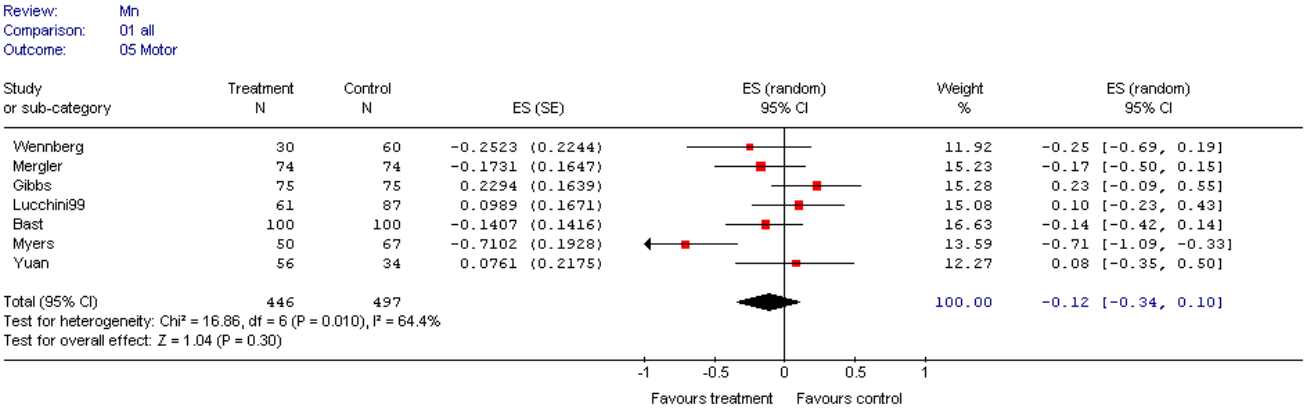
c) Language domain



d) Memory domain



e) Motor domain



f) Spatial domain

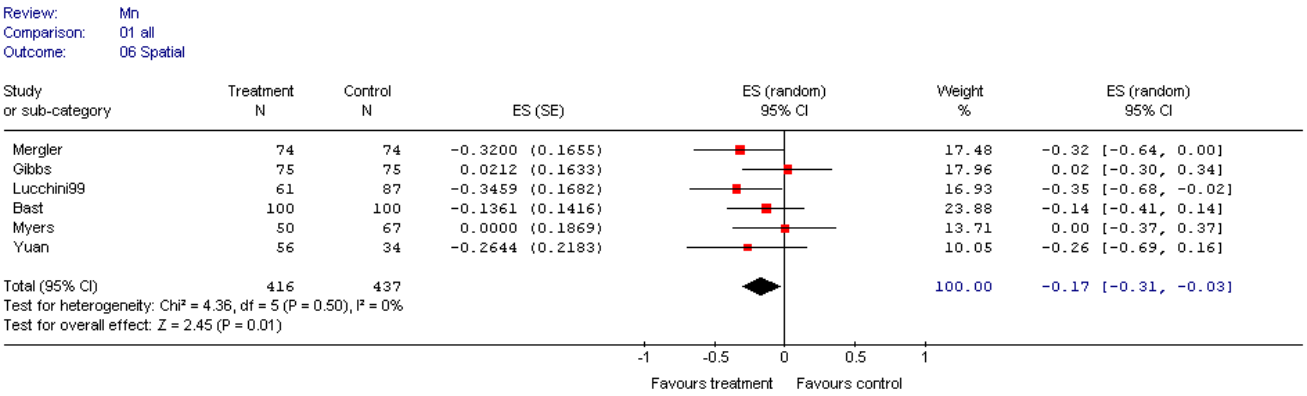


Figure 2: Exposure-response: All Domains

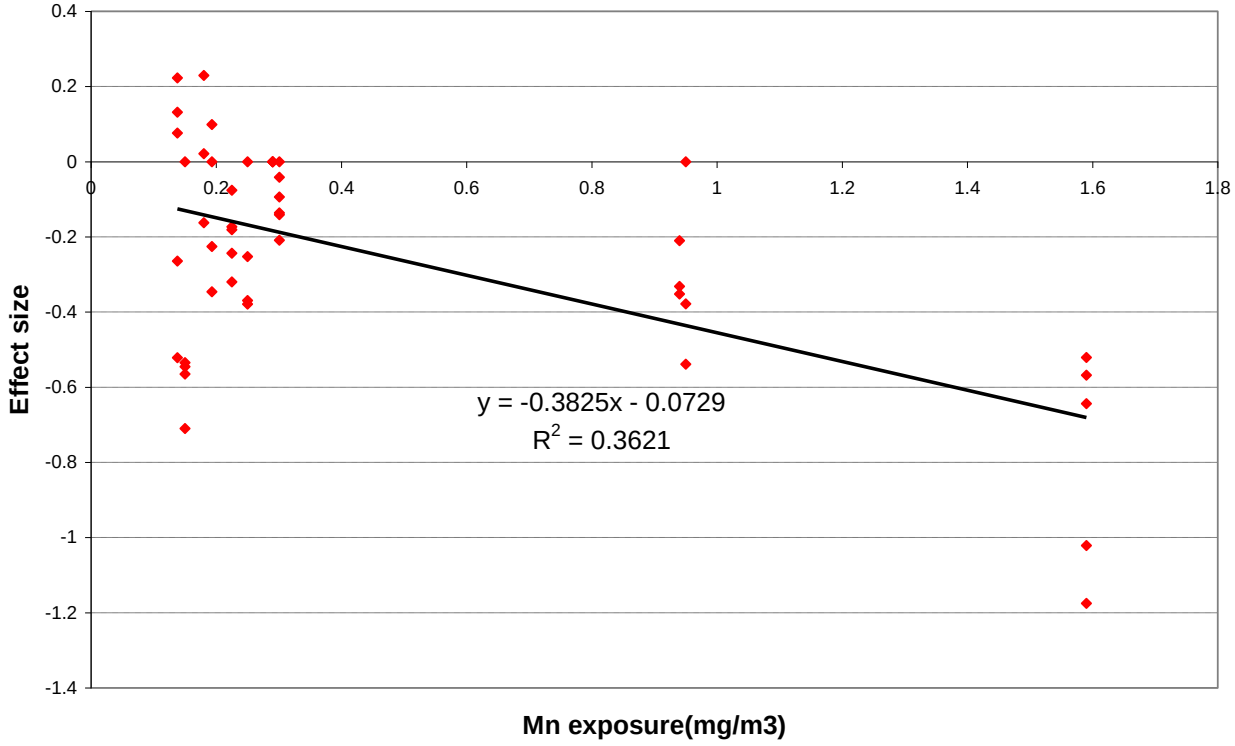


Figure 3. a) Exposure-response: attention domain

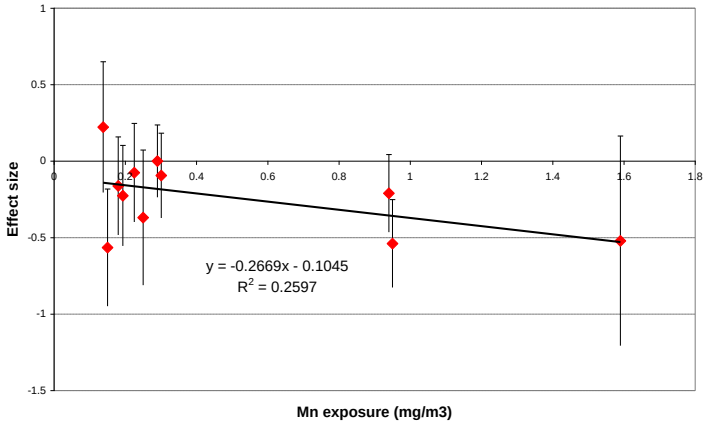


Figure 3. b) Exposure-response: executive domain

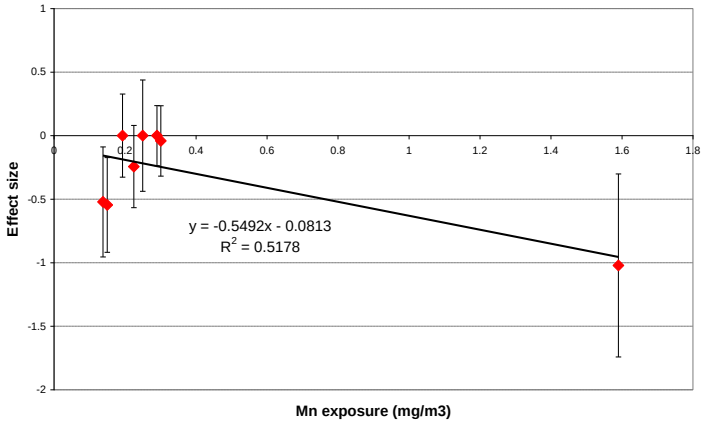


Figure 3. c) Exposure-response: language domain

