“Background” Level Lead Exposure: A Reproductive Toxicant?”

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Thanks to UAlbany, Wadsworth Center, NICHD, UCSF & Guangdong Cardiovascular Institute colleagues!

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Outline

- Historic evidence
- Biologic mechanisms
- Ongoing U.S. exposure
- Moderate-high level effects
- Low level effects
- Take home messages

Historic case series data on workplace Pb exposure & pregnancy loss

Area, time	Maternal (paternal) exposure	Losses/ Pregnancies	Infant deaths/ Births
France, mid-1800s (Paul, 1860)	Prior to work in Pb factory	0.0	0.0
	During/after work in Pb factory	72.2/100	900/1,000
	Paternal work in Pb factory	34.4/100	400/1,000
	All exposure	59.3/100	400/1,000
England, late 1800s (Legge, 1901)	During work in Pb factory	52.4/100	-
	During/after work in (Pb) china/earthenware factory	15.5/100	-
Italy, early 1900s (Torelli, 1930)	General population	4.0-4.5/100	150/100
	Work in (Pb) printing industry	24/100	320/1000
	Paternal work in (Pb) printing industry	14/100	-
Italy, early 1900s (Torelli, 1930)	Work in Pb mine	22.1/100	469/1000
	Paternal work in Pb mine	276/100	-

Hertz-Picciotto, Am J Ind Med 2000;38:300-309; Legge, J Hyg 1901;1:96-108; Paul, Archives Generale de Medecine 1860;15:513-533; Torelli, Med Lav 1930;3:110-121

Pb-based pills used as abortifacients in 19th-20th Century England

PLUMBISM FROM THE INGESTION OF DIACHYLON AS AN ABORTIFACIENT.

BY

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and

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OBSERVATIONS BY DR. HALL.

DURING the last few years outbreaks of lead poisoning of varying extent and severity have occurred in different localities which could not be traced to the ordinary sources of plumbism, such as water contamination or dangerous occupation. The cases were always limited to women of child-bearing age, and eventually the source of the poisoning was traced to the custom of taking diachylon as an abortifacient.

In a paper read before the Yorkshire Branch of the British Medical Association at Bradford in January, 1904,* I recorded 30 cases of this kind, and referred in detail to the numerous articles which have appeared in various journals from time to time on this subject (vide Bibliography at end of paper).

This custom of taking diachylon, instead of diminishing, has spread over such a large area of country, and assumed such serious proportions, that steps must be taken to check it, or if possible to stop it altogether. How this may best be done remains to be settled, but it is not so simple a matter as might at first sight appear.

The subject is a somewhat delicate one, which cannot easily be ventilated in the public press, or by the circulation of warning notices. Moreover, there is the fear that publication might tend to spread the evil, instead of reducing it.

History and Extent of Spread.—The first cases were observed at Leicester and were reported in 1893 by Dr. Pope.

After that the practice seems to have been less prevalent for a while, or at least to have spread but very slowly, for I can find no further record of cases until 1898, that is, five years later, when cases were reported in the neighbouring city of Birmingham. In 1899 it had reached Nottingham in considerable vigour, where it has remained ever since.

At that time it had certainly not reached as far north as Sheffield, nor did it do so to any extent until some two or three years later, since when the number of cases has steadily increased in the locality. Inquiries which I have made from all the neighbouring centres show that it has reached various smaller or larger towns still further north, such as Barnsley and Doncaster, and that a few cases have occurred in Leeds, including one death, but this seems to be its northern limit. So far as I can ascertain, it has not been recorded in any of the other large Yorkshire towns, Bradford, Halifax, Huddersfield, Hull, York, etc.* It has not affected the Manchester or Liverpool districts.

Further north at Newcastle-on-Tyne it appears to be quite unknown.

To the east of this affected Midland area I cannot hear of any cases, either at Lincoln, Gainsborough, or Retford.

To the south of Leicester a certain number of cases, with one death, have been reported to me by the courtesy of Dr. Horace Savory of Bedford.

Inquiries from various hospital authorities in London point to its not occurring there.

The area over which the practice of using diachylon as an abortifacient has spread is thus bounded on the north by the upper part of South Yorkshire, on the south by Bedfordshire, and on each side by the width of the counties of Leicester, Warwickshire, Notts, and East Derbyshire. This area comprises a large number of manufacturing towns, each containing thousands of the working classes, together with a country between largely occupied by mining populations.

Local Statistics as to Prevalence of the Custom.—Dr. Ransom has attempted to obtain some details as to the extent of this custom in and around Nottingham—that is, in the southern half of the area; whilst I have attempted to do the same in and around Sheffield.

A circular suggested by Dr. Ransom has been forwarded to every medical man within an area of some twenty or thirty miles of Sheffield, asking for information.

About 200 have replied. Of these 50 have had such cases of plumbism under their care during the last two years (vide Appendix A).

From their replies one can account for one or two hundred cases in this district during the last two years.

One may add to these the large number of women who come to our hospitals suffering from plumbism every month, and even then get a very modest estimate of the extent of the practice.

And this for two reasons: In the first place, a considerable number of medical men have told me they have had such cases but have not answered my circular for fear of making a breach of professional secrecy, whilst the fear of being found out prevents a large number of sufferers from going to their medical men at all.

I believe we shall not be far wrong in saying that several hundred women have taken diachylon in this district alone during the last two years.

From the previous statement one is warranted in saying that this abuse of diachylon is a grave public scandal; for, apart from the social and moral questions connected with it, there is the added evil of the harmful effects of the drug itself.

Unfortunately this is not limited to the severe abdominal pains and headache which immediately follow its use—themselves a cause of sufficiently serious suffering—but there is the prolonged anæmia, with complete inability to carry on the duties of a household for many weeks or months after the drug has been stopped.

