



Online supplementary material

Online supplementary Tables and Figures

Online supplementary Table S1. NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Studies included in meta-analysis.

	Bowler et al. (2012) [37]	Bowler et al. (2015) [42]	Bowler et al. (2016) [28]	Ghazali et al. (2013) [38]	Iqbal et al. (2018) [43]	Kim et al. (2011) [36]	Lucchini et al. (2014) [40]	Mergler et al. (1999) [30]	Guarneros et al. (2013) [39]	Viana et al. (2014) [41]	Standridge et al. (2008) [34]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	CD	CD	Yes	Yes	Yes	CD	No	CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	CD	CD	Yes	Yes	Yes	CD	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	No	No	No	No	No	No	No	No
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No	No	No	No	No	No	No	No
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes

10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes
Rating (Good, Fair, or Poor)	Fair-Good	Fair-Good	Fair	Fair	Poor	Good	Good	Good	Fair	Fair-Good	Fair-Good

Available at: <http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>. CD, cannot determine; NA, not applicable; NR, not reported.

Online supplementary Table S2. NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Studies non-included in meta-analysis.

	Beuter et al. (1999) [31]	Santos Burgoa et al. (2001) [32]	Rodríguez-Agudelo et al. (2006) [33]	Solís Vivanco et al. (2009) [35]	Cabral Pinto et al. (2018) [44]	Kornblith et al. (2018) [45]	Rafiee et al. (2019) [46]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	No	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	CD	Yes	Yes	CD	Yes	CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	CD	Yes	Yes	CD	Yes	CD
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	Yes	Yes	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	No	No	No	No
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No	No	No	No
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	CD	NA	Yes
Rating (Good, Fair, or Poor)	Good	Fair	Good	Good	Fair	Fair	Fair

Available at: <http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>. CD, cannot determine; NA, not applicable; NR, not reported.

Online supplementary Table S3. Correlation between cognitive function and exposure to Mn. Overall heterogeneity and as a function of the cognitive domain assessed.

Cognitive function Correlation	N of studies	N of determinations	Heterogeneity				
			Q	df	p (Chi ²)	I ² (%)	Tau ² Tau
Attention	2	18	94.66	7.00	0.000	82.04	0.05 0.22
Attention and working memory	2	7	14.13	6.00	0.028	57.54	0.01 0.11
Executive functions	1	3	1.65	2.00	0.437	0.00	0.00 0.00
Fluency	1	1	0.00	0.00	1.000	0.00	0.00 0.00
General cognitive functioning	3	6	21.99	5.00	0.001	77.26	0.02 0.15
Intelligence	1	4	8.58	3.00	0.035	65.06	0.02 0.15
Memory	2	15	64.63	14.00	0.000	78.34	0.03 0.17
Processing speed	1	1	0.00	0.00	1.000	0.00	0.00 0.00
Verbal comprehension	1	1	0.00	0.00	0.000	0.00	0.00 0.00
All domains	3	56	233.92	55.00	0.000	76.49	0.03 0.16

Online supplementary Table S4. Correlation between cognitive function and exposure to Mn. Overall heterogeneity and as a function of the type of exposure to Mn evaluated.

Cognitive function Correlation	N of studies	N of determinations	Heterogeneity				
			Q	df	p (Chi ²)	I ² (%)	Tau ² Tau
Air Mn	1	21	16.37	20.00	0.693	0.00	0.00 0.00
Axillary Hair Mn	1	8	106.45	7.00	0.000	93.42	0.18 0.42
Blood Mn	1	1	0.00	0.00	1.000	0.00	0.00 0.00
Hand Fingernails Mn	3	10	21.92	10.00	0.009	58.94	0.02 0.14
Saliva Mn	1	8	2.36	7.00	0.938	0.00	0.00 0.00
Scalp Hair Mn	1	8	21.35	7.00	0.003	67.21	0.03 0.16
All types of exposure to Mn evaluated	4	56	233.92	55.00	0.000	76.49	0.03 0.16

Online supplementary Table S5. Standardized mean differences (SMDs). Cognitive function. Overall heterogeneity and as a function of the cognitive domain assessed..

Cognitive function. SMD	N of studies	N of determinations	Heterogeneity				
			Q	df	p (Chi ²)	I ² (%)	Tau ² Tau
Attention	2	8	6.03	7.00	0.536	0.00	0.00 0.00
Attention and working memory	2	4	0.33	3.00	0.955	0.00	0.00 0.00
General cognitive functioning	2	5	2.08	4.00	0.722	0.00	0.00 0.00
Intelligence	1	1	0.00	0.00	1.000	0.00	0.00 0.00
Memory	2	5	8.11	4.00	0.088	50.70	0.02 0.15
Processing speed	1	2	0.58	1.00	0.448	0.00	0.00 0.00
Verbal comprehension	1	1	0.00	0.00	1.000	0.00	0.00 0.00
All domains	3	26	25.67	25.00	0.425	2.62	0.00 0.02

Online supplementary Table S6. Standardized mean differences (SMDs). Cognitive function. Overall heterogeneity and as a function of the type of exposure to Mn evaluated.

Cognitivefunction SMD	N of studies	N of determinations	Heterogeneity					
			Q	df	p (Chi²)	I² (%)	Tau²	Tau
Air Mn & blood Mn	1	2	0.02	1.00	0.874	0.00	0.00	0.00
Air Mn, blood & urine Mn	1	16	7.36	15.00	0.947	0.00	0.00	0.00
Scalp Hair, axillary hair, fingernails & saliva Mn	1	8	23.84	7.00	0.021	57.46	0.07	0.26
All types of exposure to Mn evaluated	3	26	25.67	25.00	0.425	2.62	0.00	0.02

Online supplementary Table S7. Correlation between motor function and exposure to Mn. Overall heterogeneity and as a function of the motor domain assessed.

Motor function Correlation	N of studies	N of determinations	Heterogeneity					
			Q	df	p (Chi²)	I² (%)	Tau ₂	Tau
Eye-hand coordination and motor speed	2	10	9.75	9.00	0.371	7.74	0.00	0.03
Hand strength	1	2	0.01	1.00	0.924	0.00	0.00	0.00
Postural balance	1	16	16.40	15.00	0.356	8.53	0.00	0.05
Self-directed manual speed	1	2	1.00	1.00	0.000	0.34	0.00	0.00
Tremor	1	6	99.61	5.00	0.000	94.98	0.10	0.32
All domains	3	36	139.97	35.00	0.000	74.99	0.03	0.18

Online supplementary Table S8. Correlation between motor function and exposure to Mn. Overall heterogeneity and as a function of the type of exposure to Mn evaluated.

Motor function Correlation	N of studies	N of determinations	Heterogeneity					
			Q	df	p (Chi²)	I² (%)	Tau ₂	Tau
Air Mn	1	12	108.83	11.00	0.000	89.89	0.05	0.22
Axillary Hair	1	2	0.13	1.00	0.719	0.00	0.00	0.00
Blood	1	8	2.15	7.00	0.951	0.00	0.00	0.00
Hand Fingernails	1	2	0.64	1.00	0.425	0.00	0.00	0.00
Saliva	1	2	0.06	1.00	0.809	0.00	0.00	0.00
Scalp Hair	2	10	5.37	79.00	0.801	0.00	0.00	0.00
All types of exposure to Mn evaluated	3	36	139.97	35.00	0.000	74.99	0.03	0.18

Online supplementary Table S9. Standardized mean differences (SMDs). Motor function. Overall heterogeneity and as a function of the motor domain assessed.

