PERQUE INTEGRATIVE HEALTH ACADEMY

TOXICANT EXPOSURE THROUGH THE LIFE CYCLE- WOMEN'S HEALTH CARE 2021

Lyn Patrick ND

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DISCLOSURES

Medical Director, Environmental Medicine Education International www.emeiglobal.com

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www.environmentalhealthsymposium.com

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CONCEPTION/PREGNANCY

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KEY FINDINGS

1. A GREATER NUMBER OF WOMEN ARE ENTERING PREGNANCY WITH PRE-EXISTING CONDITIONS.
2. THE NUMBER OF WOMEN EXPERIENCING BOTH PREGNANCY COMPLICATIONS AND CHILDBIRTH COMPLICATIONS INCREASED 31.5%.
3. WOMEN WITH PREGNANCY COMPLICATIONS ARE TWICE AS LIKELY TO HAVE CHILDBIRTH COMPLICATIONS.
4. THE NUMBER OF WOMEN DIAGNOSED WITH POSTPARTUM DEPRESSION INCREASED BY NEARLY 30%.

↑16.4% PREGNANCY COMPLICATIONS ↑14.2% CHILDBIRTH COMPLICATIONS

https://www.bcbs.com/the-health-of-america/reports/trends-in-pregnancy-and-childbirth-complications-in-the-us#key-findings

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CHEMICALS DETECTED IN PREGNANT WOMEN IN U.S. IN 2003-2004

Certain polychlorinated biphenyls, organochlorine pesticides, PFCs, phenols, PBDEs, phthalates, polycyclic aromatic hydrocarbons, and perchlorate were detected in 99–100% of pregnant women.

***Environ Health Perspect* 119:878–885 (2011). doi:10.1289/ehp.1002727**

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Contents lists available at SciVerse ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Multiple environmental chemical exposures to lead, mercury and polychlorinated biphenyls among childbearing-aged women (NHANES 1999–2004): Body burden and risk factors

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Environ Res. 2013 February ; 121: 23–30. doi:10.1016/j.envres.2012.10.005.

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ABSTRACT

Background: Lead, mercury and polychlorinated biphenyls (PCBs) are neurotoxicants with intergenerational health consequences from maternal body burden and gestational exposures. Little is known about multiple chemical exposures among childbearing-aged women.

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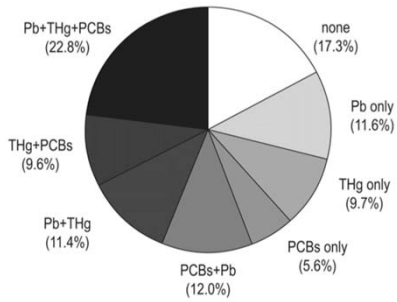

Percentage of child-bearing aged women in US with xenobiotic combinations at or above median (NHANES data 1999-2004)
Environ Res. 2013 February ; 121: 23–30. doi:10.1016/j.envres.2012.10.005.

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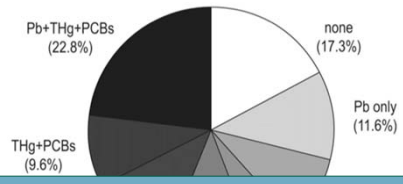

Consuming any fish in the prior 30 days was associated with having two or more xenobiotic levels at or above the median. Domestic and imported sea food and freshwater fish consumption are significant predictors of adult methyl mercury and PCB levels and to a lesser extent, lead.

Percentage of child-bearing aged women in US with xenobiotic combinations at or above median (NHANES data 1999-2004)
Environ Res. 2013 February ; 121: 23–30. doi:10.1016/j.envres.2012.10.005.

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DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHaD): PREDICTING DAMAGE FOR GENERATIONS

pptoxIV

Developmental Origins of Health and Disease: Integrating Environmental Influences

Jerrold J. Heindel, John Balbus, Linda Birnbaum, Marie Noel Brune-Drisse, Philippe Grandjean, Kimberly Gray, Philip J. Landrigan, Peter D. Sly, William Suk, Deborah Cory Slechta, Claudia Thompson, and Mark Hanson

Endocrinology 2016: 17–22, 2016

Windows of development (zygote/embryo/fetal development by trimester/post-natal developmental stages) determine the effect and longevity of that effect (intergenerational)

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POST BIRTH PROBLEMS THROUGHOUT LIFE SET UP FROM EXPOSURES IN UTERO

Exposure occurs in utero:

- **mercury, lead, cadmium, arsenic bioconcentrate in placental tissue and, in the case of arsenic, *can cause significant oxidative damage to neonatal brain tissue***
- **Exposure to the developing fetus can result in alterations in gene expression in fetal liver involving steroid metabolism and estrogen signaling pathways that can lead to endocrine disruption and tumor formation in later life.**

Toxicology and Applied Pharmacology. Published online Feb 5, 2007. doi:10.1016/j.taap.2007.01.018

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METALS

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METALS AND PROVEN EPIGENETIC CHANGES

Arsenic: hypo and hypermethylation; Upon entry into the body iAs is detoxified by SAMe, which is a universal methyl donor, including to DNA methyl transferases(DNMTs)which are reduced when SAMe is used up by iAs, and the effect has been proven to be long lasting

Nickel: hypermethylation and histone methylation changes

Cadmium: hypo and hyper methylation, histone changes, and microRNA changes; In steel workers exposed to inhaled Cd, increased micro RNA 146a was regulated by nuclear factor – kappa B, which represents ***an important causal link between inflammation and cancer***

Mercury: hypo and hypermethylation in brain tissue

Hou et al

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LEAD

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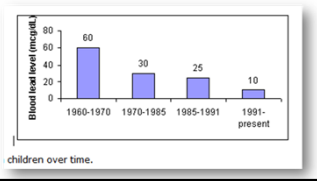
REGULATORY ACTIONABLE LEAD LEVELS: BLOOD

CDC 2012 <5ug/dl for children 1-5(97.5% percentile)

500,000 US Children above 5ug/dl as of 2012
ATSDR.CDC.GOV



children over time.

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LEAD STORAGE DEPOTS

IN:

- 90% of exposure from inhalation, ingestion, etc. ends up in cortical bone in a lead matrix instead of a calcium matrix. The largest soft tissue repository is the liver (33% of soft tissue lead) followed by kidney, pancreas, ovary, spleen, prostate, adrenal, brain, fat testes, cardiac muscle.

