THE PHIME STUDY: FROM BRESCIA TO TARANTO

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University of Brescia

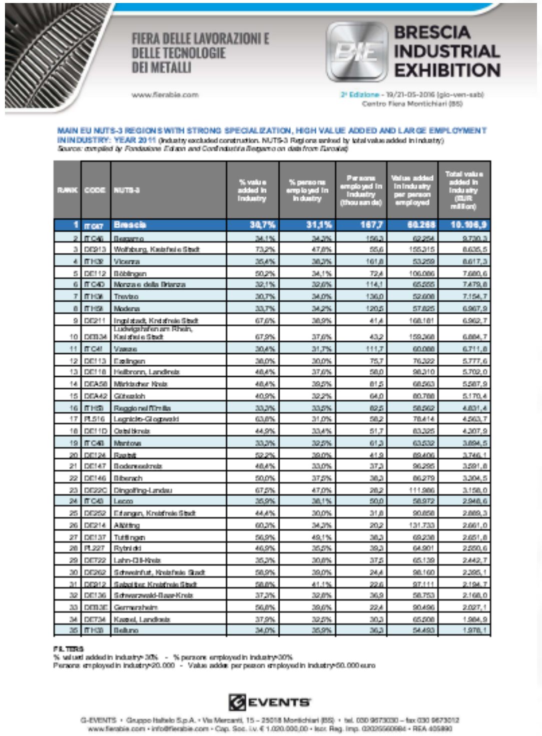
THE PUBLIC HEALTH IMPACT OF METALS/MANGANESE EXPOSURE PROJECT

PHIME

- Study site
- Subjects and findings
- Future perspectives and Issues

STUDY SITES

- automotive
- metallurgy
- surface treatment
- robotics
- weapons



FIERA DELLE LAVORAZIONI E DELLE TECNOLOGIE DEI METALLI

BRESCIA INDUSTRIAL EXHIBITION

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Centro Fiera Montichiari (BS)

MAIN EU NUTS-3 REGIONS WITH STRONG SPECIALIZATION, HIGH VALUE ADDED AND LARGE EMPLOYMENT IN INDUSTRY: YEAR 2011 (Industry excluded construction. NUTS-3 Regions ranked by total value added in industry)
Source: compiled by Fondazione Edison and Confindustria Bergamo on data from Eurostat)

RANK	CODE	NUTS-3	% value added in Industry	% persons employed in Industry	Persons employed in Industry (thousands)	Value added in Industry per person employed	Total value added in Industry (EUR million)
1	ITC47	Brescia	30,7%	31,1%	167,7	60.268	10.106,9
2	ITC46	Bergamo	34,1%	34,3%	156,3	62.254	9.730,3
3	DE913	Wolfsburg, Kreisfreie Stadt	73,2%	47,8%	55,6	155.315	8.635,5
4	ITH32	Vicenza	35,4%	38,3%	161,8	53.259	8.617,3
5	DE112	Böblingen	50,2%	34,1%	72,4	106.086	7.680,6
6	ITC4D	Monza e della Brianza	32,1%	32,6%	114,1	65.555	7.479,8
7	ITH34	Treviso	30,7%	34,0%	136,0	52.608	7.154,7
8	ITH54	Modena	33,7%	34,2%	120,5	57.825	6.967,9
9	DE211	Ingolstadt, Kreisfreie Stadt	67,6%	38,9%	41,4	168.181	6.962,7
10	DEB34	Ludwigshafen am Rhein, Kreisfreie Stadt	67,9%	37,6%	43,2	159.368	6.884,7
11	ITC41	Varese	30,4%	31,7%	111,7	60.088	6.711,8
12	DE113	Esslingen	38,0%	30,0%	75,7	76.322	5.777,6
13	DE118	Heilbronn, Landkreis	48,4%	37,6%	58,0	98.310	5.702,0
14	DEA58	Märkischer Kreis	48,4%	39,5%	81,5	68.563	5.587,9
15	DEA42	Gütersloh	40,9%	32,2%	64,0	80.788	5.170,4
16	ITH53	Reggio nell'Emilia	33,3%	33,5%	82,5	58.562	4.831,4
17	PL516	Legnicko-Głogowski	63,8%	31,0%	58,2	78.414	4.563,7
18	DE11D	Ostalbkreis	44,9%	33,4%	51,7	83.325	4.307,9
19	ITC4B	Mantova	33,3%	32,5%	61,3	63.532	3.894,5
20	DE124	Rastatt	52,2%	39,0%	41,9	89.406	3.746,1
21	DE147	Bodenseekreis	48,4%	33,0%	37,3	96.295	3.591,8
22	DE146	Biberach	50,0%	37,5%	38,3	86.279	3.304,5
23	DE22C	Dingolfing-Landau	67,5%	47,0%	28,2	111.986	3.158,0
24	ITC43	Lecco	35,9%	38,1%	50,0	58.972	2.948,6
25	DE252	Erlangen, Kreisfreie Stadt	44,4%	30,0%	31,8	90.858	2.889,3
26	DE214	Altötting	60,3%	34,3%	20,2	131.733	2.661,0
27	DE137	Tuttlingen	56,9%	49,1%	38,3	69.238	2.651,8
28	PL227	Rybnicki	46,9%	35,5%	39,3	64.901	2.550,6
29	DE722	Lahn-Dill-Kreis	35,3%	30,8%	37,5	65.139	2.442,7
30	DE262	Schweinfurt, Kreisfreie Stadt	58,9%	39,0%	24,4	98.160	2.395,1
31	DE912	Salzgitter, Kreisfreie Stadt	58,8%	41,1%	22,6	97.111	2.194,7
32	DE136	Schwarzwald-Baar-Kreis	37,3%	32,8%	36,9	58.753	2.168,0
33	DEB3E	Germersheim	56,8%	39,6%	22,4	90.496	2.027,1
34	DE734	Kassel, Landkreis	37,9%	32,5%	30,3	65.508	1.984,9
35	ITH33	Belluno	34,0%	35,9%	36,3	54.493	1.978,1

FILTERS
% valued added in industry>30% - % persons employed in industry>30%
Persons employed in industry>20.000 - Value added per person employed in industry>50.000 euro

EVENTS

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The Blacksmith's House
Bronze age, Val Camonica

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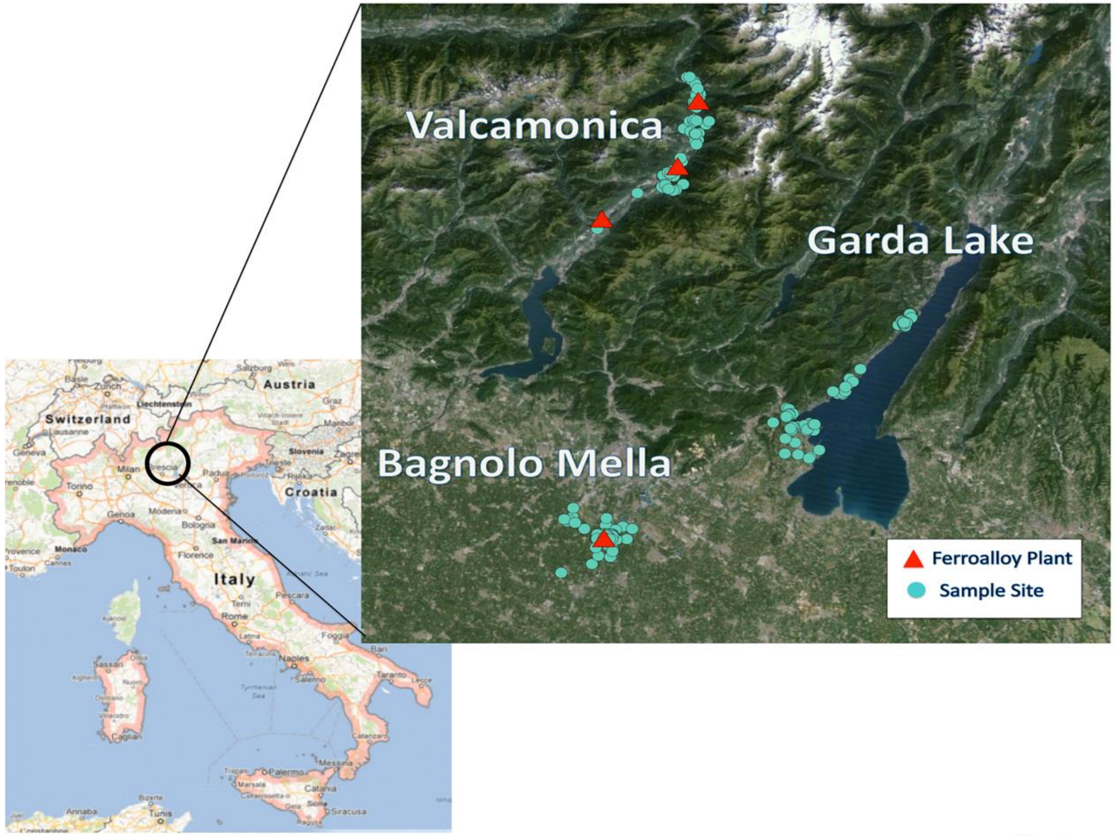
WORKERS

Ferroalloy production (Si-Mn, Fe-Mn, Fe-Cr)
Exposure ⇒ Mn (MnO_2, Mn_3O_4), Fe, Pb, Zn, Cu, Cr, Cd