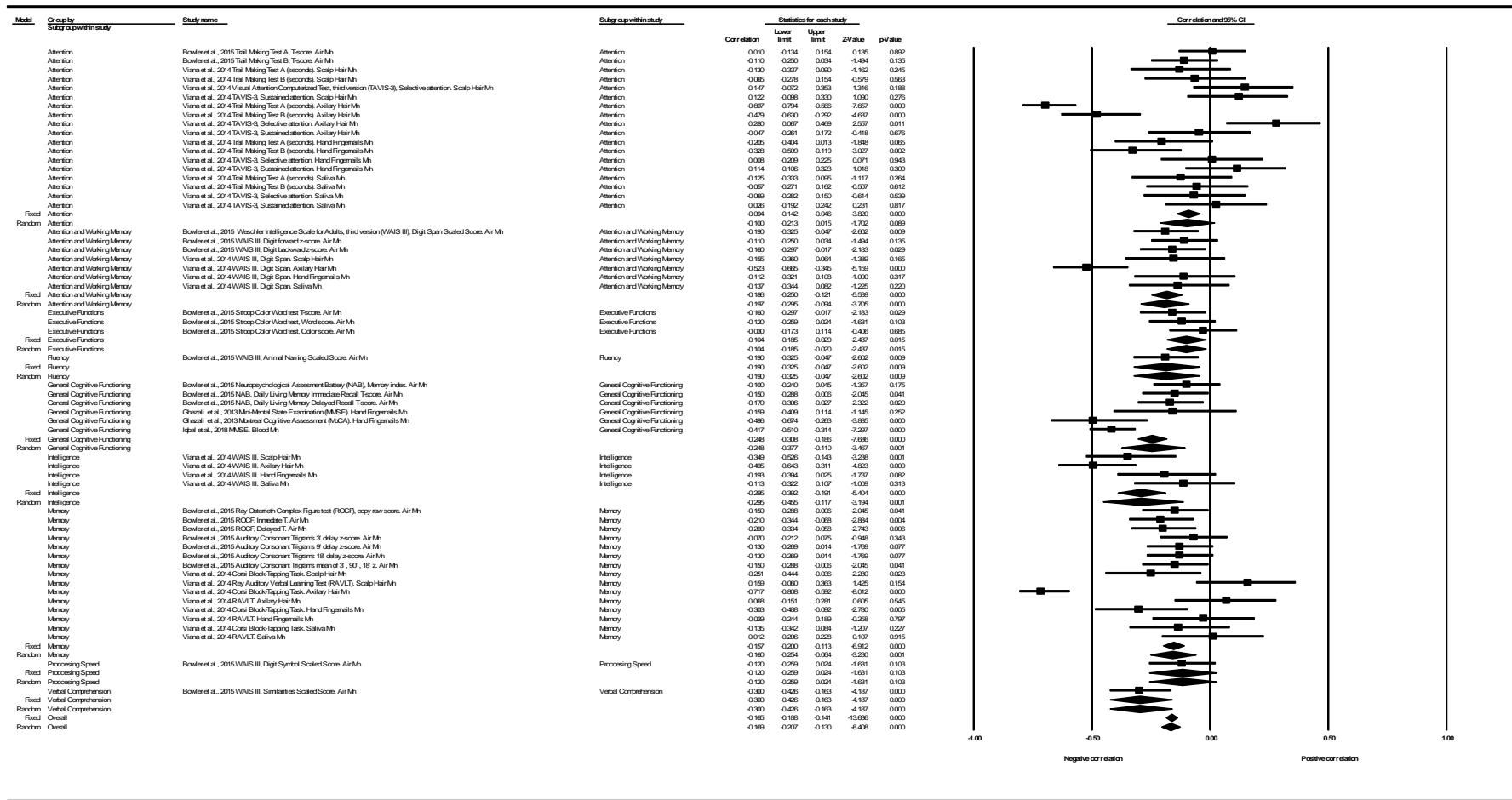
Motor function SMD	N of studies	N of determinations	Heterogeneity					
			Q	df	p (Chi ²)	I ² (%)	Tau ₂	Tau
Bradykinesia	1	1	0.00	0.00	1.000	0.00	0.00	0.00
Eye-hand coordination and motor speed	2	4	0.82	3.00	0.846	0.00	0.00	0.00
Eye-hand coordination	1	4	2.21	3.00	0.530	0.00	0.00	0.00
Finger and hand dexterity	1	2	13.09	1.00	0.000	92.36	0.41	0.64
Hand strength	1	2	0.34	1.00	0.557	0.00	0.00	0.00
Motor coordination	1	6	3.55	5.00	0.616	0.00	0.00	0.00
Motor evaluation	1	1	0.00	0.00	1.00	0.00	0.00	0.00
Olfactory performance	2	5	5.78	4.00	0.216	30.83	0.02	0.15
Postural balance	1	8	7.11	7.00	0.417	1.59	0.00	0.04
Postural sway	2	24	23.85	23.00	0.412	3.56	0.00	0.03
Reaction time	1	2	0.18	1.00	0.668	0.00	0.00	0.00
Self-directed manual speed	2	4	1.34	3.00	0.719	0.00	0.00	0.00
Tremor	1	8	3.43	7.00	0.842	0.00	0.00	0.00
All domains	7	71	146.69	70.00	0.000	52.28	0.02	0.16

Online supplementary Table S10. Standardized mean differences (SMDs). Motor function. Overall heterogeneity and as a function of the type of exposure to Mn evaluated.

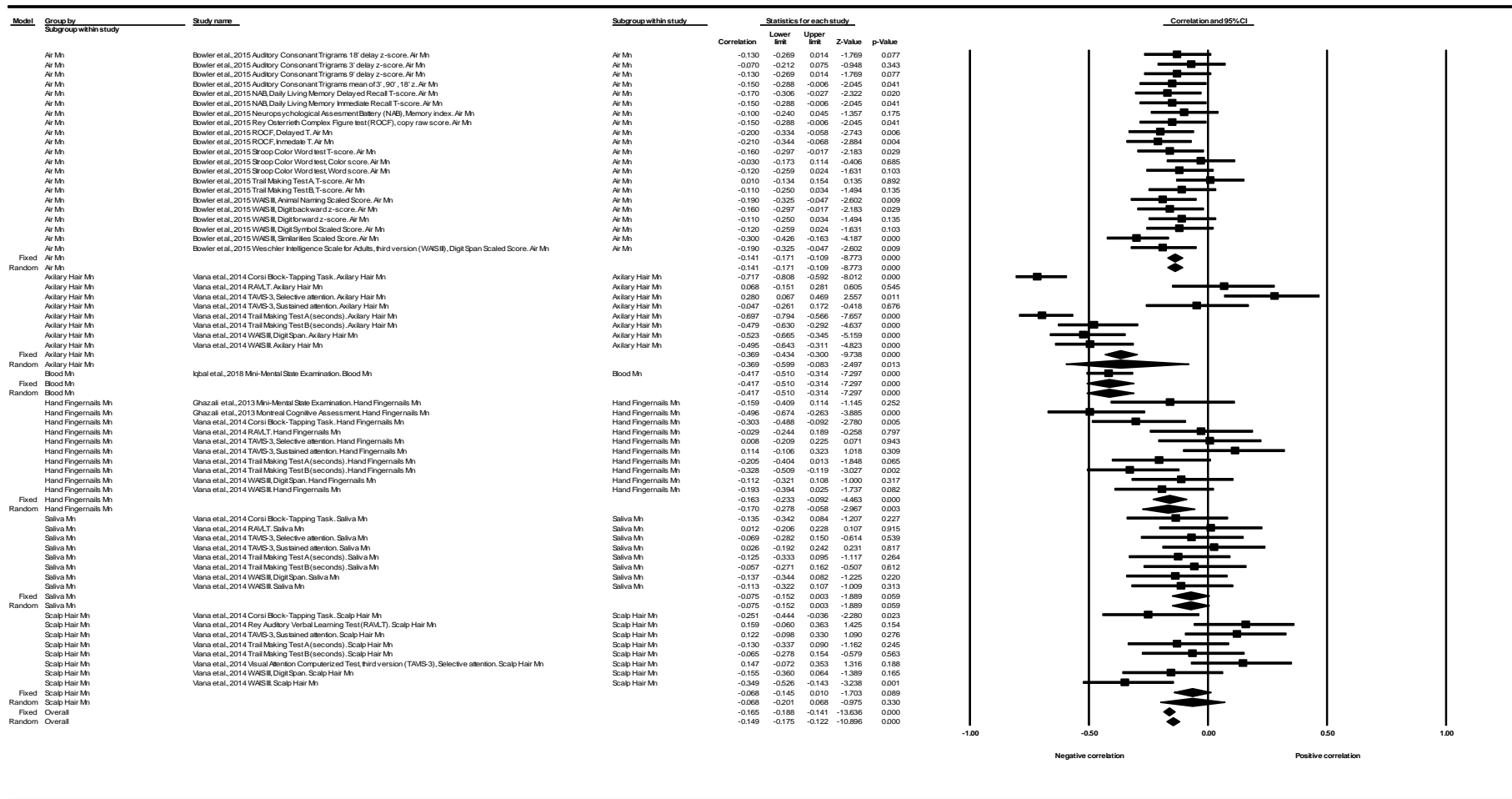
Motor function SMD	N of studies	N of determinations	Heterogeneity					
			Q	df	p (Chi ²)	I ² (%)	Tau ²	Tau
Air Mn & blood Mn	2	20	21.86	19.00	0.291	13.10	0.00	0.06
Air Mn, blood & urine Mn	1	31	35.47	30.00	0.226	15.42	0.00	0.06
Blood Mn	1	6	22.74	5.00	0.000	78.01	0.11	0.33
Blood & Hair Mn	1	8	7.11	7.00	0.417	1.59	0.00	0.04
Hair Mn	1	4	0.44	3.00	0.932	0.00	0.00	0.00
Scalp hair, Axillary hair, Fingernails & Saliva Mn	1	2	1.06	1.00	0.303	5.92	0.00	0.05
All types of exposure to Mn evaluated	7	71	146.69	70.00	0.000	52.28	0.02	0.16