OUT:

- A study of lead-stable isotope signatures revealed that approximately 40-70 percent of blood lead in adults comes from bone lead.
- 10-88% of blood lead may come from bone due to increased mobilization of bone during pregnancy. Approximately 80 percent of cord blood may result from liberated bone.

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological profile for Lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

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QUESTIONS

In 1976-1980, 88% of children in U.S. had BLL over 10 mcg/dL- is that lead still in their bodies?

What kind of screening should the women of childbearing age undergo in Flint, Michigan?

Should we think about treatment for blood lead levels over 2.0 mcg/dL?

What will happen to these children if they receive no treatment for their lead exposure?

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National Toxicology Program
U.S. Department of Health and Human Services

Table 1.1: NTP conclusions on health effects of low level Pb by life stage

Life Stage	Blood Pb Level	NTP Conclusion	Principal Health Effects	Bone Pb Evidence
Children	<5µg/dL	*Sufficient*	Decreased academic achievement and specific cognitive measures, increased incidence of ADHD and problem behaviors	Tibia and dentin Pb are associated with ADHD, behavior, and cognition.
		Limited	Delayed puberty and decreased IQ, decreased kidney function in children age 12 years or older	The one available study of bone Pb in children does not support an association with postnatal growth.
	<10µg/dL	*Sufficient*	Delayed puberty, reduced postnatal growth, decreased IQ, decreased hearing, increased IgE*(not health outcome)	No data
		Limited	Increased hypersensitivity/allergy by skin prick test to allergens	No data
		Inadequate	Asthma, eczema, non-allergy immune function, cardiovascular effects, renal function children under age 12	No data
Adults	<5µg/dL	*Sufficient*	Decreased glomerular filtration rate	The one available study of bone Pb in the general population supports an association between bone Pb and decreased kidney function.
	<10µg/dL	*Sufficient*	Increased blood pressure, increased risk of hypertension, increased cardiovascular-related mortality; maternal blood Pb associated with reduced fetal growth	The association between bone Pb and cardiovascular effects is stronger than for blood. Maternal bone Pb is associated with reduced fetal growth.
		Limited	Psychological effects, decreased cognitive function, decreased hearing, increased incidence of ALS and essential tremor; maternal blood Pb associated with increased incidence of spontaneous abortion and preterm birth	The association between bone Pb and cognitive decline is stronger than for blood.

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health

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LEAD AND PREGNANCY

Nearly 1% of women aged 20–39 living in the United States have a blood lead concentration (BPb) greater than or equal to 5 µg/dL (n = 420,000)

In the 2003-2006 National Health and Nutrition Examination Survey (NHANES) survey, the 95th percentile for blood lead levels among women aged 15-49 was 2.4 micrograms per deciliter (µg/dL).

"CDC has not identified an allowable exposure level, level of concern, or any other bright line intended to connote a safe or unsafe level of exposure for either mother or fetus. Instead, CDC is applying public health principles of prevention to intervene when prudent."

"Due to lead transfer across the placenta, their children [referring to pregnant women with a BLL of 5 µg/dL] are at risk of being born with BPb above the CDC reference level of 5 µg/dL and are being exposed to a neurotoxicant, for which no threshold for harmful effects has been identified at a period of heightened vulnerability"

Karwowski et al. Environmental Health 2014, 13:77

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CDC RECOMMENDATIONS

"Interventions beginning at blood lead levels (BLLs) **≥5 µg/dL** in pregnant women.

Pregnant women with blood lead concentrations of **10 µg/dL** or higher should be removed from occupational lead exposure.

If the blood lead level is in the range of **5 to 9 µg/dL,** efforts should be made to identify and reduce lead exposure on the job and review appropriate use of personal protective equipment.

Source identification beyond obtaining a thorough environmental and occupational history should be con ducted for BLLs **≥15 µg/dL** in collaboration with the local health department, which will conduct an environ mental investigation of the home environment in most jurisdictions and an investigation of the work environment (in some jurisdictions)"

Reference:
http://www.cdc.gov/nceh/lead/publications/leadandpregnancy2010.pdf

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REFERENCES FOR LEAD IN PREGNANCY

Lead: standard surveillance definitions and classifications. [http://www. cdc.gov/nceh/lead/data/definitions.htm]

Centers for Disease Control and Prevention Advisory Committee on Childhood Lead Poisoning Prevention: A Review of Evidence of Health Effects of Blood Lead Levels <10 µg/dl in Children. Atlanta: U.S. Department of Health and Human Services; 2004.

Gundacker C, Hengstschlager M: The role of the placenta in fetal exposure to heavy metals. Wien Med Wochenschr 2012, 162:201–206.

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GESTATIONAL HYPERTENSION

The prevalence of gestational hypertension has been shown to be increased even at blood lead levels less than 5 µg/dL.

A cohort of 705 women aged 12-34 years who presented for prenatal care at one of three clinics in New Jersey with mean BLL = 1.2 ± 0.03 µg/dL and found maternal blood lead significantly associated with gestational hypertension.

Arch Environ Health 2002; 57(5):489-95.

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SPONTANEOUS ABORTION

Odds ratios for spontaneous abortion in comparison with group with < 5µg/dL :

5-9 µg/dL = 2.3

10-14 µg/dL = 5.4

>15 µg/dL = 12.2

Am J Epidemiol 150(6):590-7.

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PRENATAL LEAD AND OUTCOMES

In some but not all studies, higher prenatal lead exposure (blood lead (BPb) 10-20 µg/dL) is associated with a wide range of adverse pregnancy outcomes:

- shorter gestational lengths
- reduced birth weight, length, and head circumference
- deficits in infant mental and decreased child IQ

Elevated prenatal exposure to lead may be associated with adult-onset psychiatric disorders such as schizophrenia.

Environ Health Perspect 2014;122:1134–1140

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LEAD AND THYROID FUNCTION IN PREGNANT WOMEN

Comparing women in two locations, one in a town with industrial lead pollution and one without. Those living in the lead-exposed area had:

- Lower mean FT4, no change in TSH
- Higher mean TPO Ab
- Higher mean BPb (20.00 ± 6.99 vs. 5.57 ± 2.01 µg/dL).

RISK: gestational hypothyroidism = fetal neurodevelopmental damage

Environ Health Perspect 2014;122:1134–1140.

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LEAD AND ANEMIA IN PREGNANCY

Threshold value of blood Pb for δ-ALAD inhibition was extremely low (approximately 5 µg/dl)

50 % inhibition of δ-ALAD activity at a BLL of 15 µg/dl

Ind J Clin Biochem (July-Sept 2012) 27(3):246–252.