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WORKERS

MANGANISM

- Clinical intoxication among workers, resembling Parkinsonism
- Main difference is the target site in the Basal Ganglia: globus pallidus instead of substantia nigra
- Not seen today but important to understand for preventive purposes

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WORKERS

- N° 300
- Follow-up 1980-2006
  - Annual air/bio-monitoring, lab profile, PFT
  - DNA banked
  - Cumulative Exposure metrics
  - 6 data points neuropsychological testing (1980-1991-1993-1997-2001-2006)

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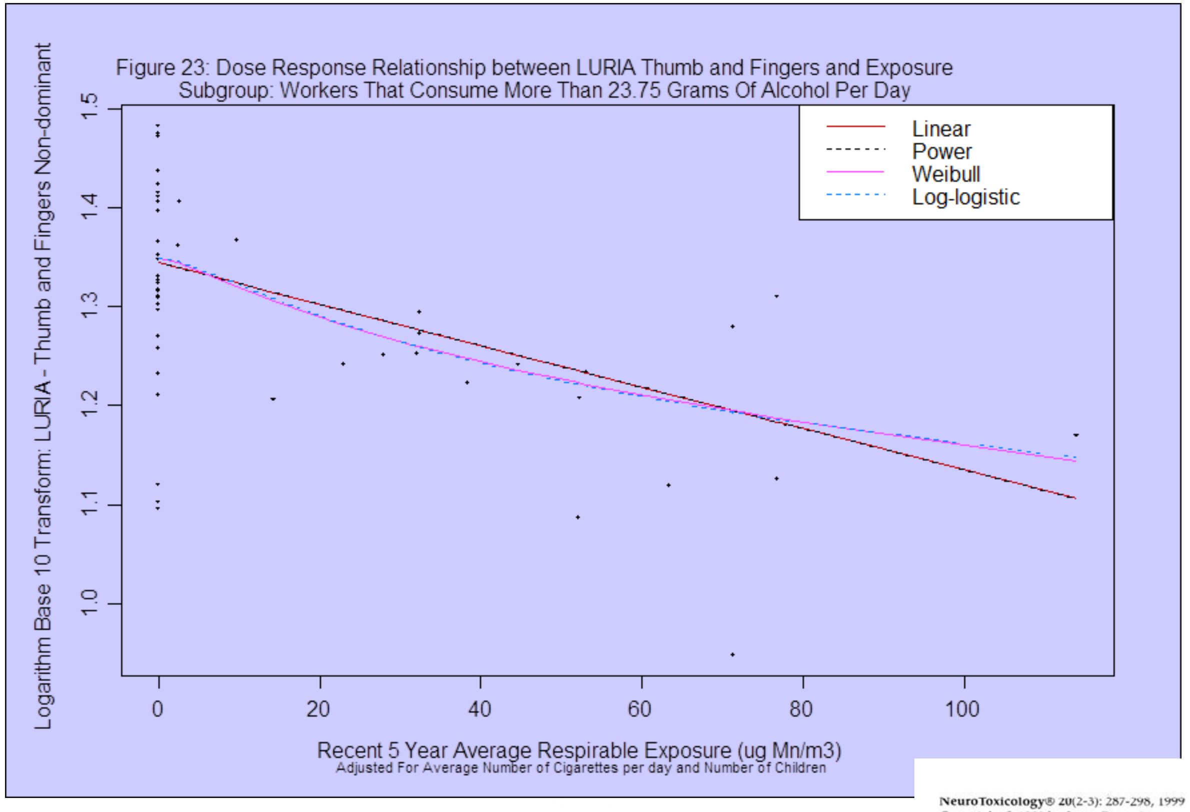
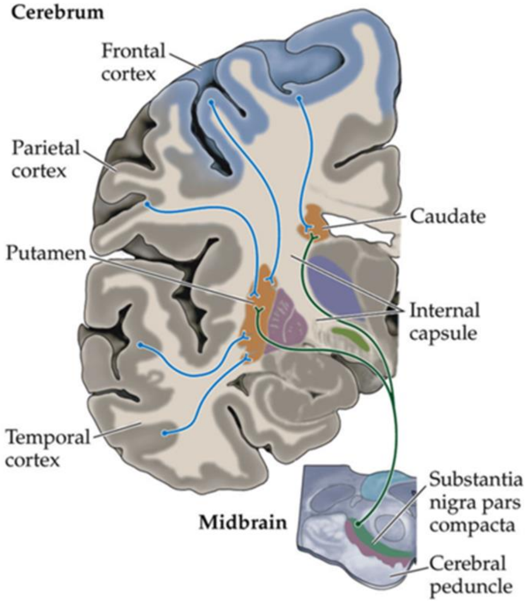
WORKERS

WORKERS





NeuroToxicology® 20(2-3): 287-298, 1999

Long Term Exposure to "Low Levels" of Manganese Oxides and Neurofunctional Changes in Ferroalloy Workers

Roberto Lucchini[1], Pietro Apostoli[1], Carmine Perrone[1], Donatella Placidi[1], Elisa Albini[1], Piera Migliorati[1], Donna Mergler[2], Marie-Pascale Sassine[2], Silvana Palmi[3], Lorenzo Alessio[1]

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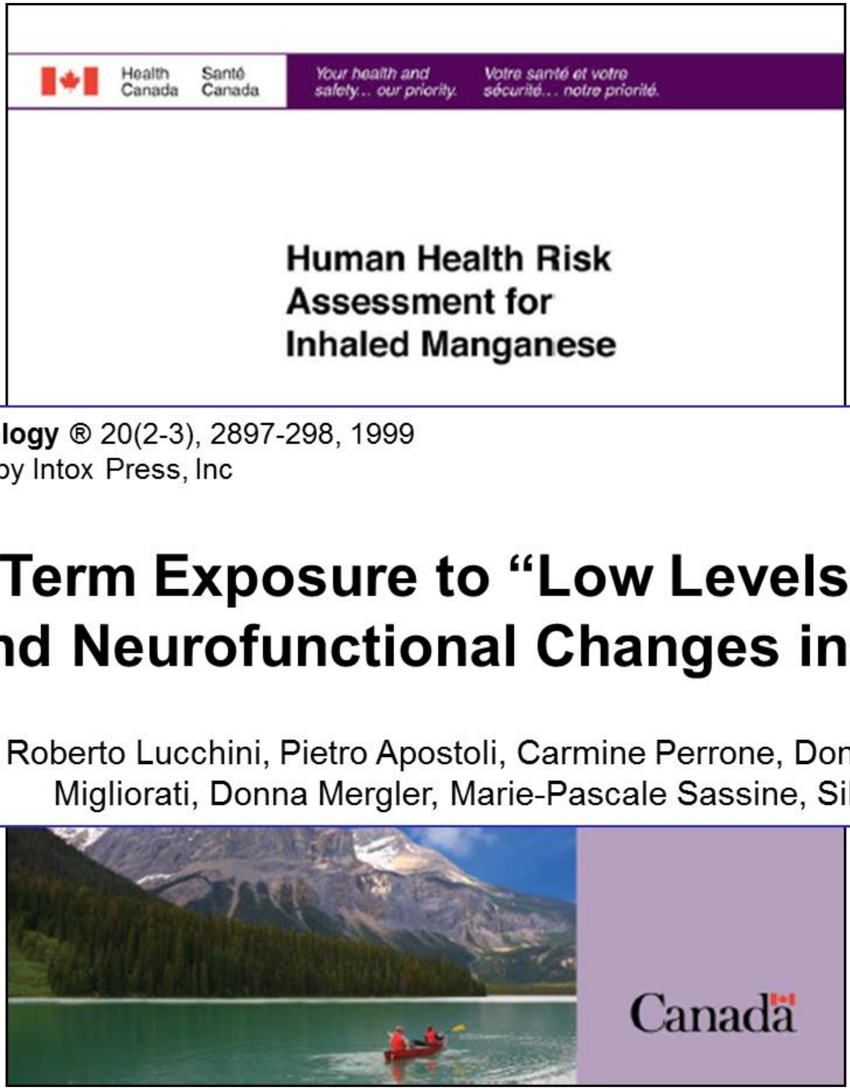
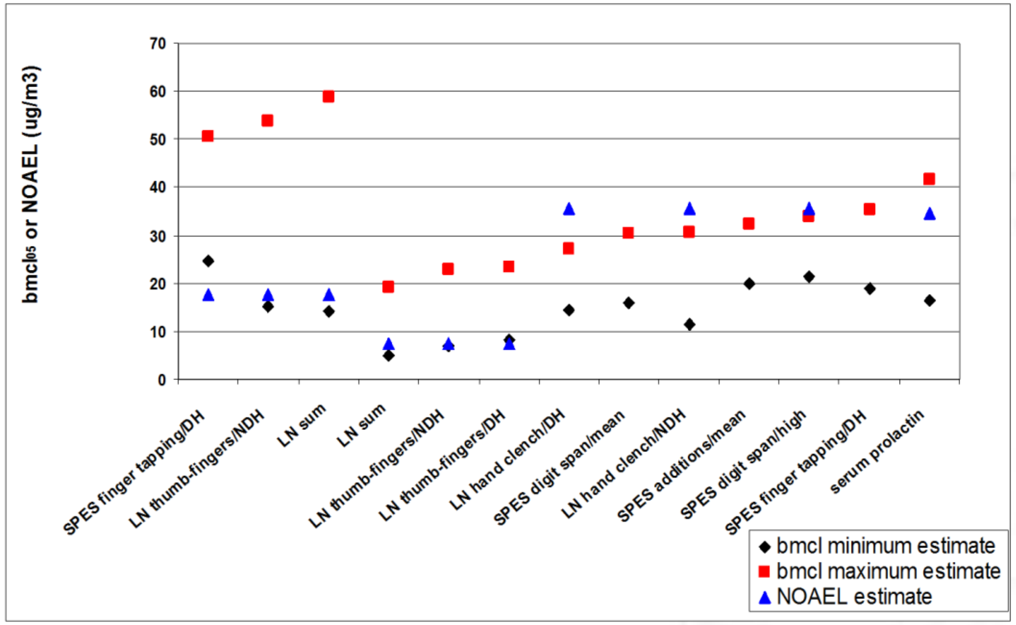
WORKERS



Health Canada Santé Canada

Your health and safety... our priority. Votre santé et votre sécurité... notre priorité.