Model	Study	Study name	Subgroup with study	Statistics for each study				Correlation and 95% CI	
	Subgroup without study			Correlation	Lower limit	Upper limit	Z-value	p-value	
		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.130	-0.289	0.014	-1.769	0.077	
		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.070	-0.212	0.075	0.948	0.343	
		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.130	-0.289	0.014	-1.769	0.077	
		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.130	-0.289	0.014	-1.769	0.077	
Random		Auditory Consonant Tigrams	Auditory Consonant Tigrams	-0.130	-0.289	0.014	-1.769	0.077	
		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
Fixed		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
Random		Corsi Block-Tapping Task	Corsi Block-Tapping Task	-0.120	-0.191	-0.048	-3.265	0.001	
		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
Random		Mini-Mental State Examination	Mini-Mental State Examination	-0.130	-0.289	0.014	-1.769	0.077	
		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
Random		Montreal Cognitive Assessment	Montreal Cognitive Assessment	-0.130	-0.289	0.014	-1.769	0.077	
		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
Random		NAB	NAB	-0.130	-0.289	0.014	-1.769	0.077	
		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
Random		RAVLT	RAVLT	-0.130	-0.289	0.014	-1.769	0.077	
		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
Random		ROCF	ROCF	-0.130	-0.289	0.014	-1.769	0.077	
		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
Fixed		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
Random		Stoop-Color Word test	Stoop-Color Word test	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
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		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-1.769	0.077	
		TAWS-3	TAWS-3	-0.130	-0.289	0.014	-		

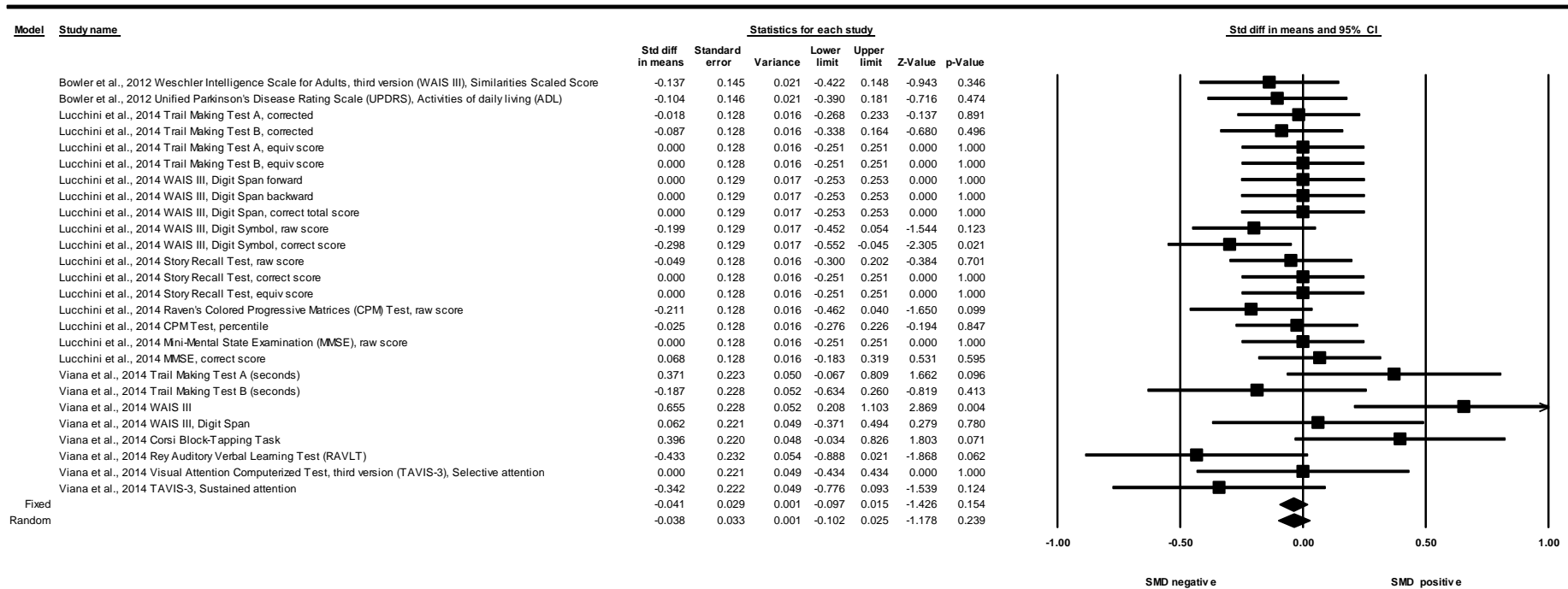
Online supplementary Figure S1. Correlation between cognitive function and Mn exposure, as a function of the cognitive test used. Note: a negative correlation indicates that the higher the Mn levels, the worse the cognitive function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