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RELATIONSHIP BETWEEN BLOOD LEAD LEVELS, ALAD, ZPP

Parameters	Control ($n = 50$)	Mild ($n = 50$)	Moderate ($n = 50$)	Severe ($n = 25$)
BLL (µg/dl)	1.84 ± 0.12	1.98 ± 0.13	2.61 ± 0.11^{ab}	3.62 ± 0.17^{abc}
ZPP (mg/g Hb)	2.44 ± 0.13	8.18 ± 0.37^{a}	11.58 ± 0.49^{ab}	16.32 ± 0.81^{abc}
ALAD (U/l)	15.14 ± 0.76	14.29 ± 0.43	12.79 ± 0.54^{a}	9.16 ± 0.69^{abc}
Fe (mg/dl)	51.46 ± 1.31	33.96 ± 1.21^{a}	24.13 ± 0.82^{ab}	17.62 ± 0.73^{abc}
Se (µmol/l)	1.71 ± 0.038	1.61 ± 0.034	1.49 ± 0.025^{ab}	1.33 ± 0.033^{abc}
Zn (µmol/l)	10.23 ± 0.16	9.57 ± 0.17^{a}	9.17 ± 0.17^{a}	8.63 ± 0.28^{ab}

Ind J Clin Biochem (July-Sept 2012) 27(3):246–252.

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MATERNAL BONE LEAD AS AN INDEPENDENT RISK FACTOR FOR FETAL NEUROTOXICITY: A PROSPECTIVE STUDY

Higher maternal trabecular bone lead levels constitute an independent risk factor for impaired mental development in infants at 24 months of age.

- 197 mother-infant pairs studied
- After adjustment for maternal age, IQ, and education; paternal education; marital status; breastfeeding duration; infant gender; and infant illness, *lead levels in umbilical cord blood and trabecular bone were significantly, independently, and inversely associated with the Mental Development Index (MDI) scores of the Bayley Scale*
- *There was* 5.4-, 7.2-, and 6.5-point decrements in adjusted MDI scores compared to the first quartile.
- A 2-fold increase in cord blood lead level (eg, from 5 to 10 microg/dL) was associated with a 3.1-point decrement in MDI score

Pediatrics 2002 Jul, 110(Pt 1):110-118

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AIR, SOIL AND DRINKING WATER STANDARDS

OSHA PEL (permissible exposure limit) 50mcg/m3 over 8 hours
OSHA >40, worker must be notified and offered exam
OSHA >60, or has 3 levels that average over 50, worker must be removed from exposure with maintenance of pay and seniority until under 40!

NIOSH at CDC: REL (recommended exposure limit) of 50 ug/m3 to keep blood lead levels of <60
AAP: Soil Level: <50ppm in normal soil
EPA: Soil standard 400ppm in play areas and 1200 in non play areas (not enforceable)

EPA Drinking Water Standards Goal 0, Action level 15ug/L

FDA Food .5ug/ml in products for infants and children

ATSDR.CDC.GOV

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GUIDELINES FOR CHELATION

"Chelation therapy during pregnancy or early infancy may be warranted in certain circumstances where the maternal or neonatal blood lead exceeds ≥45 µg/dL and in consultation with an expert in lead poisoning. Insufficient data exist regarding the advisability of chelation for pregnant women with BLL <45 µg/dL."

Reference: http://www.cdc.gov/nceh/lead/publications/leadandpregnancy2010.pdf

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CASE REPORTS OF SUCCESSFUL CHELATION DURING PREGNANCY

Severe Lead Poisoning in Pregnancy

Michael Shannon, MD, MPH*

* From the Pediatric Environmental Health Center and the Division of Emergency Medicine, Children's Hospital, Harvard Medical School, Boston, Mass

Received 17 May 2001, Accepted 15 August 2001, Available online 12 December 2005

Show less

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EDTA CHELATION IN PRENATES AND INFANTS

Over a 3-year period treatment was provided to 7 severely lead-poisoned women. A 25-year review of the medical literature identified an additional 8 cases. Among these 15 women, 70% were Hispanic, all of whom developed lead poisoning from the ingestion of soil, clay, or pottery ("tierra"). Other sources of lead poisoning were paint chip ingestion (n = 2), household renovation, and use of a complementary-alternative medication (bone meal). Lead poisoning was discovered in the third trimester in 12 (86%) subjects after the women presented with subtle but characteristic findings of severe lead poisoning, including malaise, anemia, or basophilic stippling on blood smear; one woman was identified when she presented after a generalized seizure, having a blood lead level of 104 µg/dL.

Five women received chelation therapy during pregnancy with CaNa2 EDTA, dimercaprol, or succimer. At delivery mean maternal blood lead level was 55 µg/dL, whereas mean neonatal lead level was 74 µg/dL (P = .009). Thirteen neonates underwent chelation, all within the first 28 days of life. No infant in the current series had an identifiable birth defect.

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PRECONCEPTION CARE

Because cord blood levels of Hg and Pb have been found to exceed maternal blood levels, the maternal blood levels **of 3.5 µg/L Hg** and **5.0 µg/dL Pb** are recommended for the protection of fetal health.

Ettinger AS, Wengrovitz AG, Portier C, Brown MJ. CDC. Guidelines for the identification and management of lead exposure in pregnant and lactating women. Atlanta, GA: DHHS; 2010./*Environ Health Perspect. 2009 Jan; 117(1):47-53/Environ Health Perspect. 2006 Feb; 114(2):173-5.*

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MERCURY

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NEUROTOXICANTS TARGETED: MERCURY

Approximately 15% of women of childbearing age in U.S. have blood mercury levels high enough to cause risk for neurodevelopmental damage to the fetus.