Human Health Risk Assessment for Inhaled Manganese



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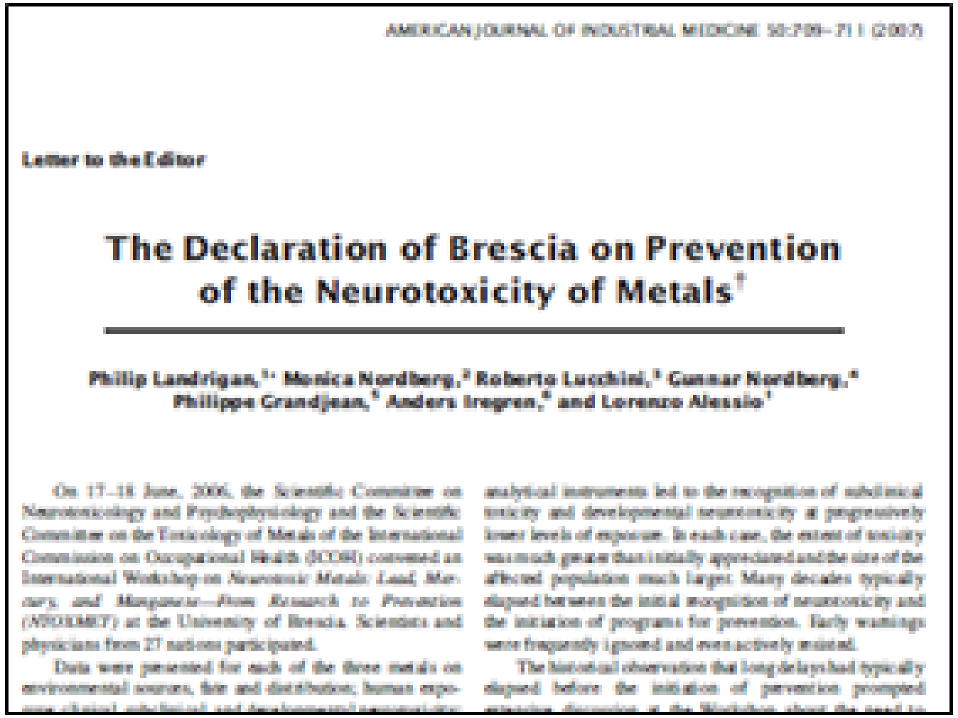
WORKERS



AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 50:709–711 (2007)

Letter to the Editor

The Declaration of Brescia on Prevention of the Neurotoxicity of Metals†

Philip Landrigan,[1]* Monica Nordberg,[2] Roberto Lucchini,[3] Gunnar Nordberg,[4] Philippe Grandjean,[5] Anders Iregren,[6] and Lorenzo Alessio[3]

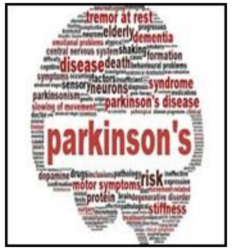
On 17–18 June, 2006, the Scientific Committee on Neurotoxicology and Psychophysiology and the Scientific Committee on the Toxicology of Metals of the International Commission on Occupational Health (ICOH) convened an International Workshop on *Neurotoxic Metals: Lead, Mercury, and Manganese—From Research to Prevention* (NTOXMET) at the University of Brescia. Scientists and physicians from 27 nations participated.

Data were presented for each of the three metals on environmental sources, fate and distribution, human expo-

analytical instruments led to the recognition of subclinical toxicity and developmental neurotoxicity at progressively lower levels of exposure. In each case, the extent of toxicity was much greater than initially appreciated and the size of the affected population much larger. Many decades typically elapsed between the initial recognition of neurotoxicity and the initiation of programs for prevention. Early warnings were frequently ignored and even actively resisted.

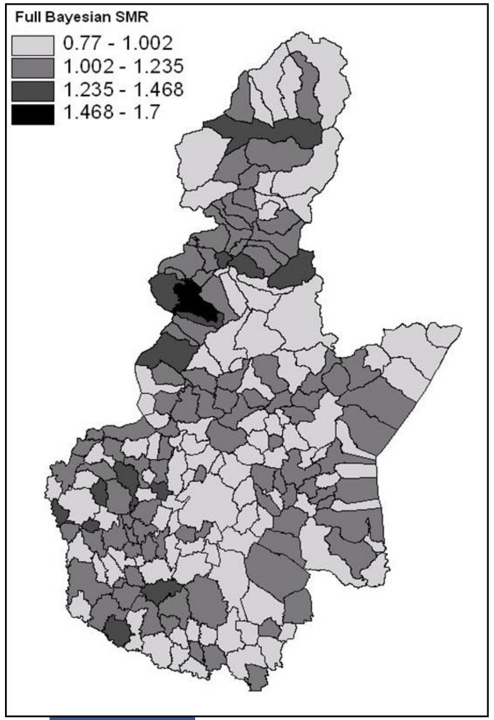
The historical observation that long delays had typically elapsed before the initiation of prevention prompted

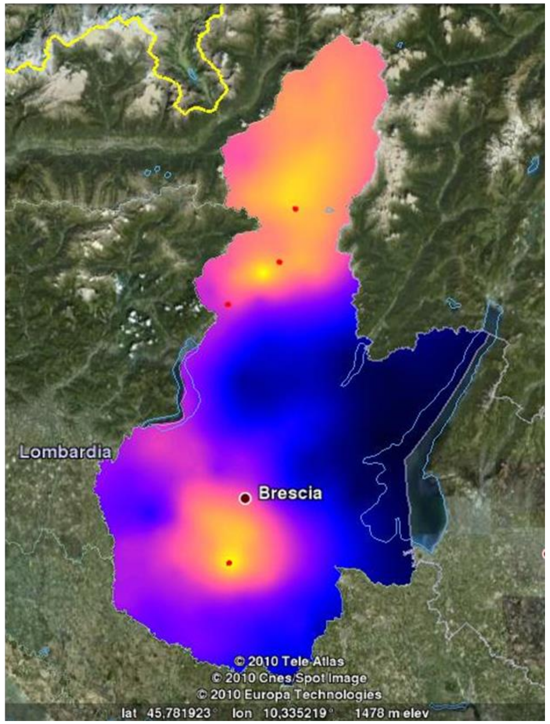
- Reduction of MMT in gasoline in China
- EU phase out proposal for fuel metallic additives



PARKINSON DISEASE

SMR Parkinsonism vs. Mn in dust
p=0.005





Study site	Cases	Population	Stand prev	Bayesian SMR
Valcamonica	324	77,708	492	1.25
Rest of the Province	2,353	826,289	321	1.00
Total Province	2,677	903,997	407	
Average ITA-EU			150	
SMR = 1.58; CI=1.41-1.76				

Lucchini et al., High Prevalence Of Parkinsonian Disorders Associated To Manganese Exposure In The Vicinities Of Ferroalloy Industries. Am J Ind Med 2007; 50: 11: 788-800

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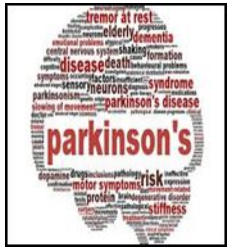
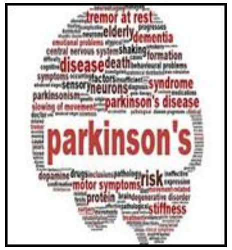


PARKINSON DISEASE

A total of 430 PD patients (38% females) were frequency matched on age and hospital admission with 446 controls with no known neurological disease.