* Since writing the above I am informed that the practice is not unknown to chemists in some of these towns, and that even in Dundee chemists have recently been asked for diachylon, apparently for this purpose.

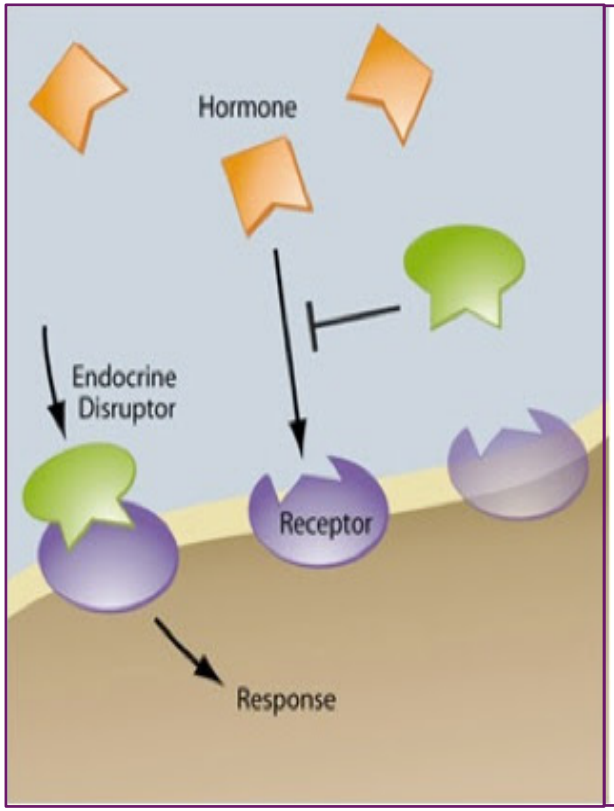
Hall & Ransom, Br Med J 1906;1:428-430.

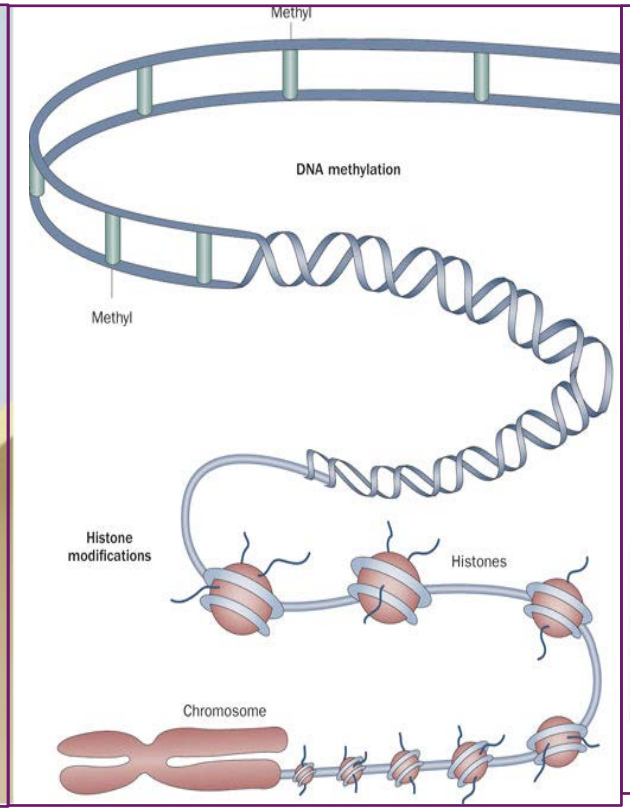
Pb associated biologic events relevant to reproduction & development