Exposure in 2nd trimester from fish in diet vs no fish

Mothers in top 10% of RBC Hg = over 9.1 ng/g (23% percent in those who consumed fish more than twice week)

- Their children had poorer performance in vocabulary and visual motor abilities at age 3
- Maternal intake of low-mercury fish associated with higher performance on same tests
- Cord-blood Hg of > 7.5 ug/L: 4X likely to have IQ <80 (EPA estimates cord blood to maternal blood ratio 1.7 so: maternal whole blood mercury of >4.4 ug/L)

PMID: 16555611 PMID: 18353804, 25757069

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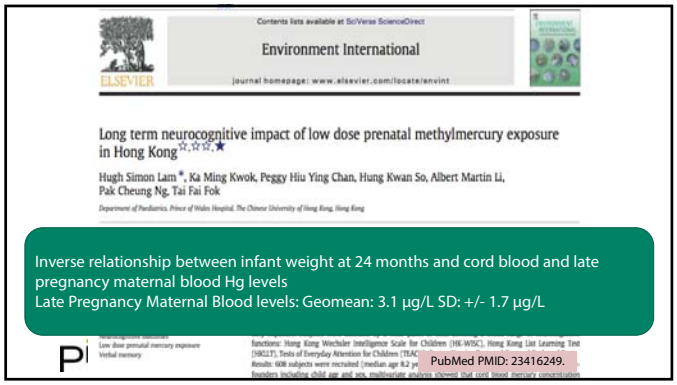

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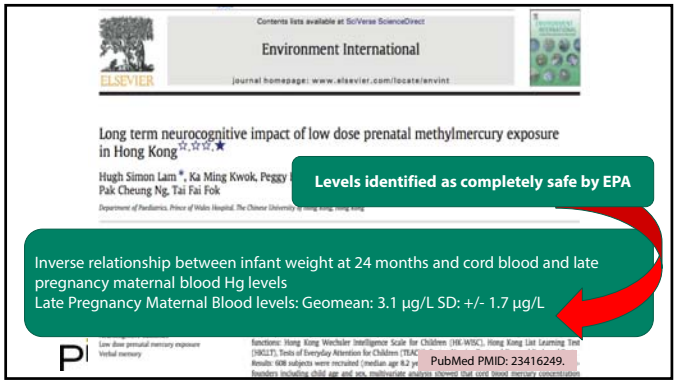

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PRENATAL MERCURY EXPOSURE AND GST SNPS

Interaction between *GSTM1*/*GSTT1* Polymorphism and Blood Mercury on Birth Weight

Bo-Eun Lee,[1] Yun-Chul Hong,[2] Hyesook Park,[1] Mina Ha,[3] Bon Sang Koo,[4] Namsoo Chang,[5] Young-Man Roh,[6] Boong-Nyun Kim,[7] Young-Ju Kim,[8] Byung-Mi Kim,[1] Seong-Joon Jo,[9] and Eun-Hee Ha[1]

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***Environ Health Perspect* 118:437–443 (2010). doi:10.1289/ehp.0900731 available via *http://dx.doi.org/* [Online 23 October 2009]**

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HG AND LOWER BIRTH WEIGHT

Results: The geometric mean levels of Hg in the maternal blood during late pregnancy and in cord blood were 3.30 µg/L and 5.53 µg/L, respectively.

For mothers with the *GSTT1* null genotype, elevated Hg levels in maternal blood during late pregnancy were associated with an increased risk of lower birth weight.

For mothers with both *GSTM1* and *GSTT1* null genotype, both maternal and cord blood Hg levels were associated with lower birth weight.

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CHILDHOOD

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HG AND CD AND CVD IN CHILDREN

Ground-level ambient air concentrations of Hg and Cd were a significant predictor of blood metal levels.

Ambient air concentrations of Hg and Cd also predicted cardiovascular dysfunction and risk including changes in left-ventricular mass, blood pressure, and heart rate.

https://doi.org/10.1016/j.envres.2020.110557

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Off the Charts

The thousands of U.S. locales where lead poisoning is worse than in Flint

By M.B. Pell and Joshua Schneyer | Filed Dec. 19, 2016, 2 p.m. GMT

A Reuters examination of lead testing results across the country found almost 3,000 areas with poisoning rates far higher than in the tainted Michigan city. Yet many of these lead hotspots are receiving little attention or funding.

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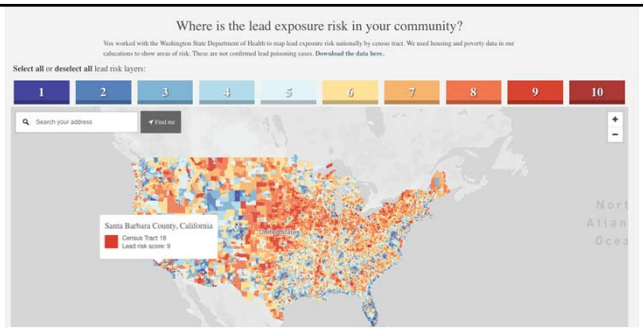

https://www.vox.com/a/lead-exposure-risk-map

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WASHINGTON DC WATER DISASTER

1st Half of 2001 – # of children with BLL > 10 mcg/dl = 0.5%

1 in 1000 houses had > than 1000 PPB lead in water

At 10 mcg/dl IQ in children drop 5-7 points

If this had occurred on a nationwide level there would be 3.5 million additional children classified as mentally retarded

http://en.wikipedia.org/wiki/Lead_contamination_in_Washington,_D.C._drinking_water#Congressional_review_of_the_2004_CDC_paper

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NO SAFE LEVEL OF LEAD

No safe level of lead exposure in the blood of children has been identified (the CDC, EPA, and American Academy of Pediatrics agree)

By the way, the same is true for drinking water. (15 ppb is simply a level that industry and municipal water providers were willing to accept.)

Lead is detectable in the blood down to 1.0 µg/dL for most labs.

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A DIRECT QUOTE FROM THE NATIONAL ACADEMY OF SCIENCES

"The combination of three environmental chemical exposures:

lead

organophosphate pesticides

and methylmercury

are responsible for greater IQ loss

than medical conditions such as preterm birth, neurodevelopmental disorders such as autism and ADHD, and socioeconomic and nutrition-related factors such as iron deficiency and non-organic failure to thrive." – David Bellinger

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WHY DID THEY QUOTE BELLINGER?

David Bellinger* and colleagues estimated the contribution of these risk factors to significant IQ loss in a population of 25.5 million children and found that lead, methylmercury and organophosphate pesticides were responsible for the majority of IQ loss.

* Professor of neurology, psychology, and environmental health at Boston Children's Hospital, Harvard Medical School, and the Harvard T.H. Chan School of Public Health,

PMID: 23515885

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ADHD

PCBs (in utero)

Lead- risk starts at blood lead levels of 1.6 µg/dL

blood lead in ages 4-15: > 2.0 µg/dL had OR 4.1, another study >2.7 µg/dL OR 7.0

Mercury (methylmercury in utero) mom's hair levels > 1 µg/gm

Pesticides

Air pollutants (Vehicular Exhaust) – aggressive behavior and attention issues by age 9

Phthalates (in utero)- delinquent and aggressive age 8

PMID: 20106937/23694812/17185283/23916943/22440811/27890345/

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LEAD- A PUBLIC HEALTH VICTORY?