Table 1. Characteristics of the study population

Characteristics	Controls		Cases	
	N	%	N	%
Age (years)				
40-50	16	*3,6*	9	*2,1*
51-60	65	*14,6*	42	*9,8*
61-69	137	*30,7*	114	*26,5*
71-80	168	*37,7*	178	*41,4*
81-90	60	*13,5*	87	*20,2*
Gender				
Female	175	*39,2*	162	*37,7*
Male	271	*60,8*	268	*62,3*
Born in Brescia prov.				
Yes	373	*83,6*	392	*91,2*
No	73	*16,4*	38	*8,8*
Tobacco smoking				
Never	240	*53,8*	258	*60,0*
Ever	206	*46,2*	172	*40,0*
Parental history of PD				
Yes	8	*1,8*	26	*6,0*
No	402	*90,1*	346	*80,5*



PARKINSON DISEASE

	Controls (exp/unexp)	Cases (exp/unexp)	OR (95% CI)[a]	Association with SNP rs22757007 (CC genotype)
Isco group 7 (already done)	75/126	92/128	1.28 (0.82, 2.00)	**0.005 (neg)**
Metal, Machinery and Related Trades Workers (72)	36/410	75/373	**1.84 (1.14, 2.97)**	**0.007 (neg)**
Blacksmiths, Toolmakers, and Related Trades Workers (722)	21/425	37/393	**2.01 (1.12, 3.61)**	**0.06 (neg)**
Metal Working Machine Tool Setters and Operators (7223)	18/428	32/398	**1.94 (1.04, 3.61)**	0.09
Sheet and structural metal workers, moulders and welders, and related workers (721)	10/436	13/417	1.58 (0.62, 4.06)	0.98
Machinery mechanics and repairers (723)	7/439	8/422	1.14 (0.37, 3.52)	0.62

a Adjusted for gender, age (continuously), smoking status, and parental history



THE PHIME STUDY

- 720 Adolescent boys-girls (11-14 yrs)
- 255 Elderly men-women (65-75 yrs)
- 24 Pregnant women

Period: 2006-2014

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THE PHIME STUDY

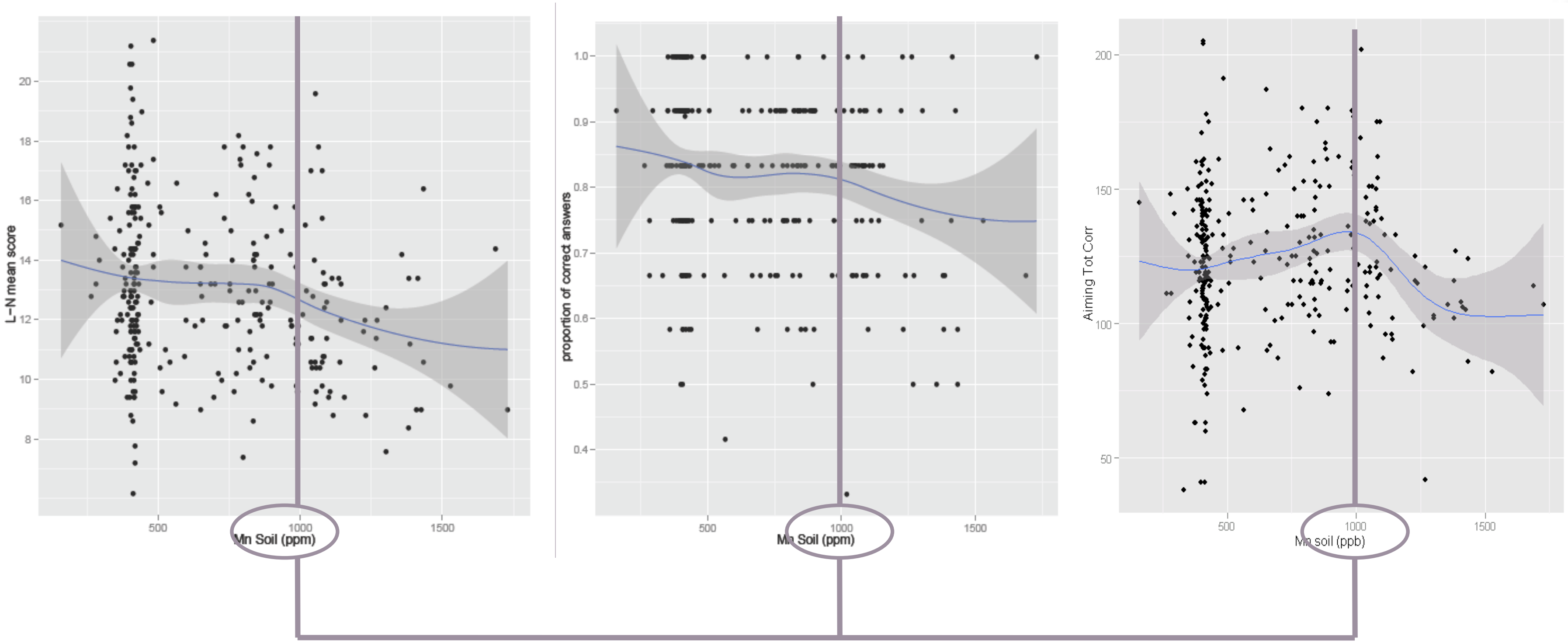
- Airborne PM10 PM2.5 (personal/stationary indoor/outdoor)
- Deposited Dust (indoor/outdoor/attic)
- Soil (surface – 10 cm layers)
- Dietary intake (Mn, Fe, Se, Zn)
- Leafy and root vegetables
- Water (public water supply/private wells)
- Biomarkers (blood, urine, hair, nails, saliva, teeth)

	Items
Measures	Anthropometrics (height, weight)
Questionnaires	Lifestyle, SES (*subjects <18 years)
	HOME environment (*subjects <18 years)
	FFQ (*subjects <18 years)
	Respiratory ISAAC
Motor/sensory testing	Luria Nebraska (5 motor coordination subtests)
	Pursuit aiming (hand dexterity)
	Danish Product Development – tremor and sway
	Swedish Performance Evaluation System – reaction time
	Swedish Performance Evaluation System – finger-tapping
	Sniffin Sticks [short PHIME-1 (10 min); full PHIME-2]
Cognitive/behavioral testing	Wechsler Intelligence Scale for Children
	California Verbal Learning Memory
	Conners' adolescent self-report scale
	Conners' parent rating scale*/teacher rating scale**
	Virtual radial arm maze
	Kaufman Brief Intelligence Test
	Cambridge Neuropsychological Test Automated Battery (CRT, RVP, SOC, CGT, SWM, PAL, ERT)
	Brown attention deficit disorder scale (self-report)
	Child Behavior Check List (*subjects <18 years)
	Adult Behavior Check List (*subjects ≥18 years)
	Social Responsiveness Scale*
Maternal testing	Raven Matrices
Brain imaging	fMRI finger tapping-working memory-olfactory stimul., T1-weighted scan, DTI, resting-state fMRI, coronal T2 FSE olfactory bulb volume, axial T2 turbo spin echo, VFA 3D FLASH for T1 mapping, B1 mapping 2D TurboFlash
BioSamples	Blood (CBC, hepatic/renal function, iron metabolism, PRL)
	Blood (Mn, Pb)
	Teeth, urine, hair, nails, saliva (Mn, Pb)
	Saliva (cortisol basal and after cold stress)
	DNA/RNA
Environmental measurements	Air personal PM10 (TXRF-metals)
	Indoor/outdoor deposited dust (ICPMS-metals)
	Soil (XRF-metals)

***Questionnaires answered by mother in regards to child. **Questionnaires answered by teacher in regards to child.**
CRT: Choice Reaction Time; RVP: Rapid Visual Information Processing; SOC: Stockings of Cambridge; CGT: Cambridge Gambling Task; SWM: Spatial Working Memory; PAL: Paired Associates Learning; ERT: Emotion Recognition Task; CBC: cell blood count; PRL: prolactin

THE PHIME STUDY

Motor Coordination | Odor identification | Hand steadiness



Cut-off soil Mn ~1000 ppm

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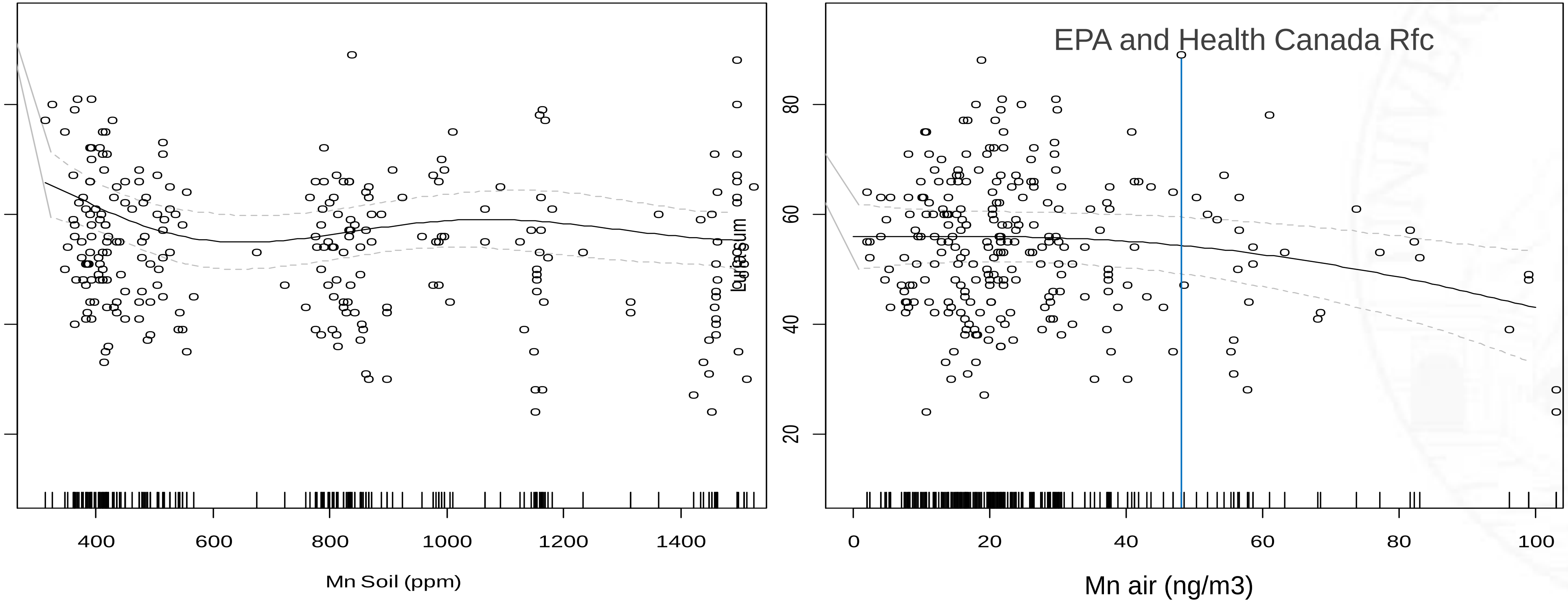
Lucchini et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. Neurotoxicology. 2012 Aug;33(4):687-96