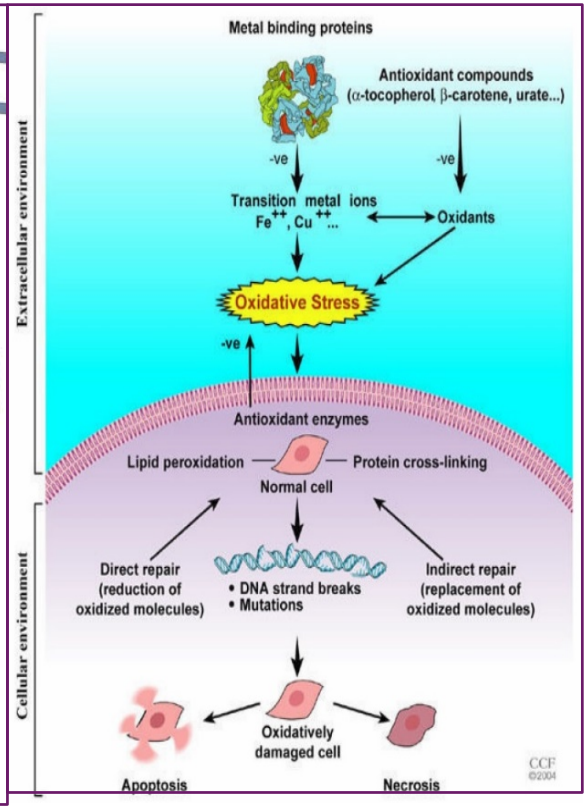
Endocrine disruption

Epigenetic reprogramming

Oxidative stress

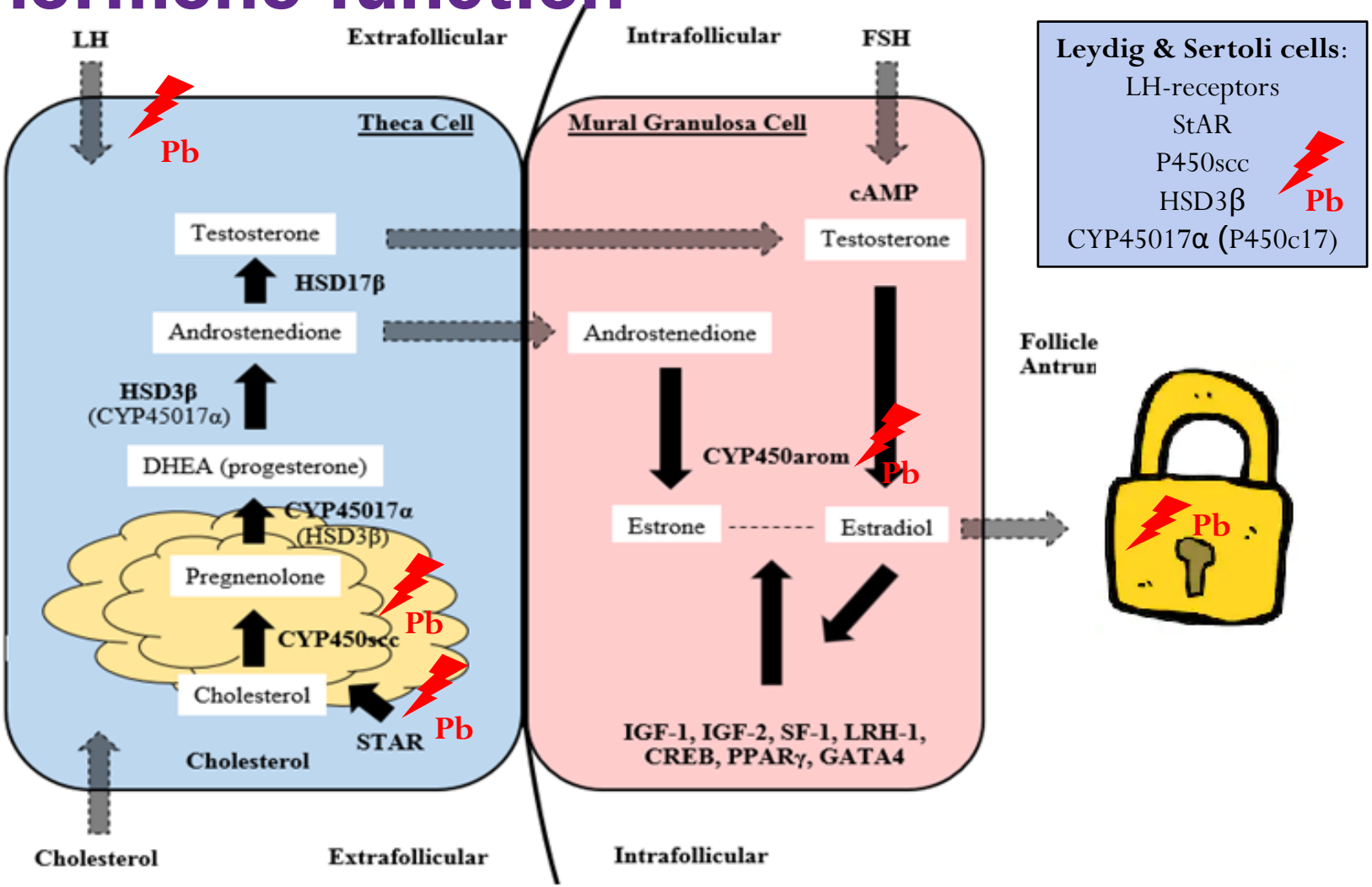






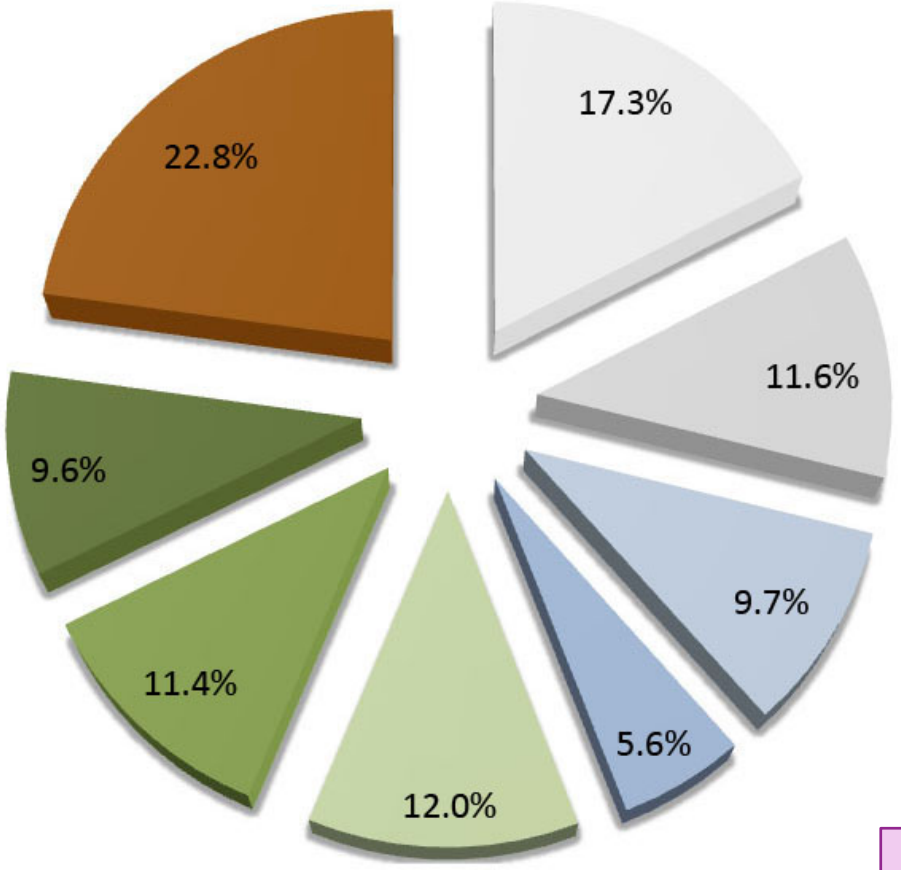
Agarwal et al., Reprod Biol Endocrinol 2005;3:28; Colborn et al. Environ Health Perspect 1993;101:378-384; Fragou et al., Toxicol Mech Methods 2011;21:343-352; Walker & Gore, Nat Rev Endocrinol 2011;7:197-207