%of children aged 1–5 years with blood lead levels ≥10 µg/dL

88% in 1976–1980

4.4% during 1991–1994

1.6% during 1999–2002

0.8% during 2007–2010 (CDC, 2013).

Currently, a blood lead level ≥5 µg/dL (down from ≥10 µg/dL) is defined as high for children and pregnant women.

Despite these improvements, an estimated 535,000 U.S. children aged 1–5 years have levels ≥5 µg/dL based on the U.S. Census Bureau 2010 data

25% of homes with children under age 6 still have a lead-based paint hazard.

the average IQ scores of children with levels of only 5–10 µg/dL are about 5 points lower than the IQ scores of children with levels less than 5 µg/dL

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ADOLESCENCE/YOUNG ADULTHOOD

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LEAD AND KIDNEY FUNCTION IN ADOLESCENTS

769 NHANES III participants (age 12-20 yo)

Higher blood lead levels were consistently associated with a lower cystatin C–estimated GFR

highest quartile of BLL : 3-10 mcg/dL

6.6 mL/min/1.73 m2–lower estimated GFR compared with those in the first quartile (<1 µg/dL).

Prevalence of CKD in the United States: estimated 26 million Americans.

Arch Intern Med. 2010 January 11; 170(1): 75–82.
doi:10.1001/archinternmed.2009.417

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LEADING CAUSES OF DEATH – FEMALES – ALL RACES AND ORIGINS – UNITED STATES, 2017

All races and origins[1], Female, by Age Group

	Age Group[1]					
Rank[2]	1-19 years	20-44 years	45-64 years	65-84 years	85+ years	All ages
1	Unintentional injuries 32.7%	Unintentional injuries 30.0%	Cancer 34.2%	Cancer 27.0%	Heart disease 27.7%	Heart disease 21.8%
2	Cancer 11.0%	Cancer 16.0%	Heart disease 16.3%	Heart disease 19.9%	Alzheimer's disease 10.9%	Cancer 20.7%
3	Suicide 10.3%	Heart disease 9.0%	Unintentional injuries 6.9%	Chronic lower respiratory diseases 8.5%	Cancer 9.9%	Chronic lower respiratory diseases 6.2%
4	Homicide 7.4%	Suicide 7.6%	Chronic lower respiratory diseases 5.3%	Stroke 5.8%	Stroke 8.1%	Stroke 6.2%
5	Birth defects 6.4%	Homicide 3.8%	Diabetes 3.8%	Alzheimer's disease 4.4%	Chronic lower respiratory diseases 4.9%	Alzheimer's disease 6.1%

https://www.cdc.gov/women/lcod/2017/all-races-origins/index.htm

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Table 1. Common neurologic health problems associated with environmental pollutants

Problem	PAH/PM	PHTH	Solvents	PCB	OCP	OP	Cd	Pb	Hg
Poor cognition	X		X	X	X	X	X	X	X
Lower IQ							X	X	x
Special education need							X		
Memory problems	X		X	X	X			X	X
Depression	X	X	X		X	X	X	X	
Irritability/excitability			X						X
Tremors						X			X
Balance problems			X			X			
Insomnia								X	
Fatigue			X		X	X		X	X
Headache			X			X			X

PHTH – phthalates, OCP - chlorinated pesticides, OP - organophosphate pesticides, Cd – cadmium, Pb – lead, Hg - mercury

Clinical Environmental Medicine. Crinnion W, Pizzorno J. 2019 Elsevier pg 433.

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BRAIN AUTOPSIES FROM YOUNG ADULTS FROM MEXICO CITY

By 20 years of age (n=57)

84% of the olfactory bulbs exhibited tau protein

68% exhibited Lewy Neurons and vascular amyloid

36% had diffuse amyloid plaques

PMID: 32888951

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METAL NANOPARTICLES IN BRAINSTEM AND BRAIN

AD and PD both associated with PM2.5 air pollution.

substantia nigra pathology seen in mitochondria and endoplasmic reticulum and neuromelanin is co-associated with

Evidence of early damage related to both AD and PD seen in young adults with Fe, Pb, Al and Ti nanoparticles in brain autopsy samples.

These combustion and friction-derived nanoparticles are found in high levels in urban air and result from traffic pollution.

PMID: 32955466
PMID: 32888951

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ALZHEIMER'S IN THE YOUNG


Environmental Research 191 (2020) 110087

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Environmental Research

journal homepage: www.elsevier.com/locate/envres

Gait and balance disturbances are common in young urbanites and associated with cognitive impairment. Air pollution and the historical development of Alzheimer's disease in the young

Lilian Calderón-Garcidueñas [a,b,*], Ana Karen Torres-Solorio [b], Randy J. Kulesza [c],

- Prior study showed Metropolitan Mexico City residents had evidence of Alzheimer's disease in 202/203 forensic autopsy cases age 25.36 ± 9.23 y

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ALZHEIMER'S IN THE YOUNG

- 575 clinically healthy subjects, age 21.0 ± 5.7 y who were residents in Metropolitan Mexico City tested against controls from other areas with lower PM2.5 air pollution
- gait and balance testing with Tinetti and Berg tests, cognitive assessment with Montreal Cognitive Assessment added in 76 participants
- 75.4% and 34.4% had abnormal total Tinetti and Berg scores and high risk of falls in 17.2% and 5.7% respectively.
- The lowest score of Tinetti balance was for MMC resi- dents. Reynosa residents, with the lowest air pollution concentrations had the highest scores for both tests.

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MEXICO CITY VS. OTHER CITIES

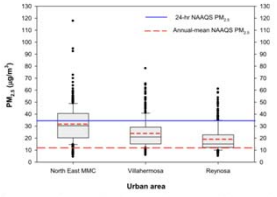

Fig. 1. $PM_{2.5}$ 24-hr averages box plots at North East MMC, Villahermosa and Reynosa for 2017. NAAQS stands for National Ambient Air Quality Standards for the USEPA. The continuous line inside the box represents the 24 h median (35 μg/m³) and the dotted line the annual mean (12 μg/m³).