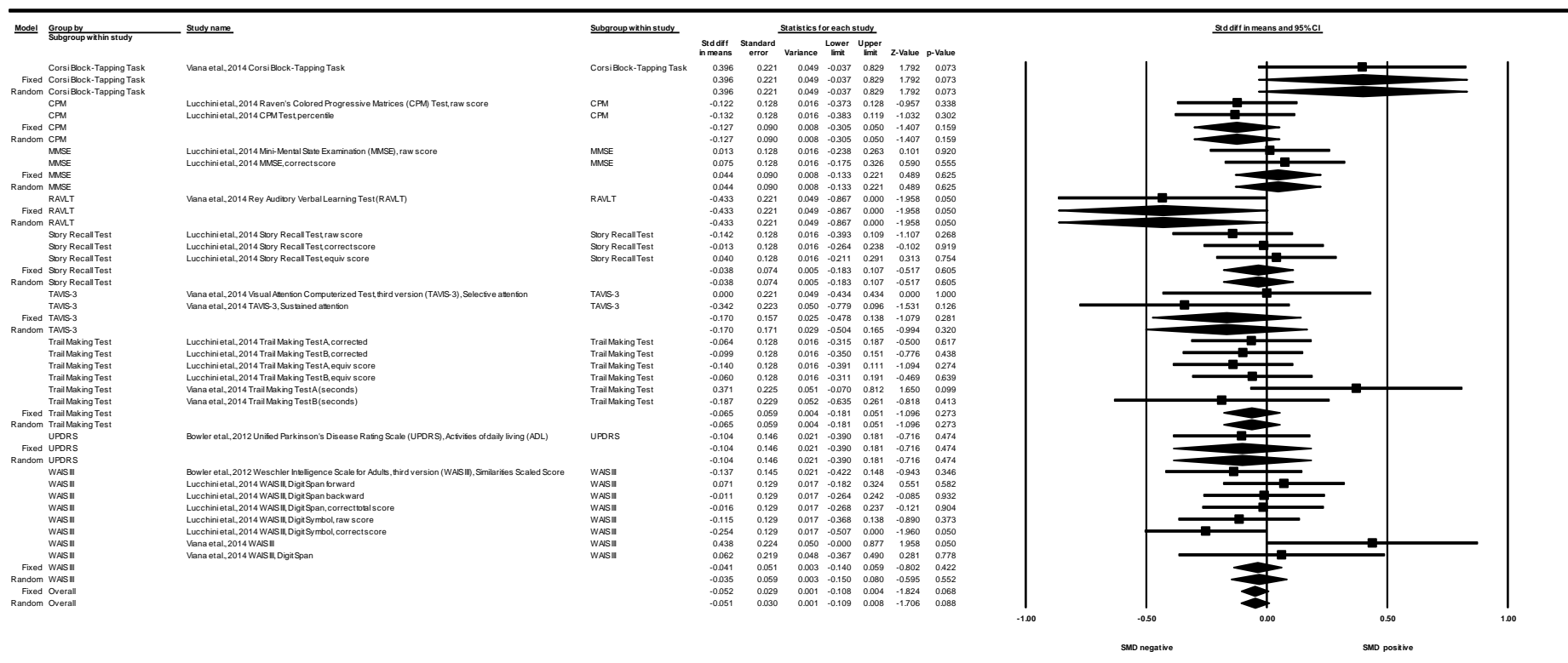
Online supplementary Figure S2. Correlation between cognitive function and Mn exposure, as a function of the cognitive domain assessed. Note: a negative correlation indicates that the higher the Mn levels, the worse the cognitive function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



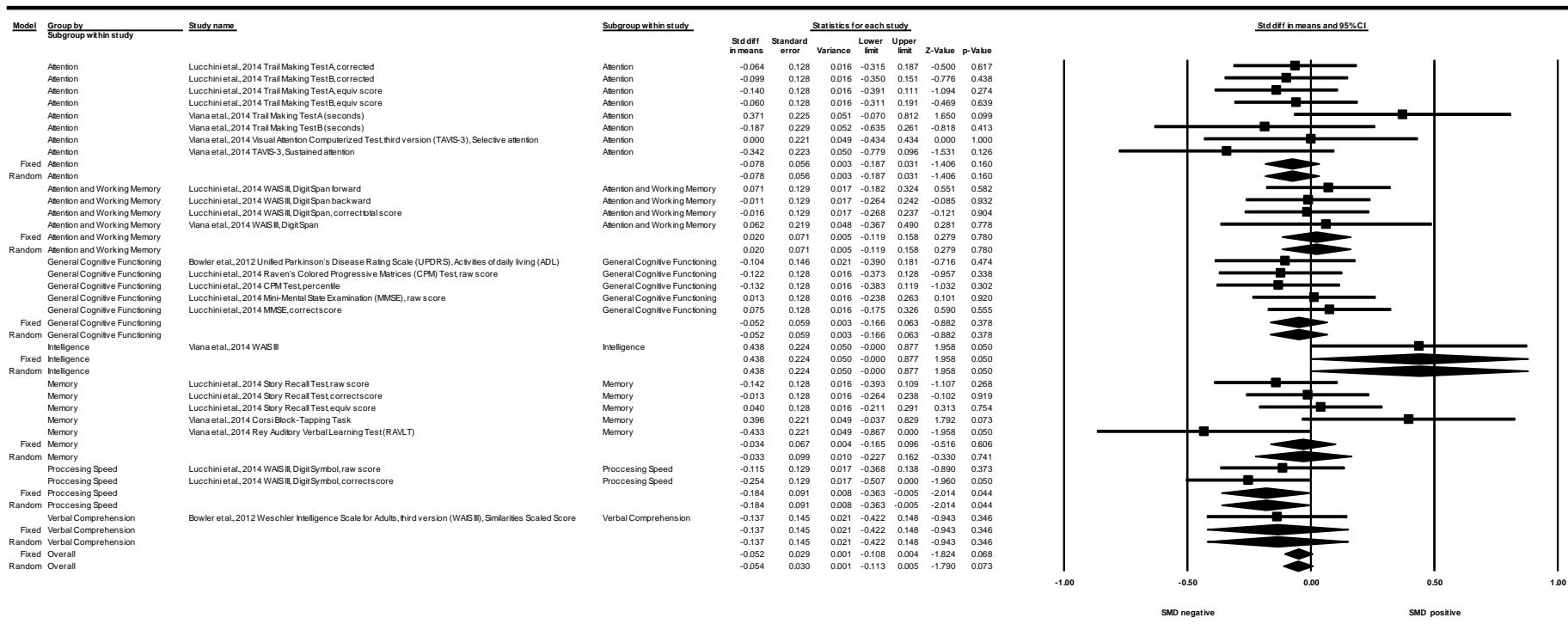
Online supplementary Figure S3. Correlation between cognitive function and Mn exposure, as a function of the type of exposure to Mn evaluated. Note: a negative correlation indicates that the higher the Mn levels, the worse the cognitive function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



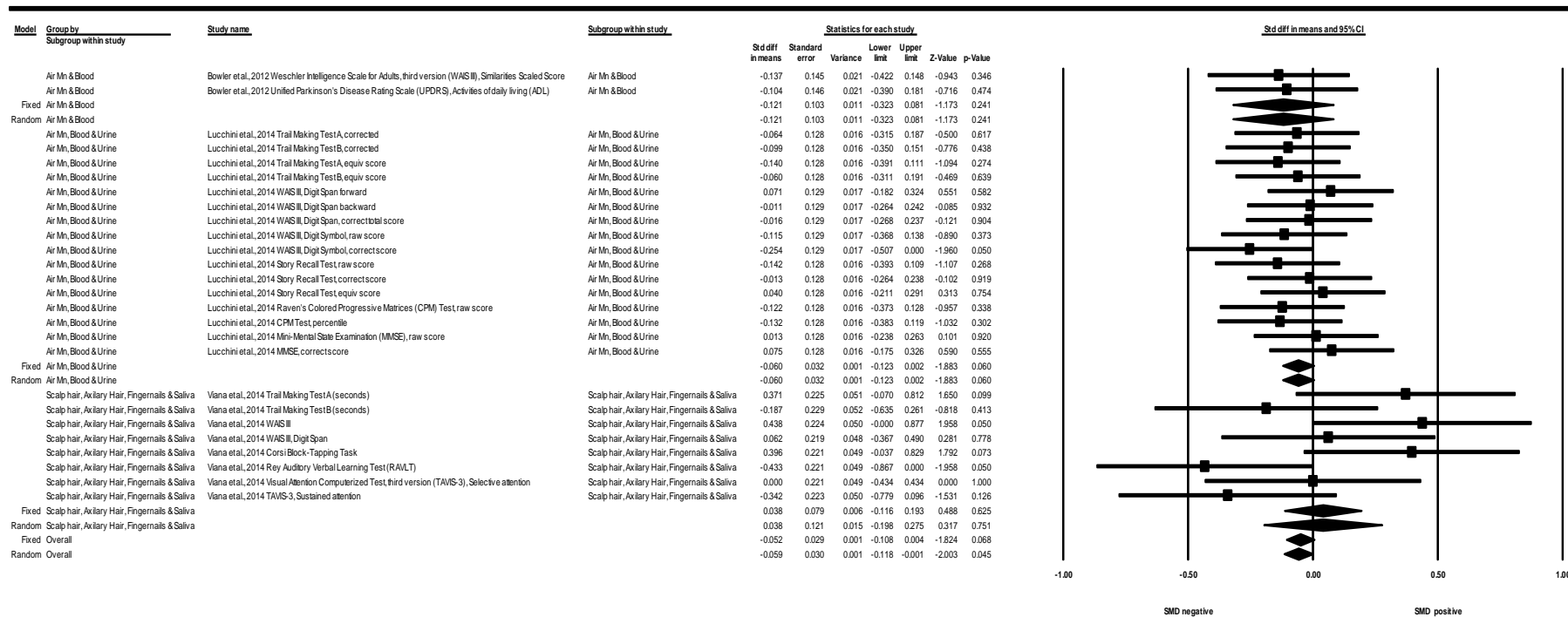
Online supplementary Figure S4. Cognitive function. Standardized mean differences (SMDs) between groups, prioritizing the use of medians versus means (when both medians and means were reported). All tests and all exposures to Mn. Note: a negative SMD indicates that the group with higher Mn levels had worse cognitive function on average.