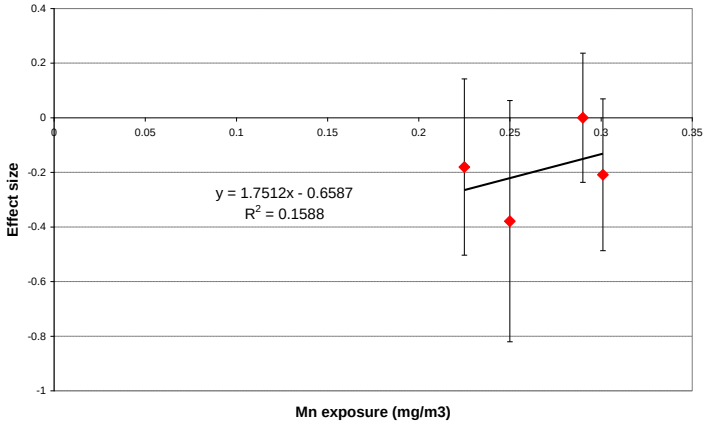


Figure 3. d) Exposure-response: memory domain

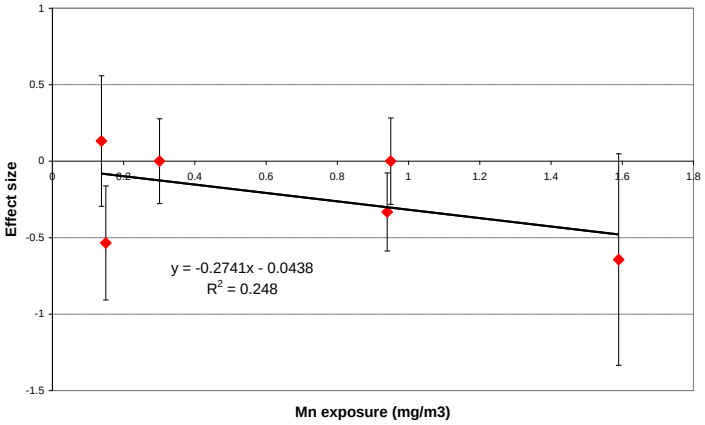


Figure 3. e) Exposure-response: motor domain

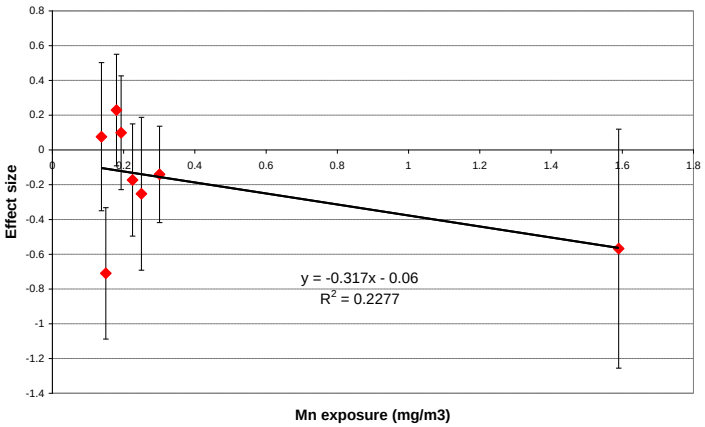


Figure 3. f) Exposure-response: spatial domain

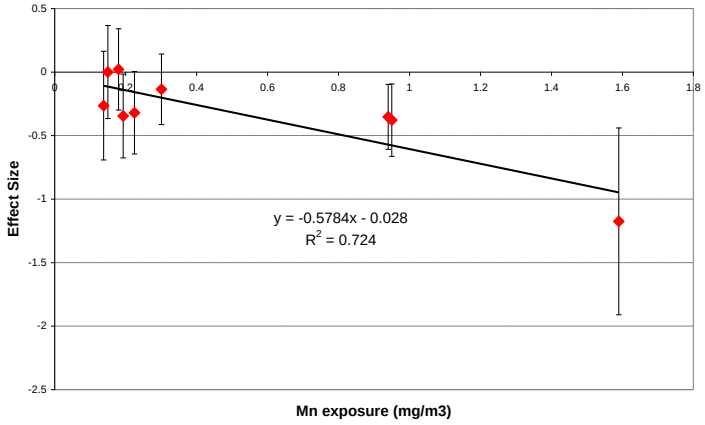


Figure 4: Funnel Plot to examine for publication bias

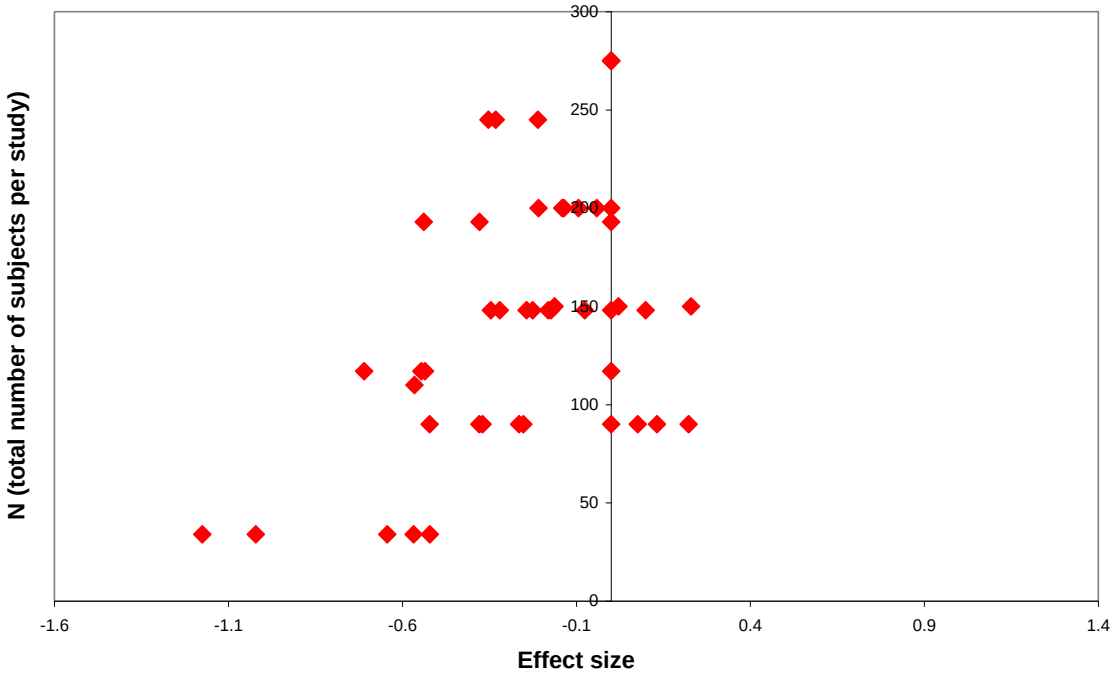


Table 1: Studies included in analysis, including study characterisitics