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LEAD AND HORMONES

Lead has been shown to cause

- potential impairment of hypothalamic-pituitary-gonadal (HPG) signaling
- disruption of reproductive hormones among peripubertal girls
- modestly higher blood lead levels (3 µg/dL vs. 1 µg/dL) were associated with later pubertal development
- menstrual abnormalities and spontaneous abortion in an occupational group
- lead-exposed female workers were found to have a higher prevalence of menstrual abnormalities, including polymenorrhea or hypermenorrhea and spontaneous abortion

Environ Health Perspect 122:229–234; http://dx.doi.org/10.1289/ehp.1206399

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EPIDEMIOLOGICAL DATA ASSOCIATING PCOS WITH BPA EXPOSURE

- BPA levels are higher in women with PCOS than controls
  (1) elevated exposure to BPA
  (2) PCOS impairs metabolism and excretion of BPA
- Biochemical changes in lab animals similar to PCOS pattern
- Within women with PCOS, BPA levels appear to be comparable in lean and overweight groups
- Serum BPA is strongly correlated with free testosterone (r=0.56), androstenedione (r=0.48), and DHEAS (r=0.46)

Semin Reprod Med. 2014; 32: 166–176.

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EXPOSURE TO LOW DOSE BPA

EPA: lowest adverse event dose, i.e. safe dose: 50ug/kg/d

Adverse effects seen at doses as low as 0.025 ug/kg/d or 0.23 ppt

- Increased postnatal weight gain
- Early sexual maturation in females
- Altered LH production (maternal dose 2ug/kg/d)
- Stimulation of mammary development (maternal dose 0.025ug/kg/d)
- Altered immune function
- Decrease in antioxidant enzymes (adult males 0.2ug/kg/d)
- Hyperactivity, aggression, altered reactivity to stimulation

Reviewed in: Environ Health Perspect 2005;113:926-933

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PROMOTION OF OBESITY BY BPA

- Induces pancreatic β–cells to increase insulin production
- Inhibits adiponectin release
- Increases expression of genes involved in adipocyte differentiation
- Alters DNA methylation in murine preadipocyte fibroblasts
- BPA increases 11β-HSD-1 (cortisone→cortisol) thus promoting adipocyte differentiation and adipogenesis
- Activation of glucocorticoid receptors
- BPA may slow metabolism, resulting in decreased food intake and activity concurrent with disrupted insulin signaling
- BPA exposure leads to abdominal fat redistribution

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PCOS

- Women come to physicians for bleeding, infertility or androgen excess
- The underlying pathophysiology of PCOS involves insulin resistance
- The long term consequences of PCOS include, diabetes, endometrial CA, obesity, etc.
- Treatments that reduce insulin levels appear to ameliorate the other pathophysiological changes in PCOS
- BPA produces effects at doses far lower than originally tested
- BPA binds to ER and other receptors and the resulting effects produce or exacerbate the pathophysiologic elements of PCOS

PMID: 25372737 PMID: 33839640

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ADULTHOOD

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LEADING CAUSES OF DEATH – FEMALES – ALL RACES AND ORIGINS – UNITED STATES, 2017

All races and origins[1], Female, by Age Group

	Age Group[1]					
Rank[2]	1-19 years	20-44 years	45-64 years	65-84 years	85+ years	All ages
1	Unintentional injuries 32.7%	Unintentional injuries 30.0%	Cancer 34.2%	Cancer 27.0%	Heart disease 27.7%	Heart disease 21.8%
2	Cancer 11.0%	Cancer 16.0%	Heart disease 16.3%	Heart disease 19.9%	Alzheimer's disease 10.9%	Cancer 20.7%
3	Suicide 10.3%	Heart disease 9.0%	Unintentional injuries 6.9%	Chronic lower respiratory diseases 8.5%	Cancer 9.9%	Chronic lower respiratory diseases 6.2%
4	Homicide 7.4%	Suicide 7.6%	Chronic lower respiratory diseases 5.3%	Stroke 5.8%	Stroke 8.1%	Stroke 6.2%
5	Birth defects 6.4%	Homicide 3.8%	Diabetes 3.8%	Alzheimer's disease 4.4%	Chronic lower respiratory diseases 4.9%	Alzheimer's disease 6.1%

https://www.cdc.gov/women/lcod/2017/all-races-origins/index.htm

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RISK FOR CHD/STROKE DOUBLES IN EARLY MENOPAUSE

Of the women, 28 percent reported early menopause, or menopause that occurs before the age of 46.

"If physicians know a patient has entered menopause before her 46th birthday, they can be extra vigilant in making recommendations and providing treatments to help prevent heart attacks and stroke"

Studies of Norwegian, Netherlands, and Seventh Day Adventist cohorts (all Caucasian) have all shown a 1.5 to 2-fold increase in CHD mortality in women with menopause at early ages (various ages <45) versus those with menopause at more average ages (various ages >49).

Menopause. 2012 Oct; 19(10): 1081–1087.

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EARLY MENOPAUSE

Early menopause has been associated with several adverse health outcomes including loss of bone mineral density and cardiovascular disease morbidity and mortality.

"Reduction of population exposures to risk factors for early age at menopause could yield significant benefits in terms of reducing chronic disease morbidity and mortality in postmenopausal life."

Environ Health Perspect 122:229–234; http://dx.doi.org/10.1289/ehp.1206399

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5 TIMES RISK FOR EARLIER MENOPAUSE WITH HIGHER TIBIAL LEAD LEVELS

Results: The mean (± SD) age at natural menopause was 50.8 ± 3.6 years. Higher tibia lead level was associated with younger age at menopause. In adjusted analyses, the average age of menopause for women in the highest tertile of tibia lead was 1.21 years younger (95% CI: −2.08, −0.35) than for women in the lowest tertile (p-trend = 0.006). Although the number of cases was small (n = 23), the odds ratio for early menopause (< 45 years of age) was 5.30 (95% CI: 1.42, 19.78) for women in the highest tertile of tibia lead compared with those in the lowest tertile (p-trend = 0.006). There was no association between patella or blood lead and age at menopause.

Conclusions: Our results support an association between low-level cumulative lead exposure and an earlier age at menopause. These data suggest that low-level lead exposure may contribute to menopause-related health outcomes in older women through effects on age at menopause.

Citation: Eum KD, Weisskopf MG, Nie LH, Hu H, Korrick SA. 2014. Cumulative lead exposure and age at menopause in the Nurses' Health Study Cohort. Environ Health Perspect 122:229–234; http://dx.doi.org/10.1289/ehp.1206399

Those who were current or ever-users of HRT had similar tibial lead levels as the premenopausal group*

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ADJUSTED ODDS RATIO (OR) AND 95% CONFIDENCE INTERVAL (95% CI) OF HAVING A NATURAL MENOPAUSE BY QUARTILE OF BLOOD LEAD AMONG US WOMEN AGED 45–55, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, 1999–2010.