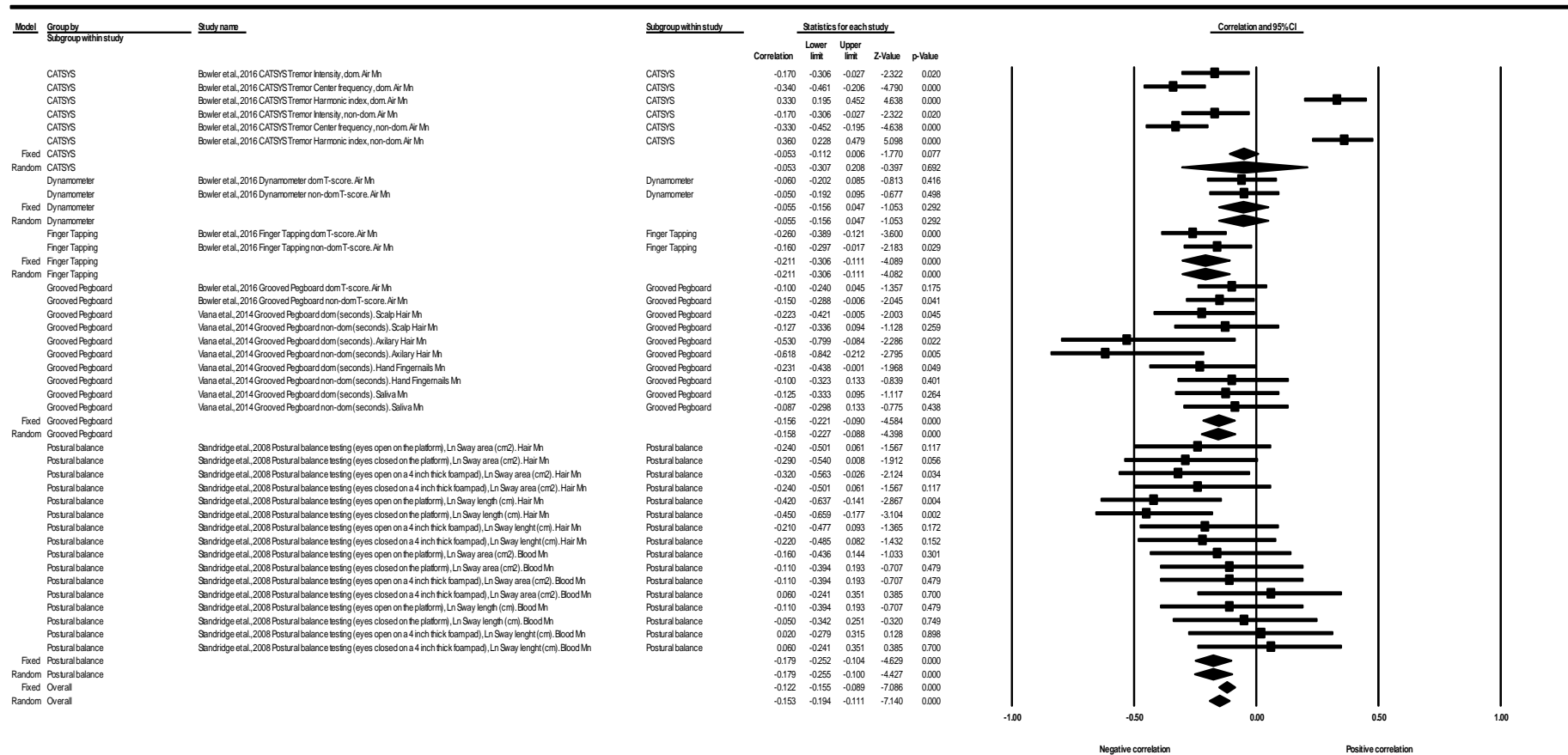
Online supplementary Figure S5. Cognitive function. Standardized mean differences (SMDs) between groups, as a function of the cognitive test used. Note: a negative SMD indicates that the group with higher Mn levels had worse cognitive function on average. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (τ^2) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



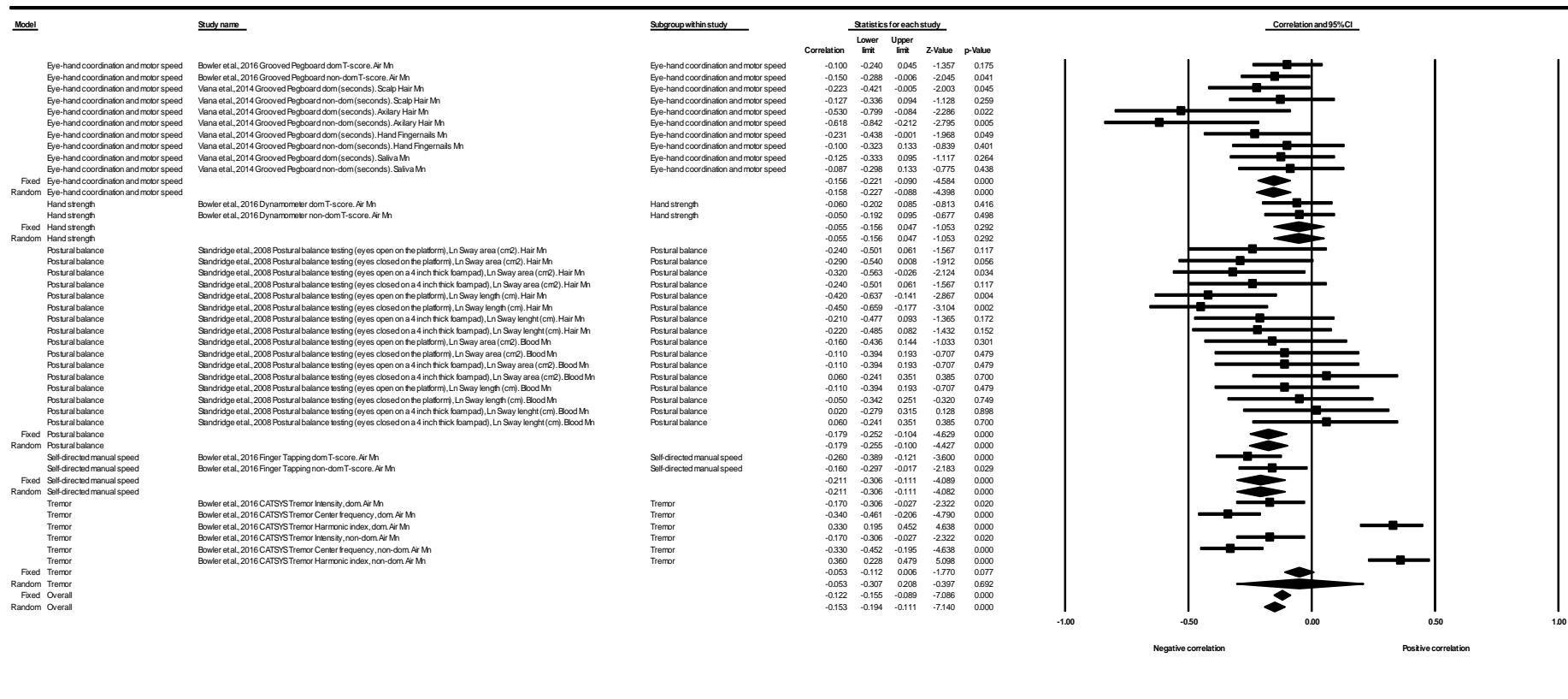
Online supplementary Figure S6. Cognitive function. Standardized mean differences (SMDs) between groups, as a function of the cognitive domain assessed. Note: a negative SMD indicates that the group with higher Mn levels had worse cognitive function on average. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