Pb impacts gonadotropin & sex-steroid hormone function



Bloom et al., Fertil Steril 2016;106:857-863; Choe et al., Sci Total Environ 2003;312:15-21; Dyer in Gore, 2007 "Endocrine-Disrupting Chemicals: From Basic Research to Clinical Practice"; Iavicoli et al., J Toxicol Environ Health B Crit Rev 2009;12:206-223

Blood Pb for U.S. women 16-49 yrs relative to U.S. median (1999-2004)



- None
- Just lead
- Just mercury
- Just PCBs
- PCBs and lead
- Lead and mercury
- Mercury and PCBs
- All three

Pregnant < non-pregnant (33%), 2003-2004

57.8% > U.S. median (~1.47 µg/dL)

CDC, 2018 "Fourth National Report on Human Exposure to Environmental Chemicals - Updated Tables, March 2018"
Thompson & Koekelheide, Environ Res 2013;121:23-30; Woodruff et al., Environ Health Perspect 2011;119:878-885

Pb crosses the placenta (~1.0) & mobilizes from skeletal compartment

Author	Area	n	Maternal blood	Cord blood	C:M ratio
Al-Saleh et al., 2011	Saudi Arabia	1,572	2.54 µg/L	2.06 µg/L	0.81
Butler Walker et al., 2006	Canadian Arctic	324	26.7 µg/L	21 µg/L	0.79
Hu et al., 2015	China	81	23.1 ng/g	22.0 ng/g	0.95
Hu et al., 1996	U.S. (postpartum)	41	3.0 µg/L	1.0 µg/L	0.33
Raghunath et al., 2000	India	148	6.4 µg/dL	5.1 µg/dL	0.80
Sakamoto et al, 2012	Japan (RBCs)	16	24.5 ng/g	14.8 ng/g	0.60

Al-Saleh et al., Int J Hyg Environ Health 2011;214:79-101; Butler Walker et al., Environ Res 2006;100:295-318; Hu et al., J Reprod Med 2015;60:21-29; Hu et al., Arch Environ Health 1996;51:52-58; Hu et al., Am J Public Health 1991;81:1070-1072; Raghunath et al., Sci Total Environ 2000;250:135-141; Sakamoto et al., Ecotoxicol Environ Saf 2012;84:179-184

Moderate-high level environmental & workplace exposure studies

Port Pirie, South Australia (Pb smelter community)

Endpoint	Outcome (n)	Maternal bld Pb (µg/dL)	Cord bld Pb (µg/dL)	P-value
Loss (<20 wks.)	Case (23)	11.3	-	>0.05
	Referent (721)	10.8	-	-
PTB (<37 wks.)	Case (30)	12.5	12.7	**<0.05**
	Referent (527)	11.2	10.0	-

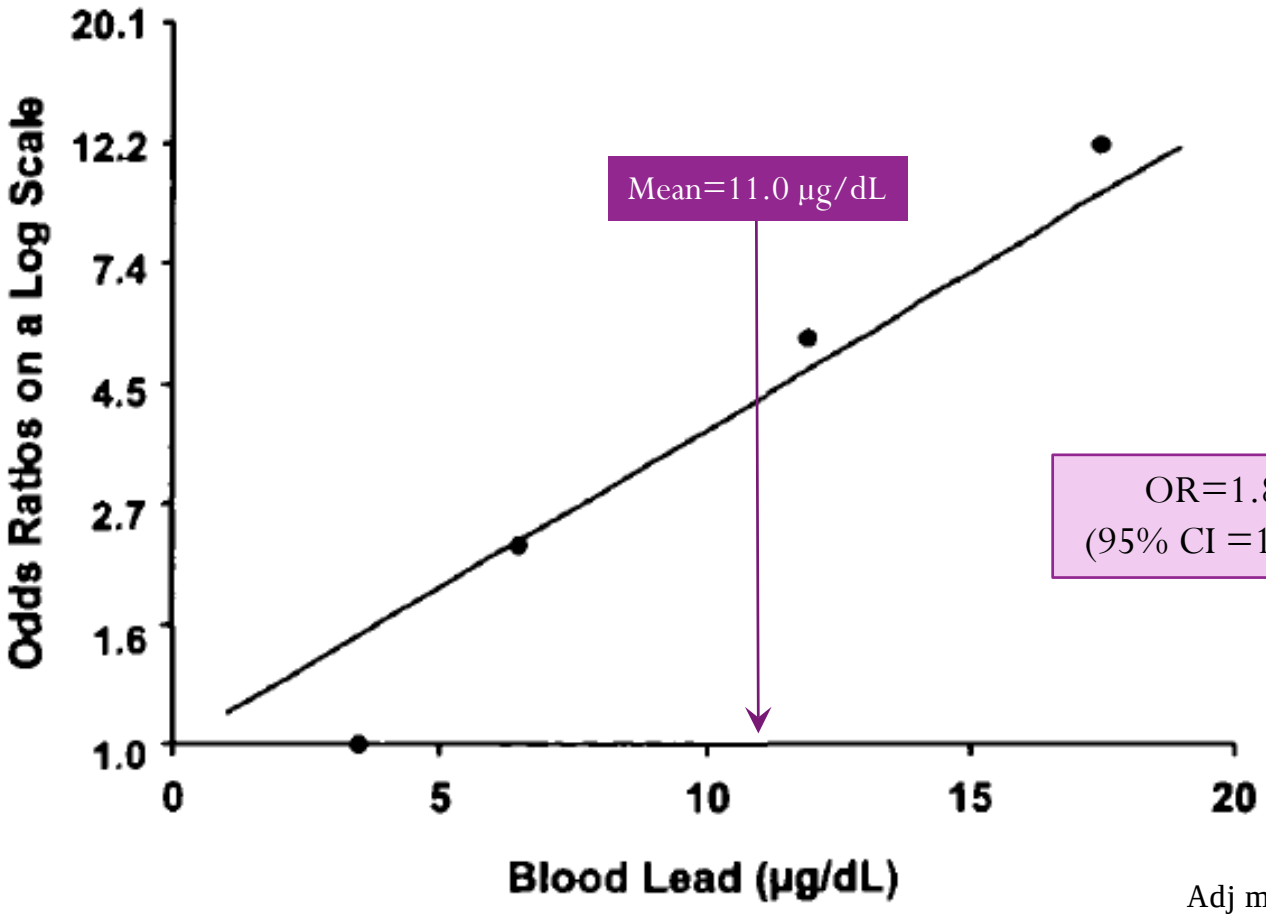
Finnish worker cohorts, 1973-1983 (1st trimester maternal, spermatogenesis paternal)