Lead Exposure Quartile	NHANES 1999–2010	NHANES 1999–2002		NHANES 2005–2008	
	n= 1782	n=815		n=541	
	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[c]
Q1 (LOD to 1.0)	Reference	Reference	Reference	Reference	Reference
Q2 (1.0 to 1.4)	1.7 (1.0 – 2.8)	1.0 (0.3–3.5)	1.1 (0.3 – 3.9)	3.0 (0.9–9.8)	3.4 (0.9 – 12.2)
Q3 (1.4 to 2.1)	2.1 (1.2 – 3.6)	1.3 (0.4–4.5)	1.2 (0.3 – 4.7)	4.9 (1.5–16.1)	4.1 (1.1 – 15.2)
Q4 (2.1 to 22.4)	4.3 (2.6–7.2)	5.1 (1.4, 18.0)	4.2 (1.2 – 15.5)	10.5 (3.1–35)	9.7 (2.8 – 33)

[a] Adjusted for age, race/ethnicity, current hormone replacement therapy, smoking and poverty

[b] Adjusted for bone alkaline phosphatase, age, race/ethnicity, current hormone replacement therapy, smoking and poverty

[c] Adjusted for femoral neck bone density, age, race/ethnicity, current hormone replacement therapy, smoking and poverty

Environ Res. 2013 February ; 121: 110–113. doi:10.1016/j.envres.2012.12.009.

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IN AND OUT OF BONE LEAD

Release of lead from bone to blood as a consequence of increased bone turnover following menopause has been proposed as a mechanism that may explain cross-sectional associations between menopause and blood lead levels.

The higher incidence of hypertension in menopausal women with higher blood lead has also been explained by this association.

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POPULATIONS AT RISK FOR BONE TURNOVER

- Menopausal women/andropausal men
- Hyperthyroidism in either sex
- Cisplatin chemotherapy
- Patients with osteoporosis or osteopenia
- Vitamin D deficiency-50% of population
- Born before 1980*

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LEAD AND HYPERTENSION IN PRE- AND POSTMENOPAUSAL WOMEN

"At blood levels 4.0-31.1 µg/dL there is a positive association between both systolic and diastolic blood pressure and risks of both systolic and diastolic hypertension among women aged 40-59."

JAMA 2003;289:1523-32.

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CONCLUSIONS OF META-ANALYSIS ON LEAD AND CARDIOVASCULAR DISEASE

1. Sufficient evidence to infer a causal relationship between lead exposure and hypertension.
2. Cross-sectional studies suggest an association between increased lead exposure and decreased heart rate variability possibly via interference with autonomic regulation at levels lower than 5 mcg/dL.
3. "the cardiovascular endpoints described above plus the substantial evidence that chronic lead exposure affects cognitive function and renal function at levels < 5 mcg/dL indicate that the CDC criterion for 10 mcg/dL is too high for adults."

Environ Health Perspect 2007;15:472-482.

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CARDIOVASCULAR DISEASE-2006

"BLOOD LEAD CONCENTRATIONS AS LOW AS 2.07 MG/DL LIKELY REPRESENT A PUBLIC HEALTH HAZARD."

Those in the highest tertile of blood lead:

(3.63-10.0 µg/dL)

- **2.5** times risk for stroke mortality
- **1.89** times risk for myocardial infarction mortality
- **1.70** times risk for cardiovascular disease mortality

"Blood lead is a much more significant risk factor for CVD and stroke than blood lipids."

NHANES 1999 to 2000, **38%** of US adults had a blood lead level above this threshold.

Circulation 2006;114:1347-1349.

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NHANES EXTENSION STUDY 2018 (same population from 2006 Circulation article)

NHANES III COHORT from 1988-94 followed out to 2011

	HR/Adj HR	POPULATION ATTRIBUTABLE (fx)	AVOIDABLE DEATHS
All cause mortality	3.79/1.37	18.0%	412,000
CV mortality	4.44/1.70	28.7%	256,000
Ischemic mortality	5.31/2.08	37.4%	185,000

19.3 yr follow up of 14,289 people in US from NHANES CDC database
4,422 people died of CVD,
The population attributed fraction for all cause mortality for lead was 18% = 412,000 "all cause" deaths from lead in the US every year.

Lanphear,Bruce March 12, 2018 DOI:https://doi.org/10.1016/S2468-2667(18)30025-2

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CADMIUM AND WOMEN: RENAL DISEASE, OSTEOPOROSIS, CVD

Even under similar conditions of cadmium exposure, women tend to have higher urine, blood, and renal cortex cadmium levels compared with men.

Women may absorb more cadmium through the gastrointestinal tract because of a higher prevalence of decreased iron stores, which increases expression of the divalent metal transporter DMT-1, the iron intestinal transporter that also mediates cadmium transport .

Risk levels start at .5 mcg/gm creatinine in urine

Environ Res. 2007;104(1):85–95

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Research

Cadmium Exposure and Cancer Mortality in a Prospective Cohort: The Strong Heart Study

Esther García-Esquinas,[1,2,3,4] Marina Pollán,[3,4] María Tellez-Plaza,[1,2,5] Kevin A. Francesconi,[6] Walter Goessler,[6] Eliseo Guallar,[2,7,8] Jason G. Umans,[9,10] Jeunliang Yeh,[11] Lyle G. Best,[12] and Ana Navas-Acien[1,2,7,13]

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Comparing highest to lowest urinary cadmium (mostly from smoking);
Adjusted Hazard ratios:
Total cancer 1.30
Lung cancer 2.27
Prostate cancer 2.40

PMID:24531129

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CADMIUM AS A XENOESTROGEN

- Population-based, case-control study of 246 women with breast cancer and 254 age-matched controls.
- Women with urinary cadmium > 0.58 mcg/g creatinine had twice the risk for breast cancer compared to those with < 0.26 mcg/g creatinine.
- After adjusting for multiple risk factors, the odds of getting breast cancer if urine levels > 0.58 mcg/gm creatinine were significantly increased (OR 2.29)
- JNCI 2006;98 (12):869.

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CADMIUM AND ENDOMETRIAL CA THE 4TH MOST COMMON CANCER FOR WOMEN

2.9-fold increased risk of endometrial cancer was associated with a long-term consistently increased cadmium intake, observed among lean or slightly overweight never-smoking women who did not use postmenopausal hormones.