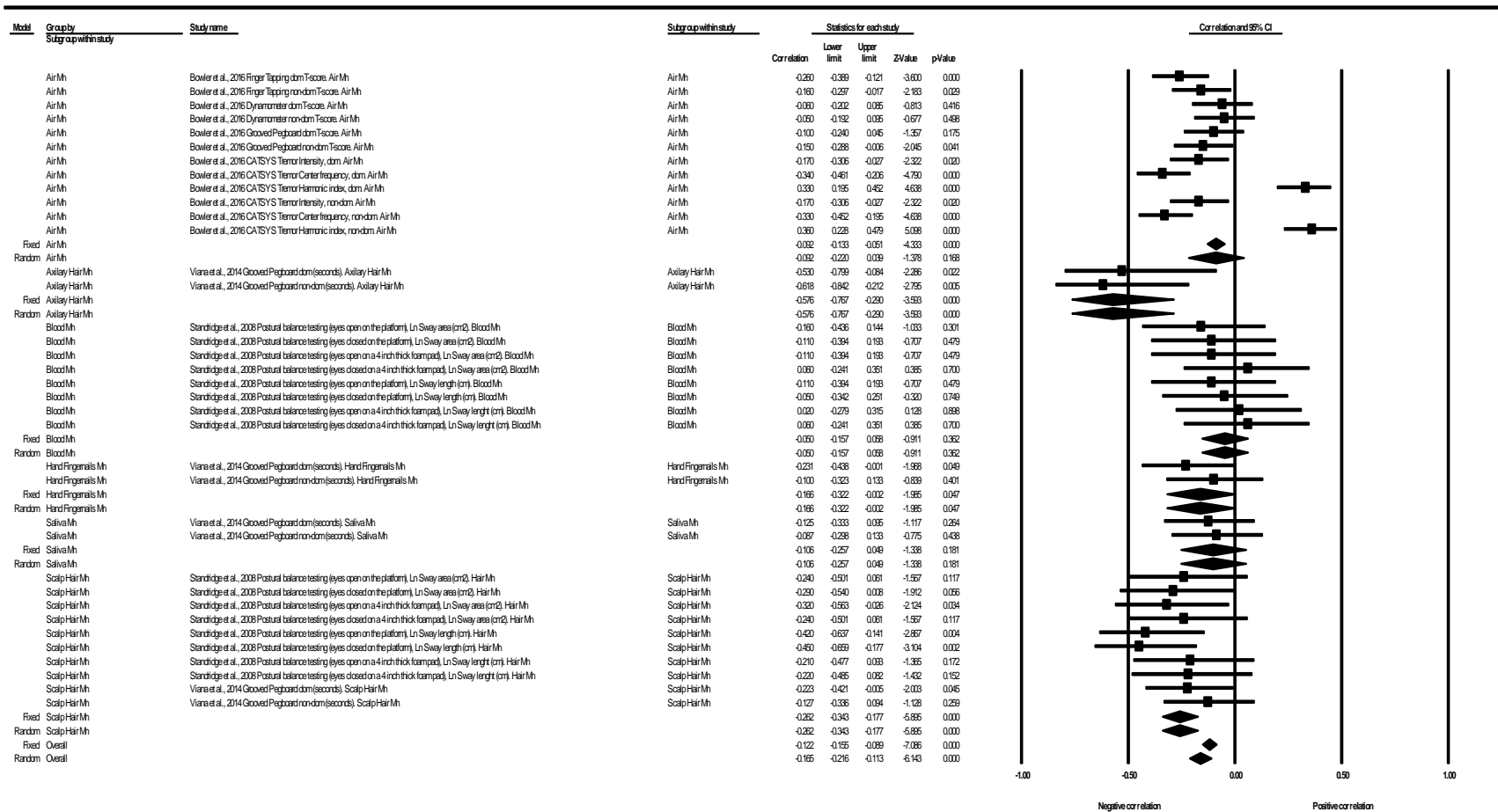
Online supplementary Figure S7. Cognitive function. Standardized mean differences (SMDs) between groups, as a function of the type of exposure to Mn evaluated. Note: a negative SMD indicates that the group with higher Mn levels had worse cognitive function on average. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



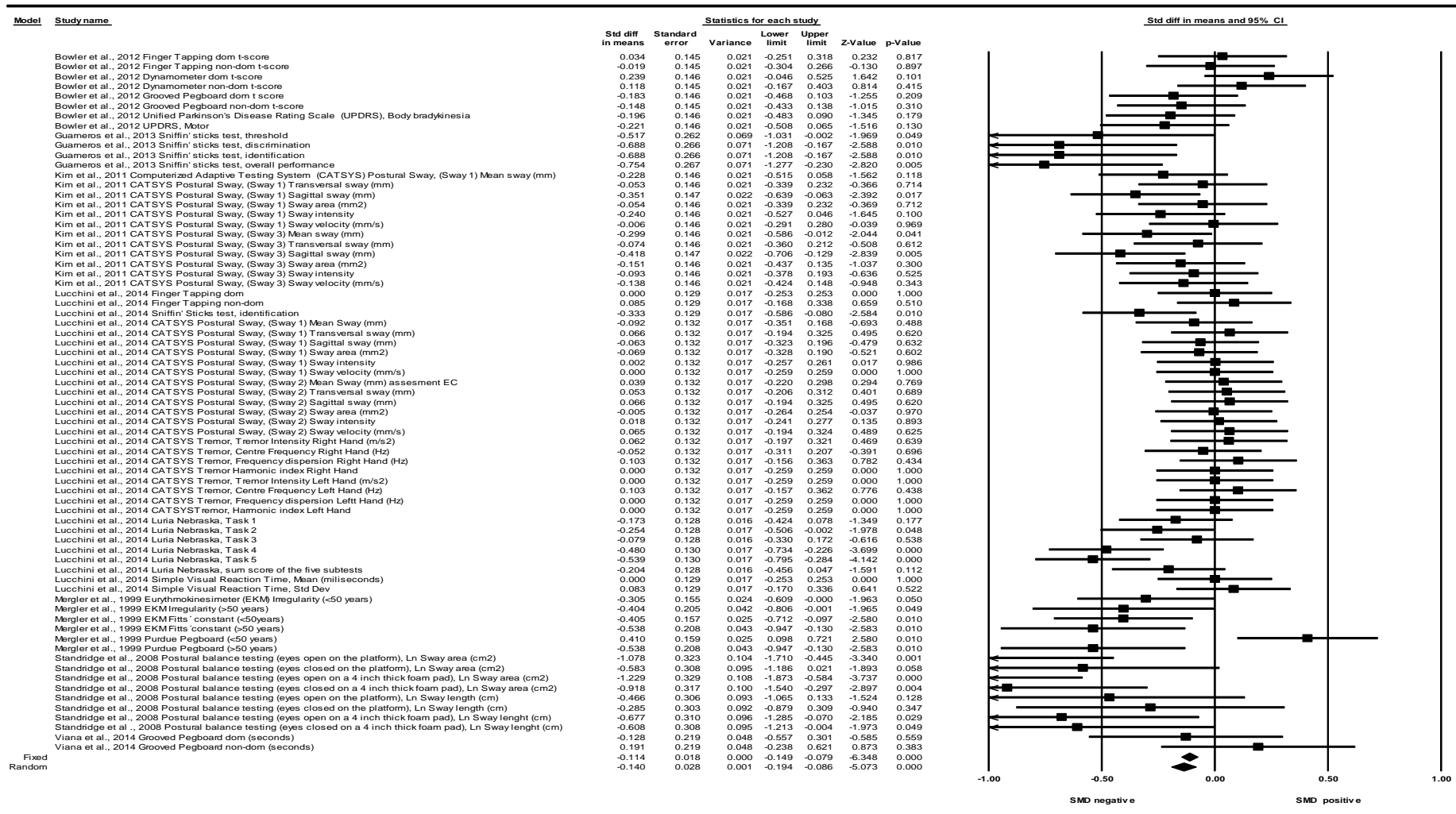
Online supplementary Figure S8. Correlation between motor function and Mn exposure, as a function of the motor test used. Note: a negative correlation indicates that the higher the Mn levels, the worse the motor function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (τ^2) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