Exposure	Bld Pb level (µg/dL)	Spontaneous loss (n)	Birth (n)	OR (95% CI)
Maternal (n=229)	<10.4	23	45	0.9 (0.5, 1.7)
	≥20.7	5	11	0.8 (0.2, 2.5)
Paternal (n=513)	20.7-29.0			
	≥39.3			

OR=2.2 for ≥20.7 µg/dL with wife <27 yrs (95% CI=1.2, 4.1)

Lindbohm et al., Scand J Work Environ Health 1991;17:95-103; Scand J Work Environ Health 1992;18:37-39; McMichael et al., J Epidemiol Community Health 1986;40:18-25

Maternal blood Pb & pregnancy loss in Mexico City, 1994-1996 (n=95)

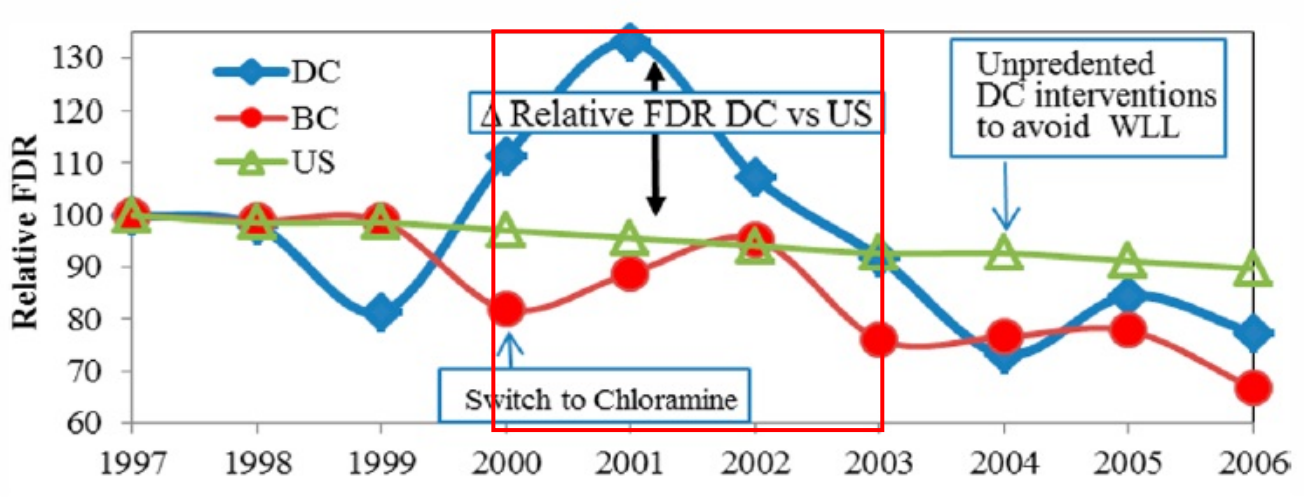


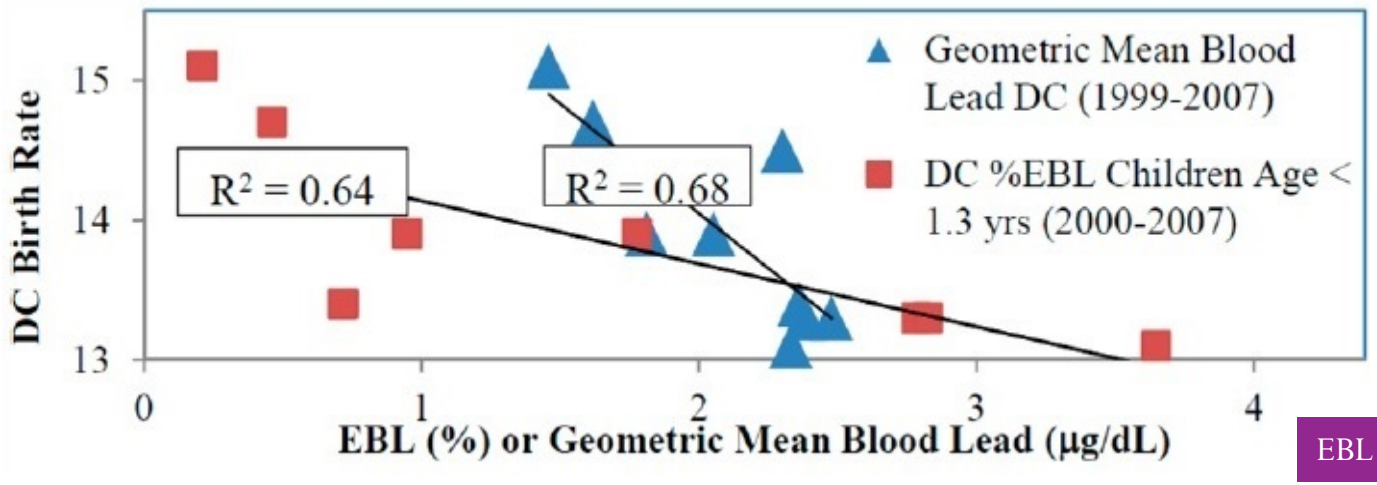
OR=1.84 per 5 µg/dL
(95% CI =1.05, 3.71, P=0.03)