THE PHIME STUDY

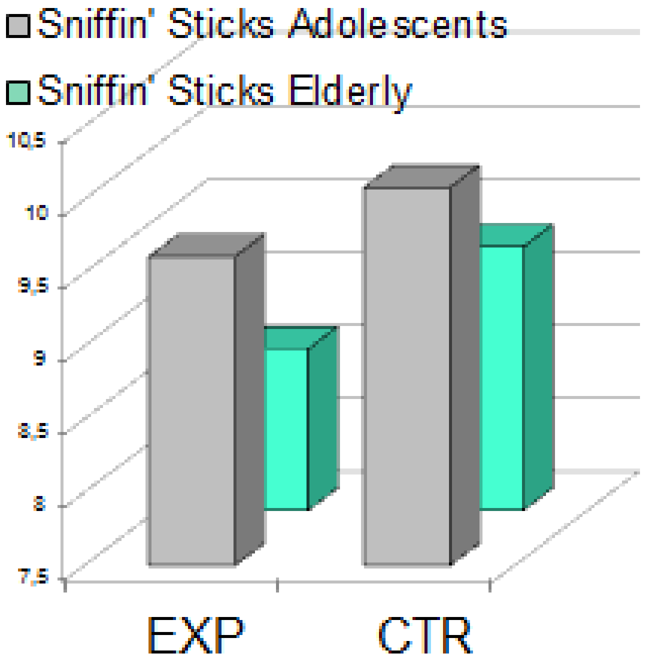


Lucchini RG et al. Neurofunctional Dopaminergic impairment in elderly after lifetime exposure to manganese. Neurotoxicol 2014;45:309-17



THE PHIME STUDY

Odor function across lifespan



Variable	Site	Mean
Adolescents		
Sniffin' Sticks P=0,005	EXP	9,61
	CTR	10,08
	ALL	9,85
Elderly		
Sniffin' Sticks P=0,021	EXP	8,60
	CTR	9,30
	ALL	8,88

Zoni et al. Olfactory functions at the intersection between environmental exposure to manganese and Parkinsonism.J Trace Elem Med Biol. 2012;26(2-3):179-82.

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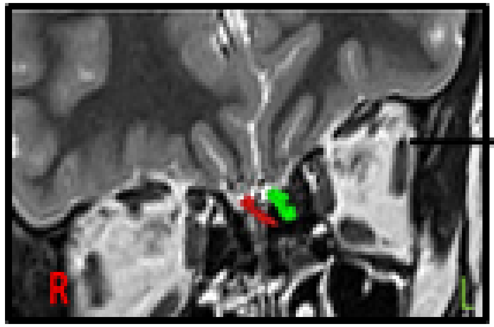
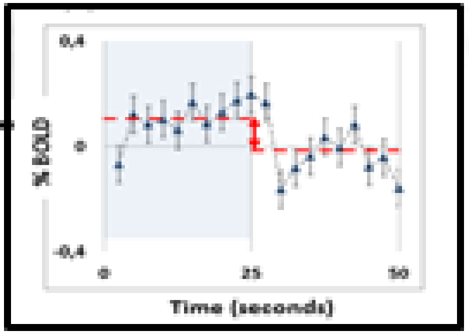
THE YOUNG ADULTS STUDY (PHIME COHORT FOLLOW UP)

OB volume and BOLD

	OB * volume mm^3	BOLD %	Odor intensity rating
Exposed (n=10)	115.5	37	5.25
Controls (n=4)	146.5	48	7





Iannilli et al. Effects of Manganese exposure on olfactory functions in teenagers: a pilot study. PLoS One. 2016 Jan 14;11(1):e0144783

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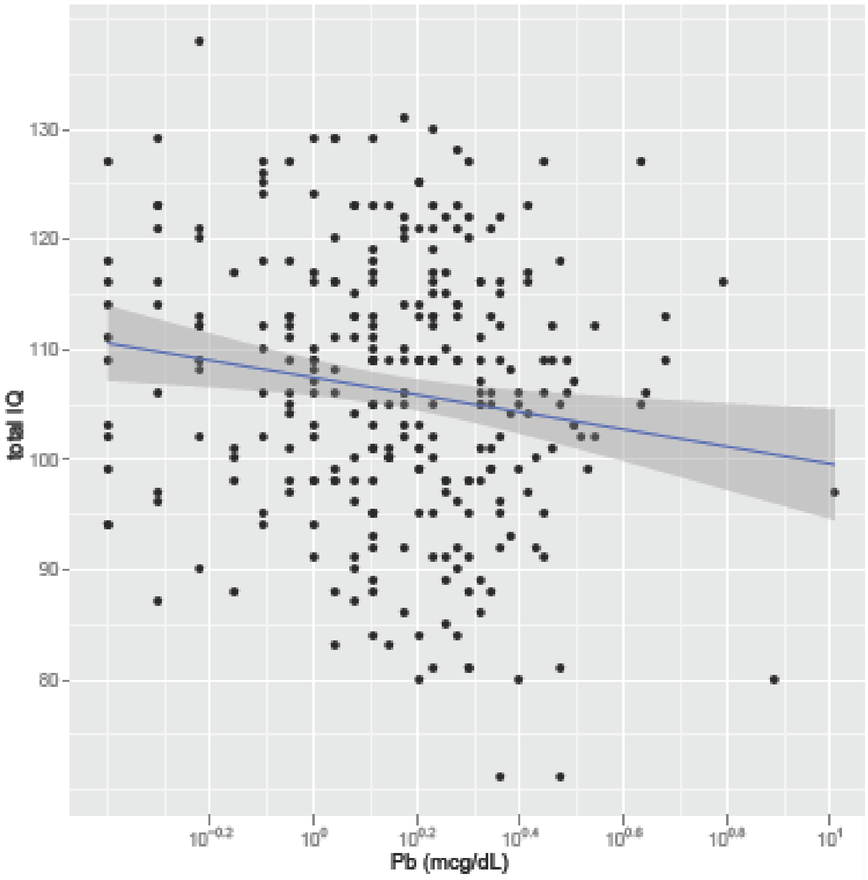
THE PHIME STUDY



Benchmark Level of BPb associated with a loss of 1 IQ-point (BML01) = 0.19 µg/dL
Lower 95% confidence limit (BMLL01) =0.11 µg/dL

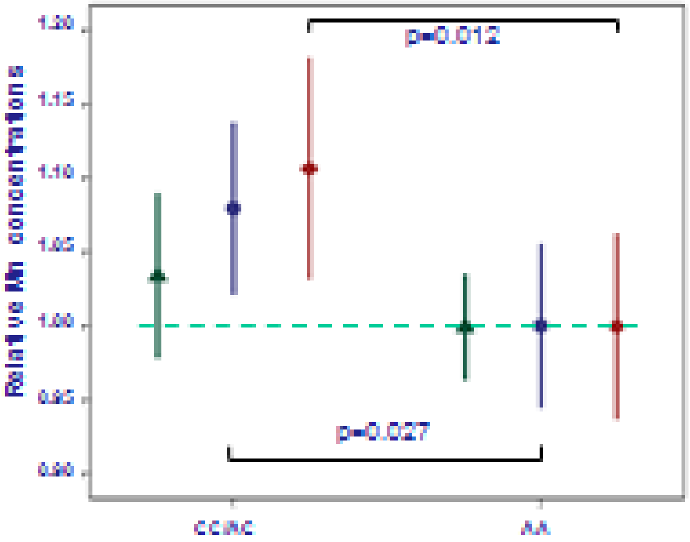


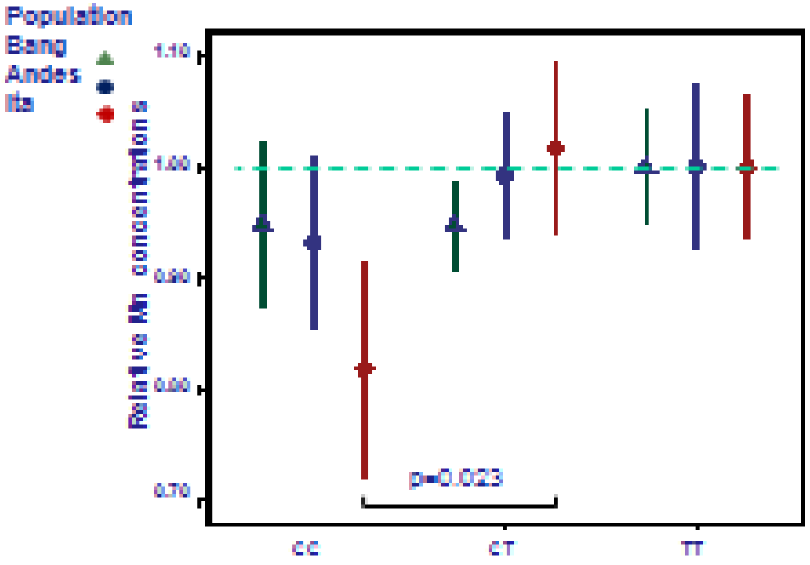
THE PHIME STUDY

Influence of SLC30A10 on elderly

rs2275707 associates with:
- increased blood Mn
- increased sway velocity

rs12064812 associates with:
- reduced blood Mn
- increased finger tapping velocity