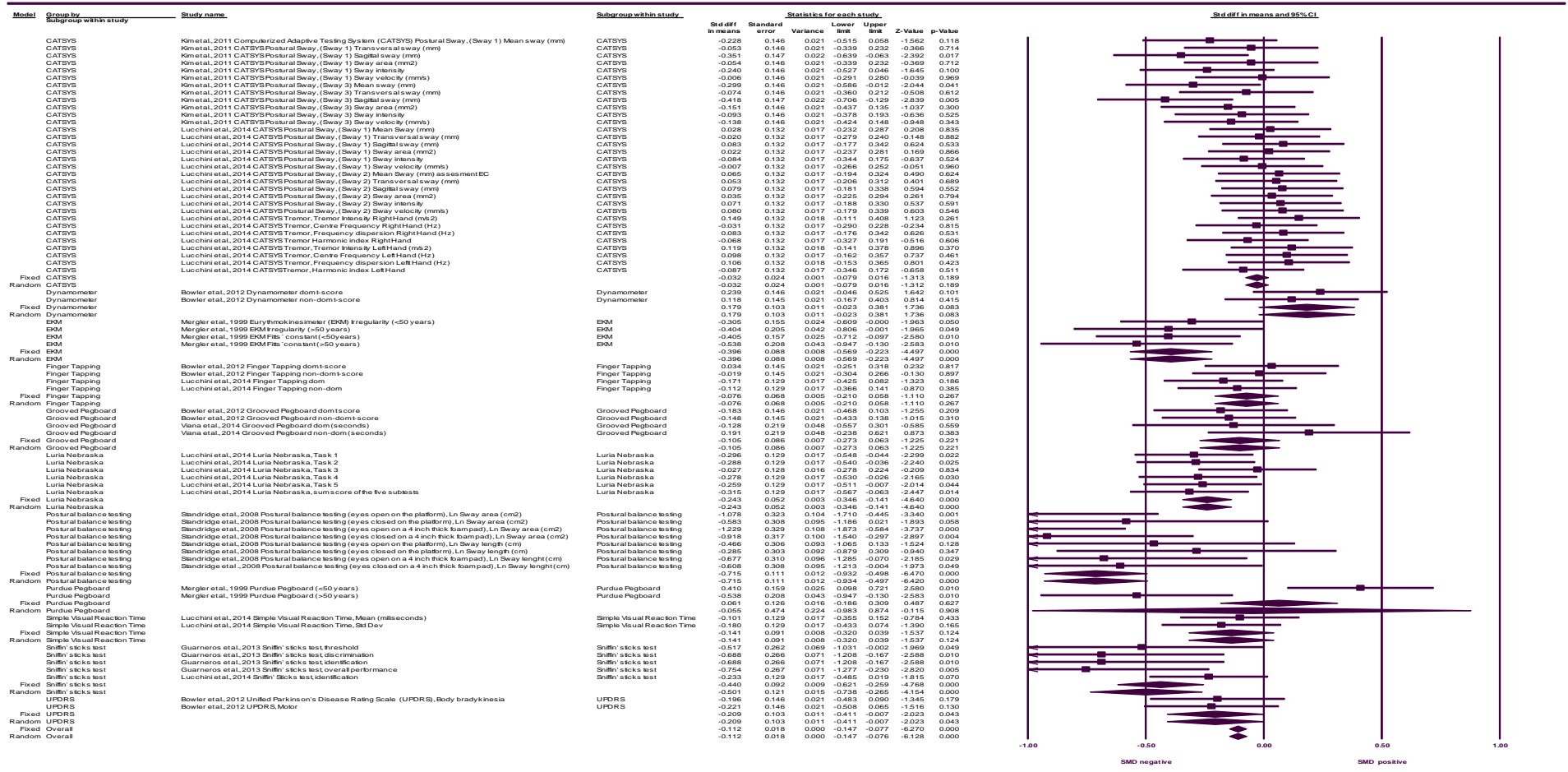
Online supplementary Figure S9. Correlation between motor function and Mn exposure, as a function of the motor domain assessed. Note: a negative correlation indicates that the higher the Mn levels, the worse the motor function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



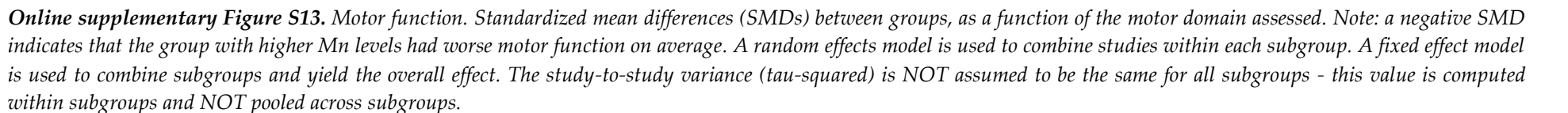
Online supplementary Figure S10. Correlation between motor function and Mn exposure, as a function of the type of exposure to Mn evaluated. Note: a negative correlation indicates that the higher the Mn levels, the worse the motor function. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



Online supplementary Figure S11. Motor function. Standardized mean differences (SMDs) between groups, prioritizing the use of medians versus means (when both medians and means were reported). All tests and all exposures to Mn. Note: a negative SMD indicates that the group with higher Mn levels had worse motor function on average.



Online supplementary Figure S12. Motor function. Standardized mean differences (SMDs) between groups, as a function of the motor test used. Note: a negative SMD indicates that the group with higher Mn levels had worse motor function on average. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.



A forest plot illustrating the association between the use of a mobile phone and the risk of COVID-19 infection. The plot displays 18 individual studies as squares with horizontal error bars, and a pooled diamond estimate at the bottom. The x-axis represents the Standardized Mean Difference (SMD) from -1.00 to 1.00, with a vertical line at 0.00. Most studies show a positive association, with the pooled estimate being approximately 0.02.

Online supplementary Figure 14. Motor function. Standardized mean differences (SMDs) between groups, as a function of the type of exposure to Mn evaluated. Note: a negative SMD indicates that the group with higher Mn levels had worse motor function on average. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is NOT assumed to be the same for all subgroups - this value is computed within subgroups and NOT pooled across subgroups.

Online supplementary appendices

Online supplementary appendix 1.1. Studies based on the same geographical areas or exposed population.