Included Studies	N (exposed/ control)	Nature of Exposure	Mean Mn (mg/m3)	Years of Exposure	Number of tests Performed	Number of positive tests (p<0.05)
Wennberg, 1991 (62)	30/60	Swedish steel smelters	0.25	9.9	9	5/9
Mergler, 1994 (40)	115/74	Quebec alloy plant	0.225	16.7	20	6/20
Lucchini, 1995 (36)	20/19	Italian ferroalloy plant	0.1	13	1	0/1
Lucchini, 1997 (37)	35/37	Italian ferroalloy plant	0.193	14.5	1	1/1
Lucchini, 1999 (38)	61/87	Italian ferroalloy plant	0.07083	15.2	8	3/8
Gibbs, 1999 (22)	75/75	U.S. Mn alloying plants	0.18	12.44	6	0/6
Deschamps, 2001 (15)	138/137	French enamel	0.29 (calc)	19.9	4	0/4
Myers, 2003 (45)	155/67	S. African Mn smelter	0.15	18.2	9	5/9
Bast-P., 2004 (3)	100/100	two Mn alloy plants	0.301	20.2	18	2/18
Yuan, 2006 (63)	56/34	Chinese welders	0.138	16.2	7	6/7
Additional studies considered in exposure-response analysis:						
Roels, 1987 (50)	141/104	Mn oxide plant	0.94	7.1	4	4/4
Roels, 1992 (49)	92/101	Flemish battery	0.948	5.3	4	4/4
Chia, 1993 (11)	17/17	Singapore Mn ore	1.59	7.4	7	6/7