Adj maternal age, clinic type, gestational age at sample, prior loss & calendar date

Borja-Aburto et al., Am J Epidemiol 1999;150:590-597; Hertz-Picciotto, Am J Ind Med 2000;38:300-309

Municipal water supply "Pb crisis" in Washington, DC (2000-2003)

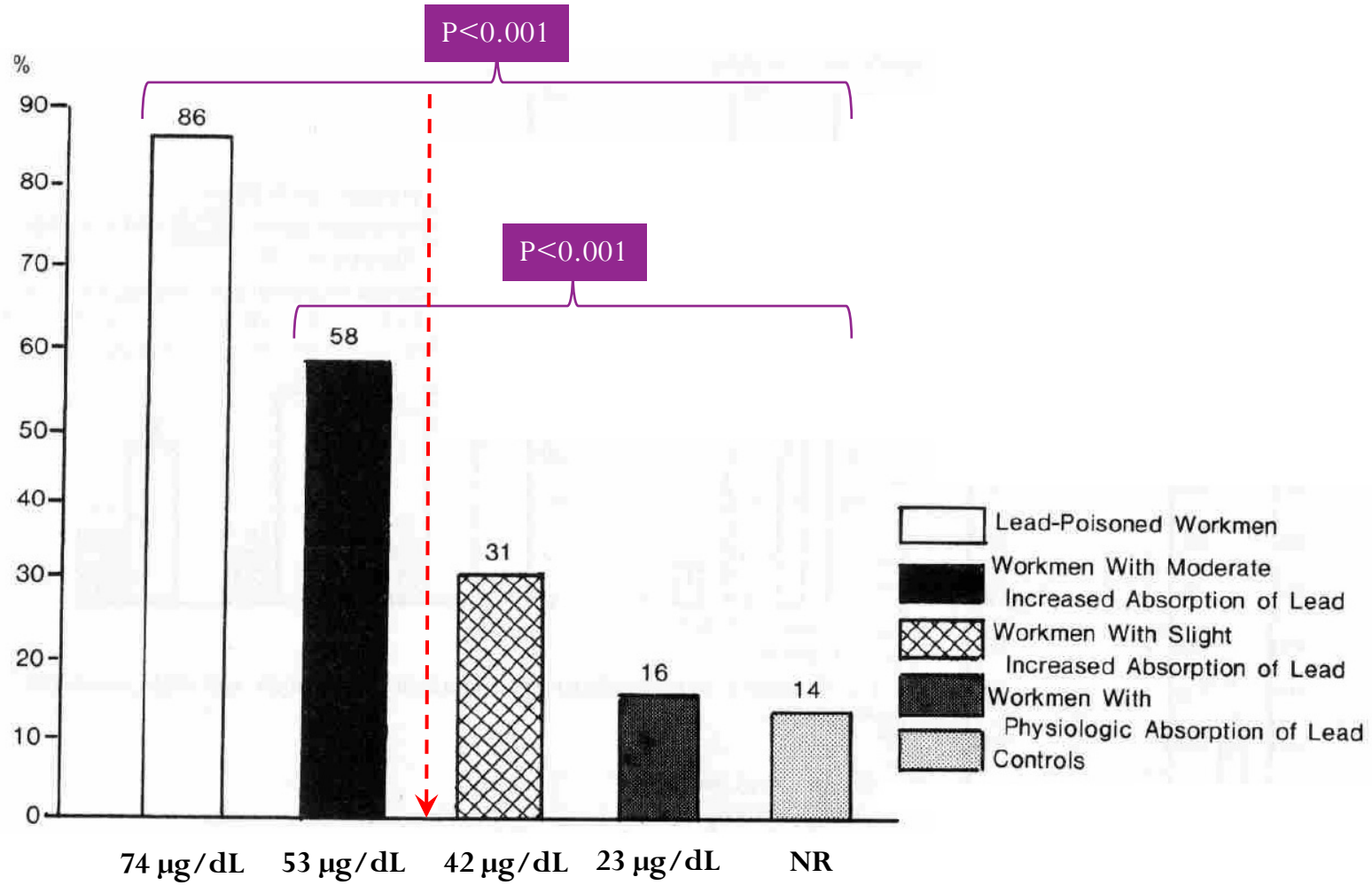




EBL >10 µg/dL

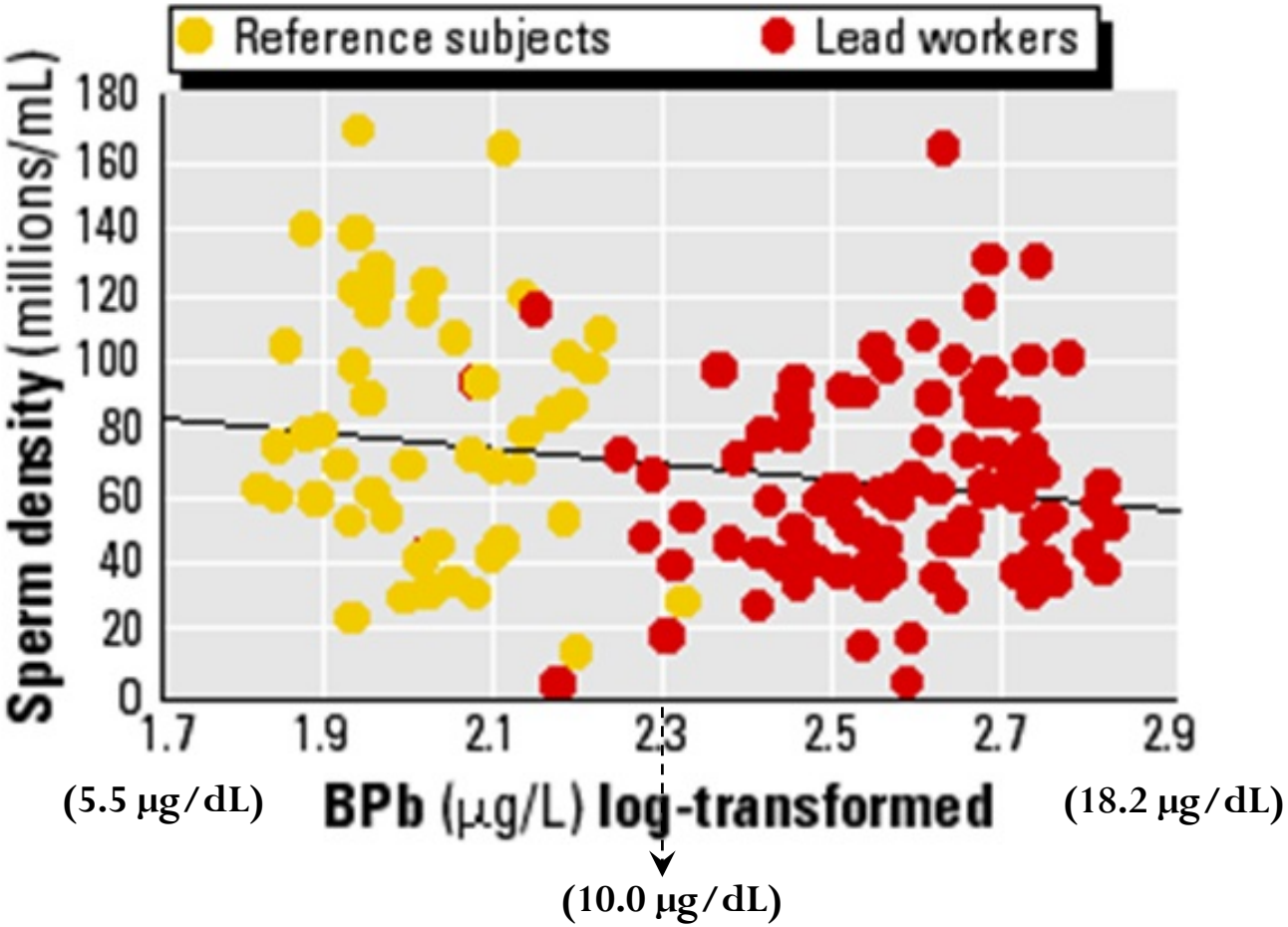