Wahlberg K et al. Common polymorphisms in the solute carrier SLC30A10 are associated with blood manganese and neurological function. Toxicological Sciences 2016;149(2):473-83

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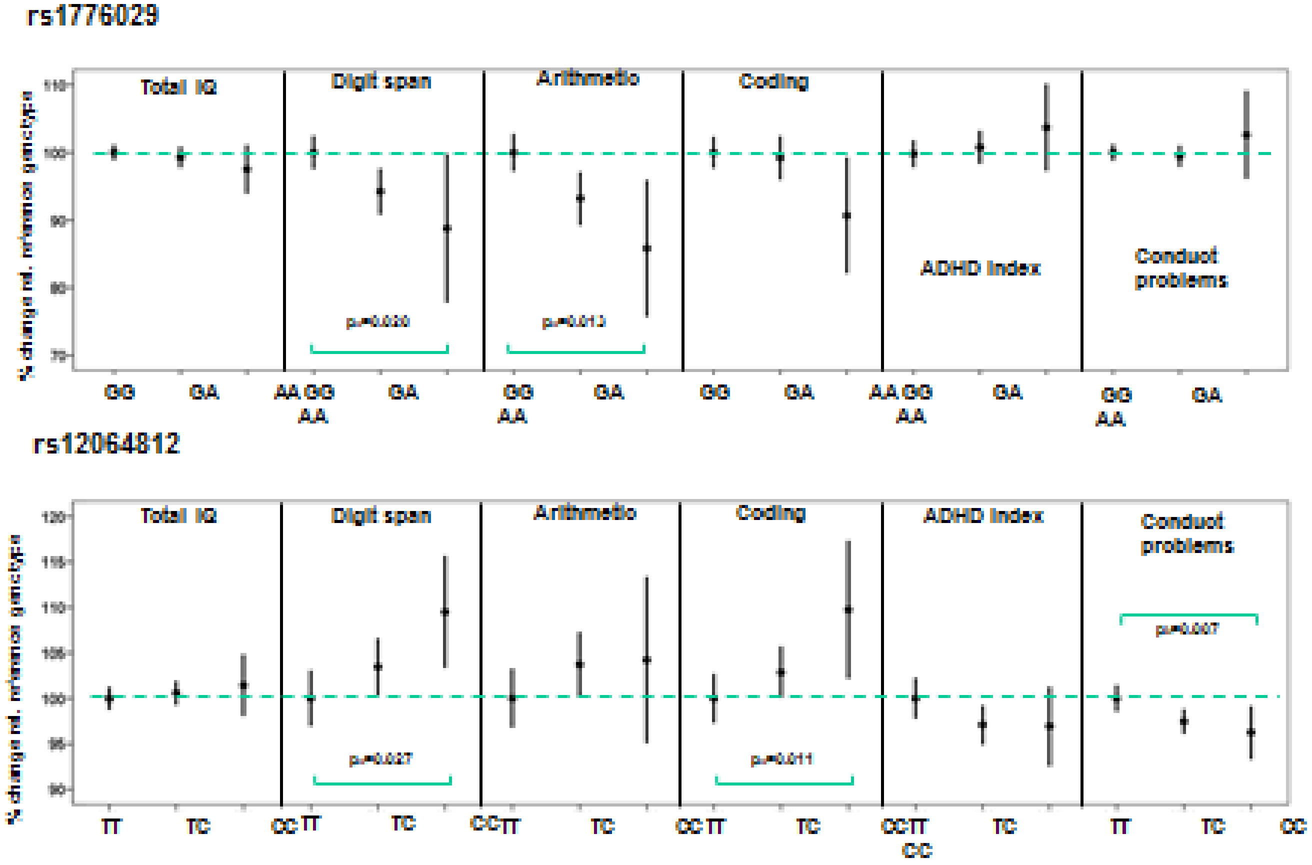
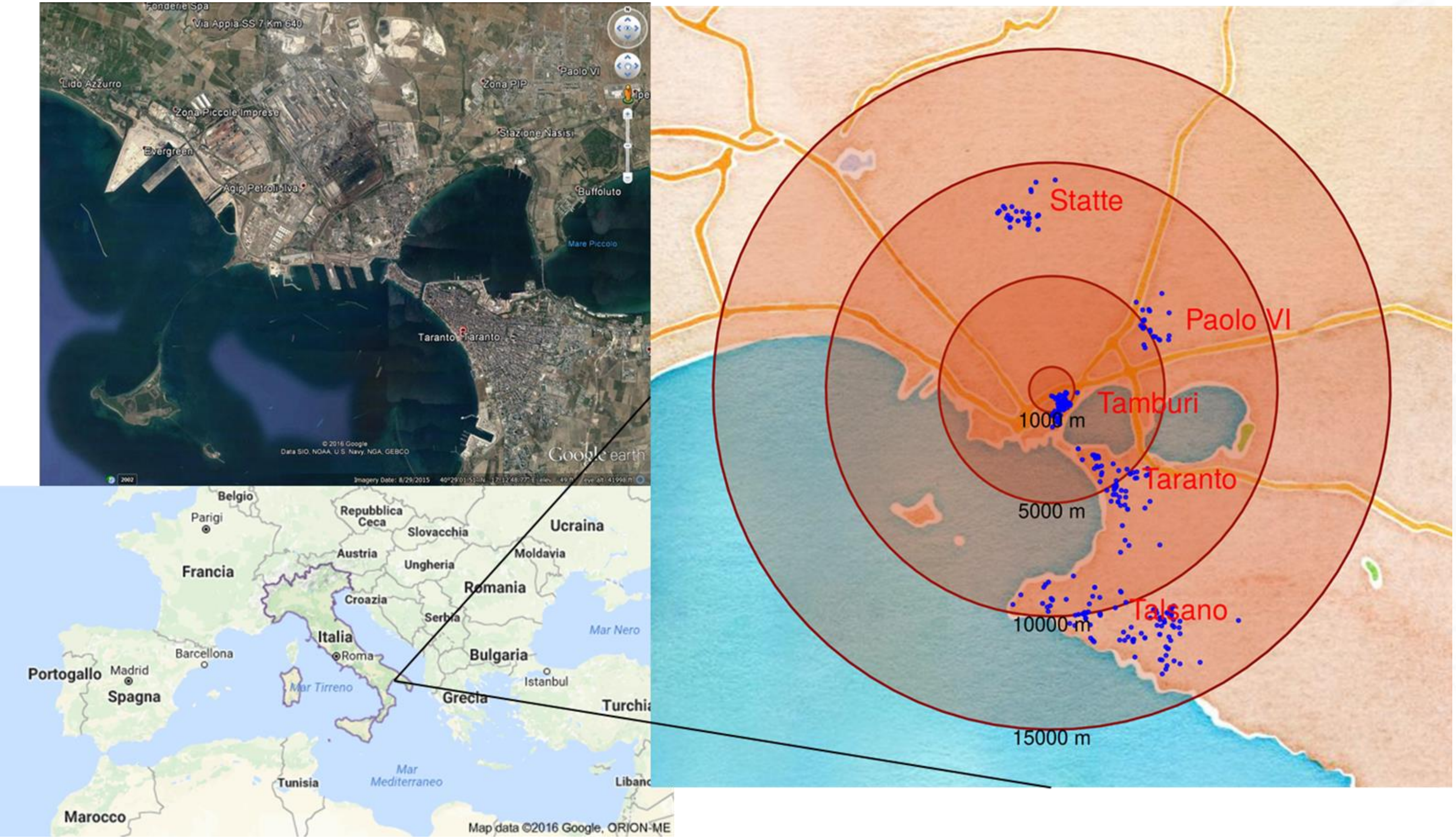
THE PHIME STUDY

Influence of SLC30A10 on children



THE BRESCIA TARANTO STUDY



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THE BRESCIA TARANTO STUDY

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THE BRESCIA TARANTO STUDY

The children-preadolescent cohort	
	Total cohort
Timeline	2006-2019
Age (years)	6-14
Sex	M/F_50%
Total population	800
Val Camonica (historical exposure)	260
Bagnolo Mella (current exposure)	300
Garda Lake (reference area)	246
TARANTO	800