Table 2: Studies excluded from analysis and reason for exclusion

Study	Year	Reason for Exclusion
Amr (1)	1993	inappropriate outcome
Bazylewicz-Walczak (4)	1996	Polish language
Bowler (9)	2005	no exposure information
Bowler (8)	2003	no exposure information
Chandra (10)	1981	inappropriate outcome
Crump (13)	1999	no control group
Emara (18)	1971	inappropriate outcome
Hochberg (29)	1996	excessive exposure; incomplete results
Hua (30)	1991	unclear exposure
Kim (32)	2005	no control group
Myers (44)	2003	no control group
Roels (51)	1999	unclear reporting of outcomes
Sinczuk-Walczak (55)	2001	inappropriate outcome
Sjogen (56)	1990	re-reporting of prior results
Sjogren (57)	1996	no exposure information
Wennberg (61)	1992	re-reporting of prior results
Zheng (64)	1999	Chinese language

Table 3: Potential confounders discussed in studies. The second column indicates the matching factors that were used in selecting controls. The third column indicates covariates that were compared between exposed and controls in each study, typically reported in frequency tables. The third column indicates the factors in particular studies that were found to significantly vary between exposed and controls.

Included Studies	Matching Factors in Selecting Controls	Comparative Factors that were listed	Significant Differences (exposed vs. controls)
Wennberg, 1991	age	age	
Mergler, 1994	age, education	age, education	
Lucchini, 1995		age,educ,vocab, smoking, alcohol	vocabulary
Lucchini, 1997		age, education, smoking, alcohol	
Lucchini, 1999		age,education,shifts, smoking, alcohol,noise	education, shifts, noise
Gibbs, 1999	race, age, pay	shifts,neuro. disease, smoking, alcohol, meds, hi	
Deschamps, 2001		sex, neuro disease, smoking, neurotoxins	
Myers, 2003		age, education, smoking, alcohol, h.i.	education, smoking, alcohol
Bast-P., 2004	age	education,shiftwork,meds smoking, alcohol, h.i.	
Yuan, 2006		age,education,income smoking, alcohol	

Table 4: Domain name and tests that comprised each domain

Domain	Studies	Tests
attention	3, 15, 22, 36, 37, 38, 40, 45, 62, 63	digit span, reaction time, additions, shapes
executive functioning	3, 15, 38, 40, 62, 63	stroop colour word, digit span (backwards), trailmaking B, symbol digit
language	3, 15, 40, 62	stroop colour, stroop word, vocabulary, word recall, digit name
memory	3, 45, 63	benton visual retention, memory testing
motor	3, 22, 38, 40, 45, 62, 63	Luria-Nebraska, tapping, Purdue pegboard, Santa Ana dexterity, pronation/supination, parallel line draw, trailmaking A, cancellationH
spatial	3, 22, 37, 38, 40, 45, 63	Movemap steady and square, tremormeter, orthokinesimeter, pursuit aiming sway, dysdiadochokinesia

Table 5: Summary effect sizes, confidence intervals and heterogeneity for all ten studies included in analysis

Domain	N	Summary Effect size	95% C.I.	Heterogeneity (I^2)
Attention	1211	-0.14	(-0.28, 0)	32.7 %
Executive	1068	-0.17	(-0.33, 0)	44.7 %
Language	713	-0.14	(-0.29, 0.01)	0 %
Memory	407	-0.13	(-0.51, 0.24)	70.7%
Motor	943	-0.12	(-0.34, 0.10)	64.4 %
Spatial	853	-0.17	(-0.17, -0.03)	0 %