Edwards, Environ Sci Technol 2013;48:739-746

Teratozoospermia among men with occupational Pb exposure & controls



Lancranjan et al., Arch Environ Health 1975;30:396-401

Higher workplace Pb associated with lower sperm concentration (n=149)



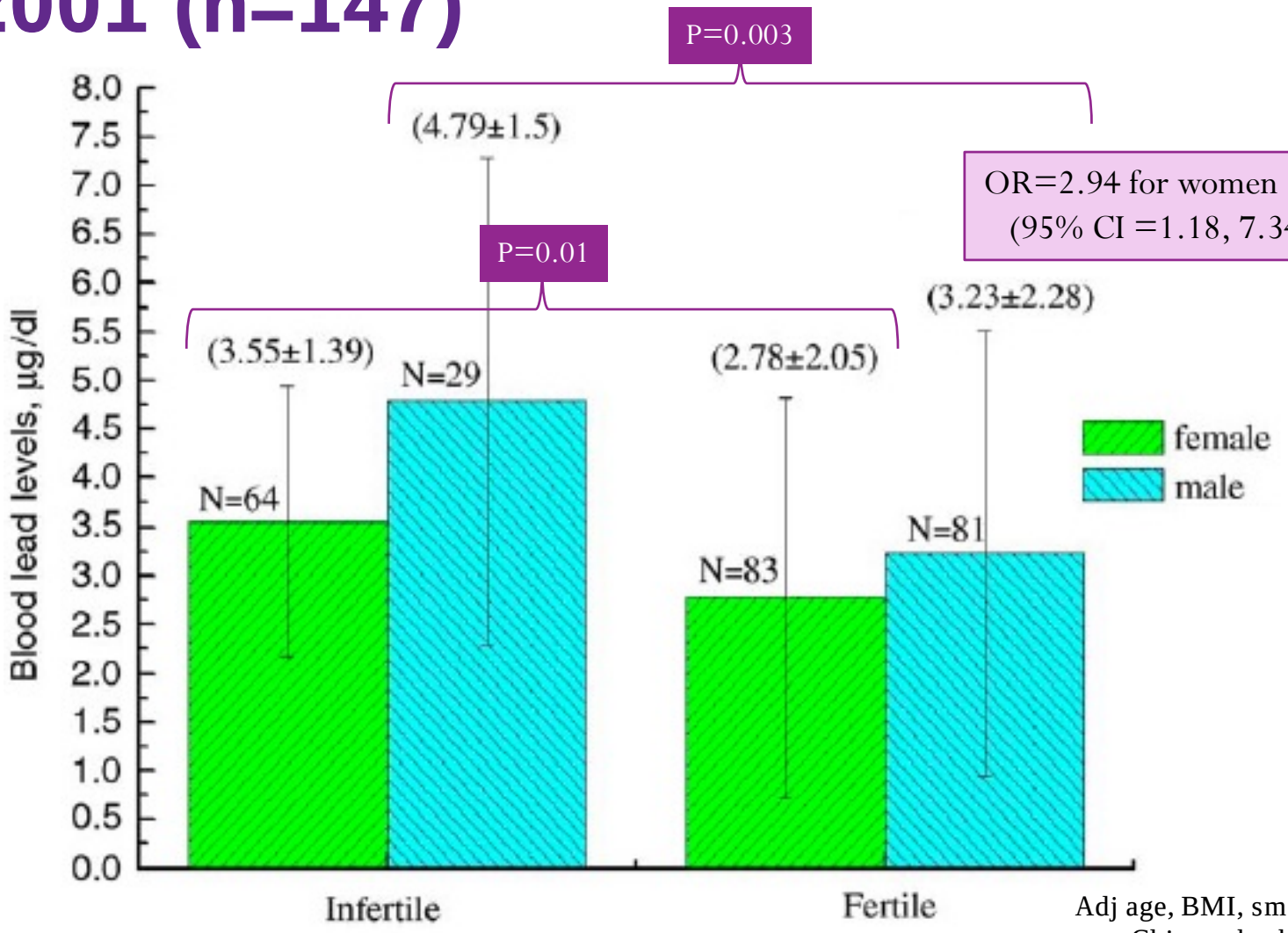
Telisman et al., Environ Health Perspect 2000;108:45-53