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THE BRESCIA TARANTO STUDY

Variable	Total (N = 214)	Zone 1 (N = 62)	Zone 2 (N = 77)	Zone 3 (N = 75)
Sex (F)	114 (53.3%)	39 (62.9%)	38 (49.4%)	37 (49.3%)
Age (years)				
Mean (SD)	8.6 (±1.5)	8.9 (±1.6)	8.2 (±1.4)	8.6 (±1.5)
Weight (kg)				
Mean (SD)	33.1 (±10.1)	35.4 (±10.9)	31.5 (±9.4)	33.0 (±10.0)
Height (cm)				
Mean (SD)	133.6 (±11.5)	134.5 (±13.5)	132.3 (±10.6)	134.0 (±10.8)
BMI Percentile & Z-Scores				
Mean (SD)	0.8 (±1.5)	1.1 (±1.5)	0.62 (±1.5)	0.66 (±1.6)
Underweight (0.00-4.99%)	9 (4.2%)	2 (3.2%)	5 (6.5%)	2 (2.7%)
Healthy (5.00-84.99%)	109 (50.9%)	27 (43.6%)	39 (50.6%)	43 (57.3%)
Overweight (85.00-94.99%)	47 (22.0%)	16 (25.8%)	20 (26.0%)	11 (14.7%)
Obese (95.00-100.00%)	49 (22.9%)	17 (27.4%)	13 (16.9%)	19 (25.3%)
Socioeconomic Status				
Low	91 (42.5%)	41 (66.1%)	26 (33.8%)	24 (32.0%)
Medium	70 (32.7%)	16 (25.8%)	25 (32.5%)	29 (38.7%)
High	53 (24.8%)	5 (8.1%)	26 (33.8%)	22 (29.3%)
BG (mg/dL)	*(N = 212)*	*(N = 62)*	*(N = 76)*	*(N = 74)*
Mean (SD)	85.5 (±6.6)	87.8 (±6.3)	85.5 (±7.1)	83.5 (±5.6)

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THE BRESCIA TARANTO STUDY

Sociodemographic Variable	BMI Z-Score	BG adjusted by BMI Z-Score
BMI Z-Score		0.337
		(-0.254, 0.928)
Zone 2 vs Zone 1	-0.223	-2.518*
	(-0.755, 0.309)	(-4.813, -0.224)
Zone 3 vs Zone 1	-0.052	-4.638***
	(-0.606, 0.501)	(-7.020, -2.255)
SES: Medium vs Low	-0.23	1.453
	(-0.729, 0.269)	(-0.699, 3.606)
SES: High vs Low	0.199	1.71
	(-0.699, 1.096)	(-2.157, 5.576)
Maternal Education: 13 years vs 5-8 years	-0.539*	-0.203
	(-1.056, -0.023)	(-2.450, 2.044)
Maternal Education: 16+ years vs 5-8 years	-1.031*	-0.761
	(-2.014, -0.048)	(-5.037, 3.514)
Constant	1.347***	87.036***
	(0.934, 1.760)	(85.089, 88.983)
R2	0.061	0.086
Adjusted R2	0.034	0.054
Residual Std. Error	1.488 (df = 204)	6.405 (df = 203)
F Statistic	2.227* (df = 6; 204)	2.726* (df = 7; 203)

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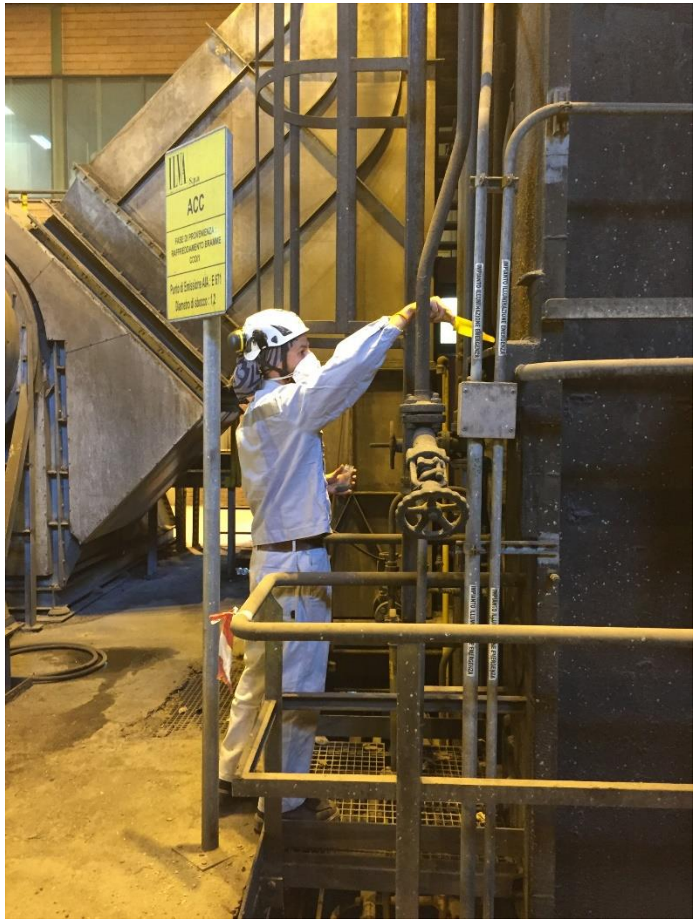
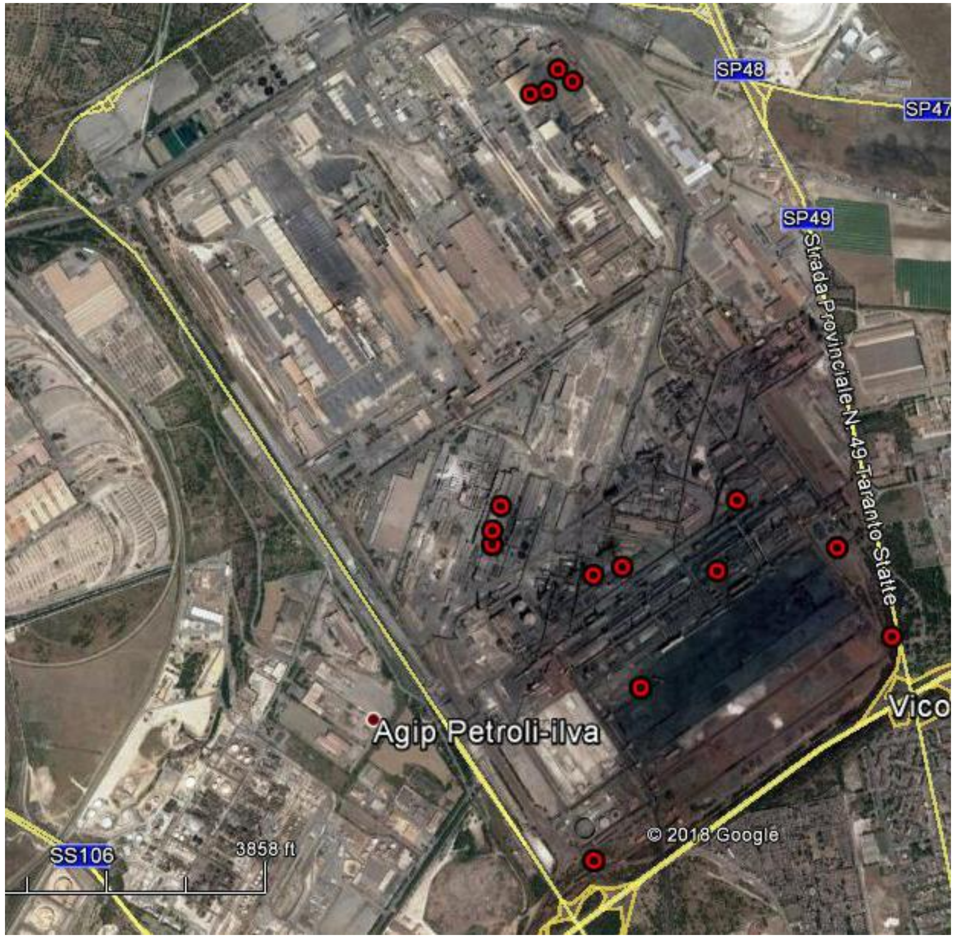
Dust Sampling