Table 6: Summary effect sizes, confidence intervals and heterogeneity for nine non-welder studies, excluding the Yuan (63) study

Domain	N	Summary Effect size	95% C.I.	Heterogeneity (I^2)
Attention	1121	-0.17	(-0.30, -0.04)	20.6 %
Executive	978	-0.12	(-0.28, 0.04)	34.4 %
Language	713	-0.14	(-0.29, 0.01)	0 %
Memory	317	-0.25	(-0.78, 0.27)	80.4 %
Motor	853	-0.15	(-0.39, 0.10)	68.9 %
Spatial	763	-0.16	(-0.30, -0.01)	3.6 %

Table 7: Summary effect sizes, confidence intervals and heterogeneity for six non-confounded studies, excluding the Lucchini studies (36, 37, 38) and Myers (45) study

Domain	N	Summary Effect size	95% C.I.	Heterogeneity (I^2)
Attention	953	-0.07	(-0.20, -0.06)	0 %
Executive	803	-0.12	(-0.29, 0.04)	26.4 %
Language	713	-0.14	(-0.29, 0.01)	0 %
Memory	290	0.04	(-0.19, 0.27)	0 %
Motor	678	-0.05	(-0.22, 0.12)	20.4 %
Spatial	588	-0.16	(-0.32, 0)	0 %

Table 8: Linear regression statistics for exposure-response relationship of each domain

Domain	R2	ANOVA p-value	β	95% C.I.
attention	0.26	0.11	-0.267	(-0.61, 0.07)
executive	0.52	0.04	-0.549	(-1.08, -0.02)
language	0.16	0.6	1.751	(-10.51, 14.01)
memory	0.25	0.32	-0.274	(-0.94, 0.39)
motor	0.23	0.23	-0.317	(-0.90, 0.27)
spatial	0.73	0.004	-0.578	(-0.90, -0.26)

Appendix 1: Formulas used for meta-analytic calculations

Effect size was calculated for each test result as Hedges ĝ (25). This effect size uses the basic formulation of ES=$(x_1-x_2)/\sigma^2$ but corrects for potential sample size disparities between the two groups.

$$\hat{g} = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2}{(N_{total}-2)}}} \times \left(1 - \frac{3}{4(n_1+n_2)-9}\right).$$

The effect sizes, ĝ, for n tests representing one domain in each study were averaged to produce an effect size for each domain (e_i).

$$e_i = \frac{\sum_{j=1}^{n} \hat{g}_j}{n}$$

The standard error of these effect sizes was estimated as:

$$se(e_i) = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{e_i^2}{2(N_i - 3.94)}},$$

where n_{1i} = number of exposed, n_{2i} = number of controls and $N_i = n_{1i} + n_{2i}$.

Meta-analysis used the inverse variance method of combining trials. This method weights each study by the inverse of its variance, which is the square of its variance.

$$w_i = \frac{1}{se(e_i)}$$

One may then compute a fixed effects pooled estimate of:

$$\hat{e}_{pooled} = \frac{\sum w_i e_i}{\sum w_i} \quad \text{with a standard error of:} \quad se(e_{pooled}) = \frac{1}{\sqrt{\sum w_i}}.$$

A heterogeneity statistic can be calculated as:

$$Q = \sum w_i (e_i - e_{pooled})^2$$

This analysis further considered a random effects model, whereby it is assumed that the effect sizes from individual studies has a random distribution, ie.:

$$es_i \approx N(es, \tau^2).$$

The variance of these effect sizes, τ^2, is given by:

$$\tau^2 = \max\left\{\frac{Q-(k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}, 0\right\}$$, where k is the number of studies.

This additional factor is added to the study weightings as below,

$$w'_i = \frac{1}{se(e_i)^2 + \tau^2},$$

and the new pooled effect size becomes,

$$\hat{e}'_{pooled} = \frac{\sum w'_i e_i}{\sum w'_i}$$ with a standard error of: $$se(e'_{pooled}) = \frac{1}{\sqrt{\sum w'_i}}.$$

In this analysis, heterogeneity was calculated by the I2 statistic (27, 28), given by,

$$I^2 = \frac{Q-(k-1)}{Q} x100\%.$$

They defined low heterogeneity as 25%, medium heterogeneity as 50% and high heterogeneity as 75%.