Midwestern US study resulted in lower but still significant OR: 1.22 HOWEVER African American women in that cohort had an OR of 4.91 (p=.0012 for endometrial CA) if their creatinine-adjusted urine Cd was

Cancer Res 2008;68(15):6435–41/ Am J Epidemiol 2009;170:1156-1164. 2017 PMID: 28742092

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Research Article

Cadmium Exposure and Pancreatic Cancer in South Louisiana

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[2] *Department of Global Community Health and Behavioral Sciences, School of Public Health and Tropical Medicine, Tulane University,*

Persons with 0.5 to <1.0 ug/g urinary cadmium levels had a **3.34** increased risk for **pancreatic cancer**
while those with 1 to <1.5 ug/g had a OR of **5.58**.
Persons with urine Cd >1.5 ug/g had a **7.70** increase in risk.

Cadmium has been hypothesized to be a pancreatic carcinogen. We test the hypothesis that cadmium exposure is a risk factor for pancreatic cancer with a population-based case-control study sampled from a population with persistently high rates of pancreatic cancer (south Louisiana). We tested potential dietary and nondietary sources of cadmium for their association with urinary cadmium concentrations which reflect long-term exposure to cadmium due to the accumulation of cadmium in the kidney

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BLOOD AND URINE CADMIUM AND CVD MORTALITY

1999 – 2004 NHANES – 8, 989 individuals comparing 80th to 20th percentiles
The adjusted hazard ratios for blood and urine cadmium were:
1.50 and 1.52 for all –cause mortality
1.69 and 1.74 for CVD mortality
1.98 and 2.53 for heart disease mortality
1.73 and 2.09 for coronary heart disease mortality.
The population risks associated with the 80th percentile of the blood (0.80 µg/L) and urine (0.57 µg/g) cadmium distributions

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Ferraro et al. *BMC Public Health* 2010, **10**:304
http://www.biomedcentral.com/1471-2458/10/304

BMC Public Health

RESEARCH ARTICLE Open Access

Low level exposure to cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999-2006

Pietro Manuel Ferraro, Stefano Costanzi, Alessandro Naticchia, Antonio Sturniolo and Giovanni Gambaro*

> 1.0 mcg/g creatinine in urine associated with albuminuria and chronic kidney disease

Abstract

Background: Environmental factors have been associated with the outbreak of chronic kidney disease (CKD). We evaluated the association of Cadmium (Cd) exposure with the risk of CKD in U.S. adults who participated in the 1999-2006 National Health and Nutrition Examination Surveys (NHANES).

Methods: 5426 subjects ≥ 20 years were stratified for values of urinary and blood Cd and a multivariate logistic regression was performed to test the association between blood and urinary Cd, CKD and albuminuria (ALB) after adjustment for age, gender, race/ethnicity, body mass index and smoking habits.

Results: Subjects with urinary Cd > 1 mcg/g and subjects with blood Cd > 1 mcg/L showed a higher association with ALB (OR 1.63, 95% CI 1.23, 2.16; $P = 0.001$). Subjects with blood Cd > 1 mcg/L showed a higher association with both CKD (OR 1.48, 95% CI 1.01, 2.17; $P = 0.046$) and ALB (OR 1.41, 95% CI 1.10, 1.82; $P = 0.007$). An interaction effect on ALB was found for high levels of urinary and blood Cd ($P = 0.014$).

Conclusions: Moderately high levels of urinary and blood Cd are associated with a higher proportion of CKD and ALB in the United States population.

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CADMIUM AND OSTEOPOROSIS RISK

"In the absence of renal tubular dysfunction, environmental exposure to cadmium increases bone resorption in women, suggesting a direct osteotoxic effect with increased calciuria and reactive changes in calciotropic hormones."

Women over 50 with urinary cadmium above 0.50ug/g creatinine increased their risk of being diagnosed with osteoporosis by 43%.

2-fold increase in urinary cadmium in non-occupationally exposed persons correlated with – 73% increased risk of fractures in women – 60% increased risk of height loss in men – (By CDC that would be 0.4 ug/g)

2008 - PMID: 18941575 1999 - PMID:10209978

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CADMIUM AND RISK FOR OSTEOPOROSIS IN 2688 WOMEN IN SWEDEN

Women with urinary Cd of ≥ 0.75 µg/g cr vs. women < 0.50 µg/g :

2.5 times more likely to have osteoporosis in femoral neck

2.0 times more likely to have it in lumbar spine.

Among those women who had never smoked the odds were higher:

3.5 increased risk for fracture of femoral neck and 3.26 X higher for lumbar spine.

The odds of any first fracture were greater in those with U-Cd ≥ 0.50 µg/g of cr

J Bone Miner Res. 2011 Mar;26(3):486-95.

LOE B3

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Toxic Metals; Urine 24 hour Non-provocation 24 hr urine

TOXIC METALS PER CREATININE		RESULT µg/g creat	REFERENCE INTERVAL	TOXIC METALS PER 24 HOURS RESULT µg/24 HOUR	REFERENCE INTERVAL	within REFERENCE	OUTSIDE REFERENCE
Aluminum	(Al)	4.4	< 35	6.4	< 30		
Antimony	(Sb)	< dl	< 0.2	< dl	< 0.2		
Arsenic	(As)	15	< 80	22	< 90		
Barium	(Ba)	3.3	< 7	4.7	< 7		
Beryllium	(Be)	< dl	< 1	< dl	< 1		
Bismuth	(Bi)	< dl	< 4	< dl	< 3		
Cadmium	(Cd)	1.2	< 1	1.8	< 1.2		
Lead	(Pb)	0.3	< 2	0.5	< 2		
Mercury	(Hg)	< dl	< 4	< dl	< 5		
Nickel	(Ni)	10	< 10	15	< 13		
Palladium	(Pd)	< dl	< 0.3	< dl	< 0.3		
Platinum	(Pt)	< dl	< 0.1	< dl	< 0.2		
Tellurium	(Te)	< dl	< 0.5	< dl	< 0.5		
Thallium	(Tl)	0.5	< 0.5	0.7	< 0.5		
Thorium	(Th)	< dl	< 0.03	< dl	< 0.03		
Tin	(Sn)	0.1	< 5	0.2	< 4		
Tungsten	(W)	0.1	< 0.4	0.2	< 0.4		
Uranium	(U)	< dl	< 0.04	< dl	< 0.04		

DXA -2.7 lumbar spine/-2.1 femur

LOE B4

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QUESTIONS???

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