Taranto, Alto Forno 2 of Ilva plant



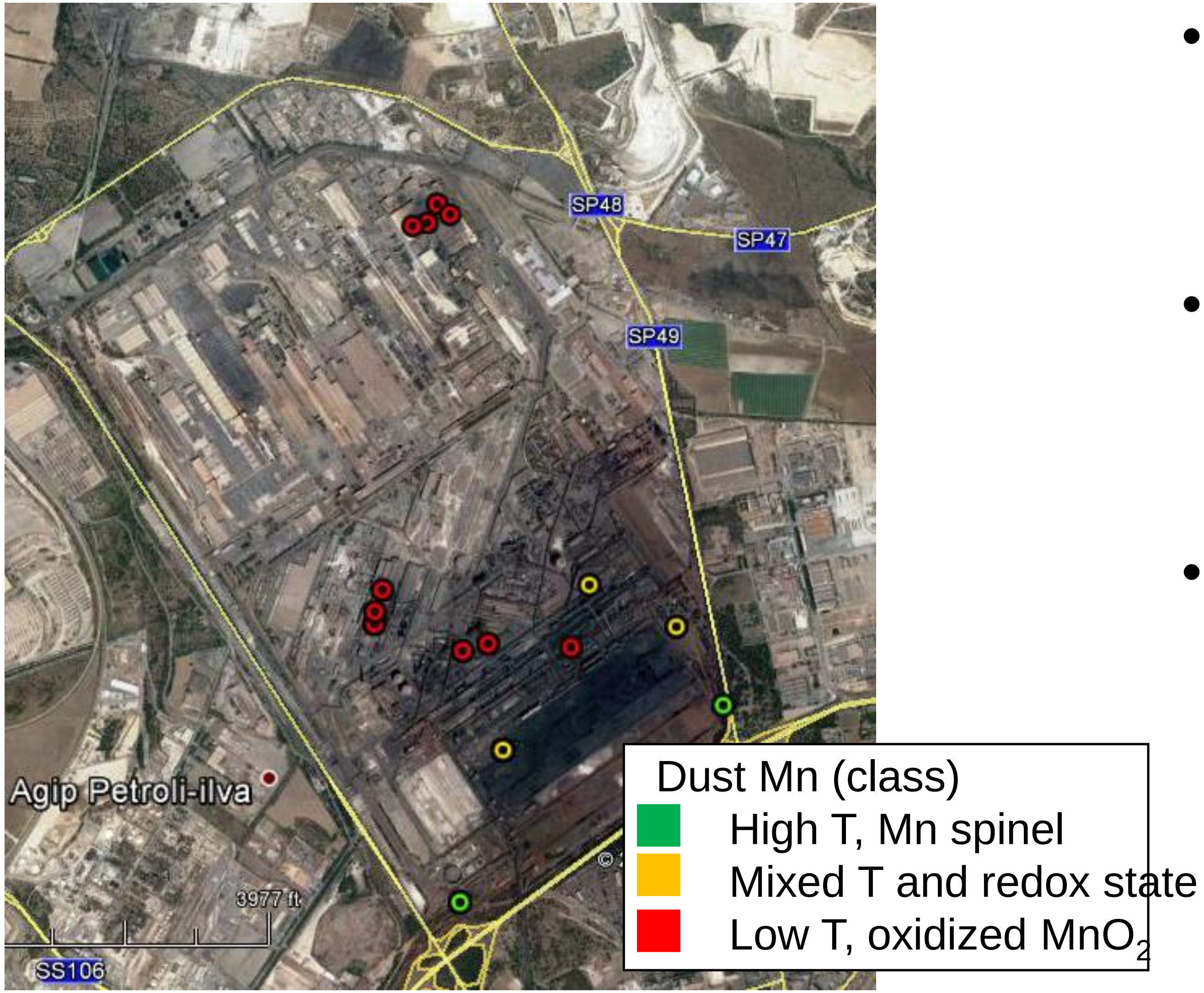
Taranto, ACC1 area of Ilva plant



Sampling locations

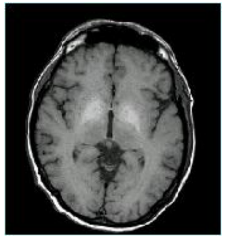
Dusts obtained from Ilva plant, and analyzed at Stanford University Stanford Synchrotron Radiation Laboratory (SSRL) and Canadian Light Source (CLS)

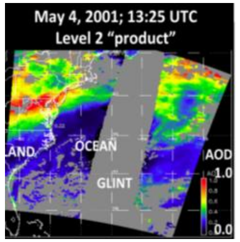
Results: Ilva Dust Characterization: Mn Speciation



- High Temperature areas of the plant have a chemical form of Mn that is primarily $(Fe,Mn)_3O_4$
- The ore storage areas have Mn speciation that mirrors ore, is primarily oxidized MnO_2
- The exposure and toxicity of MnO_2 in ores is distinct from high T dusts, and each pose unique risks

THE ONGOING STUDIES





ISSUES

- COMMUNITY ENGAGMENT
- BIOBANKING
- TRACKING SAMPLES
- SETTING DATASETS FOR ANALYSIS

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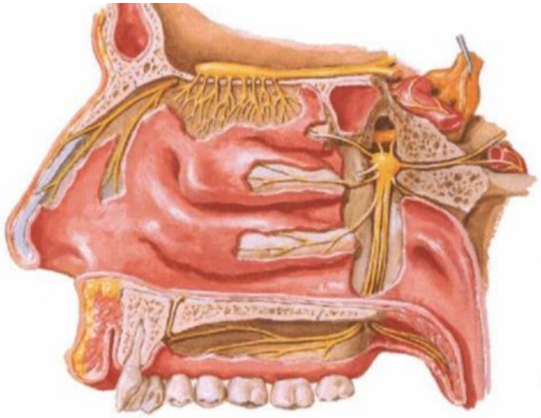
Rationale



- Mn absorption strictly adjusted to avoid toxicity
- Absorption mostly by inhalatation, especially in polluted areas
- Pollutants can be transported through the olfactory pathway

OUR PREVOUS RESULTS

- the olfactory function and anatomy are affected by occupational and environmental exposure to Mn in children and elderly residents in polluted areas

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OPEN

The nasal microbiome mirrors and potentially shapes olfactory function

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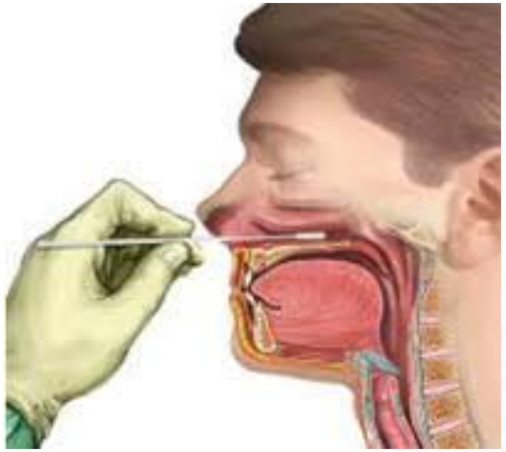
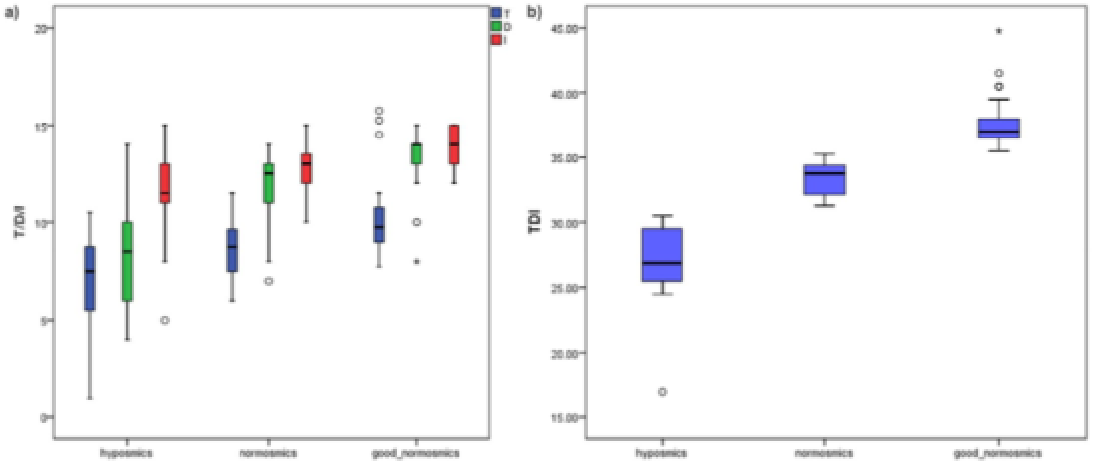
Olfactory function is a key sense for human well-being and health, with olfactory dysfunction having been linked to serious diseases. As the microbiome is involved in normal olfactory epithelium development, we explored the relationship between olfactory function (odor threshold, discrimination, identification) and nasal microbiome in 67 healthy volunteers. Twenty-eight subjects were found to have normal olfactory function, 29 had a particularly good sense of smell ("good normosmics") and 10 were hyposmic. Microbial community composition differed significantly between the three olfactory groups. In particular, butyric acid-producing microorganisms were found to be associated with impaired olfactory function. We describe the first insights of the potential interplay between the olfactory epithelium microbial community and olfactory function, and suggest that the microbiome composition is able to mirror and potentially shape olfactory function by producing strong odor compounds.





FUNDING

- NIH/NIEHS - R01ES019222-06A1, 2016 – 2021 → Manganese Exposure Windows and Neurologic Function in Adolescence
- NIH/NIEHS - P30ES023515, 2019 – 2020 → Manganese exposure, neuroimaging phenoypes and gut-microbiome interactions: a pilot study
- NIH/NIEHS - P30ES023515, 2018 – 2019 → Structural and functional brain imaging in ferromanganese workers to assess the impact of manganese exposure on neurophenotypes from early life to adulthood
- University of Brescia - UNBSCLE 9015, 2016 – 2019 → Health impacts of environmental exposure to airborne pollutants in the sites of Brescia and Taranto, Italy: increase knowledge to address preventive intervention of local and global relevance
- NIH/NIEHS – R56R01ES019222-06, 2015 – 2016 → Manganese Exposure Windows and Neurologic Function in Adolescence
- Istituto Superiore Sanità, Italy. 2014 – 2016 → Biomonitoring and toxicity of pollutants in the territory of Taranto, Italy
- NIH/NIEHS – R01ES019222, 2012 – 2016 → Neurologic function in Children Exposed to Ambient Manganese
- INAIL 60002.02/07/2012, 2012 – 2015 →Interaction between genetic predisposition and occupational/environmental exposure to chemicals like metals, pesticides and solvents in the origin of Parkinson Disturbancies
- Lombardia Region, Italy, 2011 – 2012 → Metals and Children
- EU/6th Frame Program – Food-CT-2006-016253/WPI6, 2006 – 2011 → Effects of Manganese on the Brain

PARTNERSHIP

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