Beuter et al. (1999), is the same study as Mergler et al. (1999) based on 273 healthy persons (without cognitive impairment) from Southwest Quebec (Canada) where a former Mn alloy production plant existed [30,31]. Mergler et al. was the only one reporting mean differences susceptible of meta-analysis. Anyway, in Beuter et al. study, exposure to Mn was also found to be associated with a decrease in ability to perform regular, rapid and precise pointing movements and a decrease in ability to attain high maximum rotation speeds in rapid alternated movement, and an increase in regularity of tremor oscillations.

In Bowler et al. (2012), the population of Marietta (n=100) is compared to that of Mount Vernon, Knox County, Ohio (n=90), which is considered unexposed [37]. Kim et al. (2011) is the same population study as Bowler et al. (2012) [36]. In Bowler et al. (2015 and 2016), the population of Marietta is compared with that of East Liverpool (n=86), Ohio, also highly exposed to environmental Mn from industrial sources [28,42]. The publications by Bowler et al. in 2015 and 2016 are therefore the same study, but the first presents the results for cognitive function and the last for motor function. Kornblith et al. (2018) study [45] is also the same population study as Bowler et al. 2015 and 2016, but with different analysis strategy focused on different objectives, as this study aimed to determine whether: 1) clusters or subtypes of Tremor and No Tremor symptoms exist in Mn neurotoxicity as they do in Parkinson's disease (PD), and 2) to the extent subtypes exist, whether the clustering of No Tremor symptoms and executive functioning (EF) impairment resembles the clustering seen in samples of PD patients. The study published by Standridge et al. (2008), also includes healthy (non-cognitively impaired) individuals aged 19-68 (mean 50) from Marietta, Ohio [34].

From 2011 to 2013, four published articles were identified [3,32,35,39] based on the central Mexican state of Hidalgo, where the most important Mn extraction and processing facilities of Mexico are located. In Santos Burgoa et al. (2001) study, cognitive function was finally performed in 44 subjects and 27 subjects from two communities respectively which names were not detailed [32]. Rodríguez-Agudelo et al. (2006) and Solís Vivanco et al. (2009) present data from the same population study; 288 people (168 women and 120 men) from eight communities at various distances from Mn extraction or processing facilities in the district of Molango; but focusing on motor and cognitive function respectively [33,35]. In the Guarneros et al. (2013) study, 30 subjects living <1 km from the Mn processing plant (Tolago/Chiconcoac), were compared to other 30 non-exposed subjects living 50 km from the closest source of exposure [39].

Online supplementary appendix 1.2. Studies included in the systematic review but not in any analysis strategy of the meta-analysis.

As mentioned above, Beuter et al. (1999), is the same study as Mergler et al. (1999) but without reporting data susceptible of meta-analysis [30,31].

Santos Burgoa et al. (2001), using multivariate logistic regression, reported an adjusted 11.70 fold-increase in the risk of deficient cognitive performance (Mini-Mental score of less than 17) in subjects with higher levels of Blood Mn (when blood Mn was above the 75th percentile, in comparison to the lowest population 25th percentile level). No data susceptible of being included in our meta-analysis was reported [32].

In the Rodríguez-Agudelo et al. (2006) study, considering cumulative exposure index in quartiles (to have variability below and above the cutting point), there was an association between air Mn concentrations and motor tests that assessed the coordination of two movements: Odds Ratio (OR)= 3.69; 95%CI (0.9 to 15.13) and position changes in hand movements, with statistical significance: OR= 3.09; (95%CI 1.07 to 8.92). An association with tests evaluating conflictive reactions (task that explores verbal regulations of movements) was also found: OR= 2.30; 95%CI (1.00 to 5.28). No association was found between blood Mn and poorer motor tests results. No data susceptible of being included in our meta-analysis was reported [33].

In the Solís Vivanco et al. (2009) study, when using the $0.1 \mu\text{g}/\text{m}^3$ cut-off point, there was a statistically significant association between air Mn and poor performance on the digit span test (attention impairment): OR= 1.75; 95%CI (1.01 to 3.06). When using the $0.05 \mu\text{g}/\text{m}^3$ cut-off point there was no risk of poor performance on any test (e.g. OR digit span test= 1.24; 95%CI (0.67 to 2.29). There was no statistically significant association between blood Mn concentrations and cognitive function (e.g. OR MMSE= 1.17, 95%CI (0.99 to 1.38) [35].

The study by Kornblith et al (2018) is also the same study as that by Bowler et al, 2015 and 2016, but as it was based on the identification of clusters, it also did not report any data that could be meta-analysed [45].

Cabral Pinto et al. (2018) study determined potentially toxic elements (PTEs) concentrations in Urine including Mn exposure in 103 permanent residents from the industrial city of Estarreja (Portugal), >55 years old, where only 40.2% of the subjects had a normal performance on neurological tests assessing cognitive status. 18.3% showed a mild cognitive impairment compatible (MCI) and the rest (36.6%) had a cognitive performance suggestive of dementia condition. Their linear regression models showed that aluminium ($R^2 = 38\%$), cadmium ($R^2 = 11\%$) and zinc ($R^2 = 6\%$) were good predictors of the scores of the MMSE cognitive test, but Mn was not showed as a good predictor. Specific R^2 result for Mn is not reported [44].

The article published by Rafiee et al.(2019) also met inclusion criteria for our meta-analysis, as it assessed the effects of exposure to heavy metals including Mn determined through hair obtained by volunteers in hairdressing salons (in their usual haircuts), on cognitive function in the domains of attention and executive function determined through TMT* (A and B). Finally, their results could not be included in any of our final analyses, because they reported no correlation and no difference in means between groups. Their analysis strategy was based on a difference in TMT* scores for each unit increase in exposure, determined through the additive coefficient (β) obtained through a linear regression model. Mn levels in hair were significantly associated with 0.201 and 0.204 more seconds per one $1 \mu\text{g}/\text{g}$ of Mn in TMT*-A and B score respectively, supporting the hypothesis that the higher the exposure, the worse the cognitive function [46].

Online supplementary appendix 1.3. *Studies included in some meta-analysis strategy, but which also provided other results that could not be meta-analysed.*

Kim et al. (2011) in US, reported also motor function data subsidiary to be analyzed through a SMD in our meta-analysis. In addition, they reported positive Odds Ratios ORs between abnormal Unified Parkinson's Disease Rating Scale (UPDRS) findings (scores > 0) using "Motor and Bradykinesia" criteria, with respect to study group (exposed vs. comparison town), after adjustment for covariates. Regarding correlation analysis, they showed that there was not a significant correlation between Mn-B or modeled air-Mn levels and any of the seven postural sway parameters measured using the CATSYS 2000 system (Coordination Ability Test System, Danish Product Development), but data were not shown so it was not possible to include these data in the motor function & correlation meta-analysis approach [36].

Guarneros et al. (2013) in Mexico, reported motor function data subsidiary to be analyzed through a SMD in our meta-analysis. In addition, they reported an association between Mn exposure and worse motor function in the form of Odds Ratios (ORs). The median level of hair Mn ($9.73 \mu\text{g}/\text{g}$) in subjects living <1 km from a Mn processing plant were 9-fold higher (OR=9) than median levels ($1.01 \mu\text{g}/\text{g}$) in non-exposed subjects living 50 km from the closest source of exposure, $p<0.001$. A tendential negative correlation was found between hair Mn and the performance of subjects within each group on Sniffin' sticks 3 subtests battery. Although this was clearer for the exposed than for the control subjects, none of the correlations reached significance for either group. Specific data were not shown so it was not possible to include these data in the Motor Function & correlation meta-analysis approach [39].

Iqbal et al. (2018) in Pakistan, reported cognitive function data subsidiary to be analyzed through a correlation coefficient in our meta-analysis. In addition to determining correlations, they compared

the means of Mn blood levels in 4 groups ordinarily classified based on MMSE scores. These data could not be included in the approach to SMD and cognitive function, but their results showed that mean Blood Mn levels were significantly higher in each of the cognitively impaired patients ordinal categorized according to their MMSE scores [43].