Higher workplace Pb associated with male infertility (n=4,146)

PbB (μmol/L)	No. of couples	Couples without Pregnancies, %	RR	95% Confidence Interval
All	4146	25.7		
(≤10.35 μg/dL) 0.0–0.4	681	21.3	1.0†	
Probable exposure				
Husband monitored within a 5-year period				
(≥10.35 μg/dL) 0.5–0.9	1067	26.8	1.27	1.08–1.51
1.0–1.4	625	27.8	1.35	1.12–1.63
1.5–1.9	242	29.8	1.37	1.08–1.72
2.0–2.4	112	29.5	1.50	1.08–2.02
(51.75 μg/dL) ≥2.5	65	35.4	1.90	1.30–2.59
Potential exposure				
Husband monitored last time before the 5-year period				
0.5–1.4	519	28.5	1.04	0.85–1.27
(≥31.06 μg/dL) ≥1.5	145	27.6	1.10	0.81–1.46
Husband monitored first time after the 5-year period				
0.5–1.4	622	20.9	1.23	0.99–1.53
≥1.5	68	23.5	1.34	0.82–2.03

Sallmen et al., Epidemiology 2000;11:148152

Female infertility in Taiwan, 2000-2001 (n=147)



OR=2.94 for women >2.5 µg/dL
(95% CI =1.18, 7.34; P=0.02)

Adj age, BMI, smoking, Rx use, Chinese herb use, irregular menses

Chang et al., Environ Res 2006;101:380-38

Cord blood Pb & birth outcomes in Boston, 1979-1981 (n=4,354)

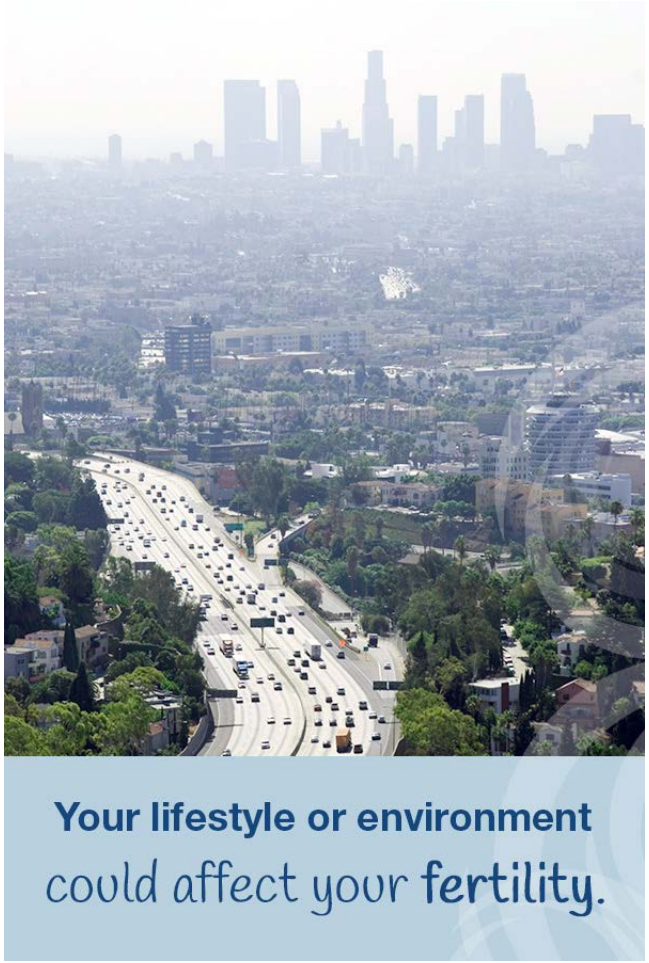
Outcome	0-4.9 µg/dL	5.0-9.9 µg/dL	10.0-14.9 µg/dL	≥15.0 µg/dL	RR (95% CI) per µg/dL
LBW	7.7%	7.0%	8.4%	9.8%	1.05 (1.00, 1.10)
SGA	9.4%	10.9%	12.3%	17.7%	1.02 (0.98, 1.05)
IUGR	1.5%	2.0%	2.4%	3.9%	1.06 (1.00, 1.13)
PTB	7.8%	6.3%	8.2%	5.9%	0.98 (0.93, 1.02)

- Longer GA with higher Pb (P=0.0002), no association with BW (P=0.21)
- Adj maternal age, marital & working status, education, race, PI, parity, smoking, EtOH & coffee consumption, diabetes & delivery hematocrit & mode

Bellinger et al., Environ Res 1991;54:151-158

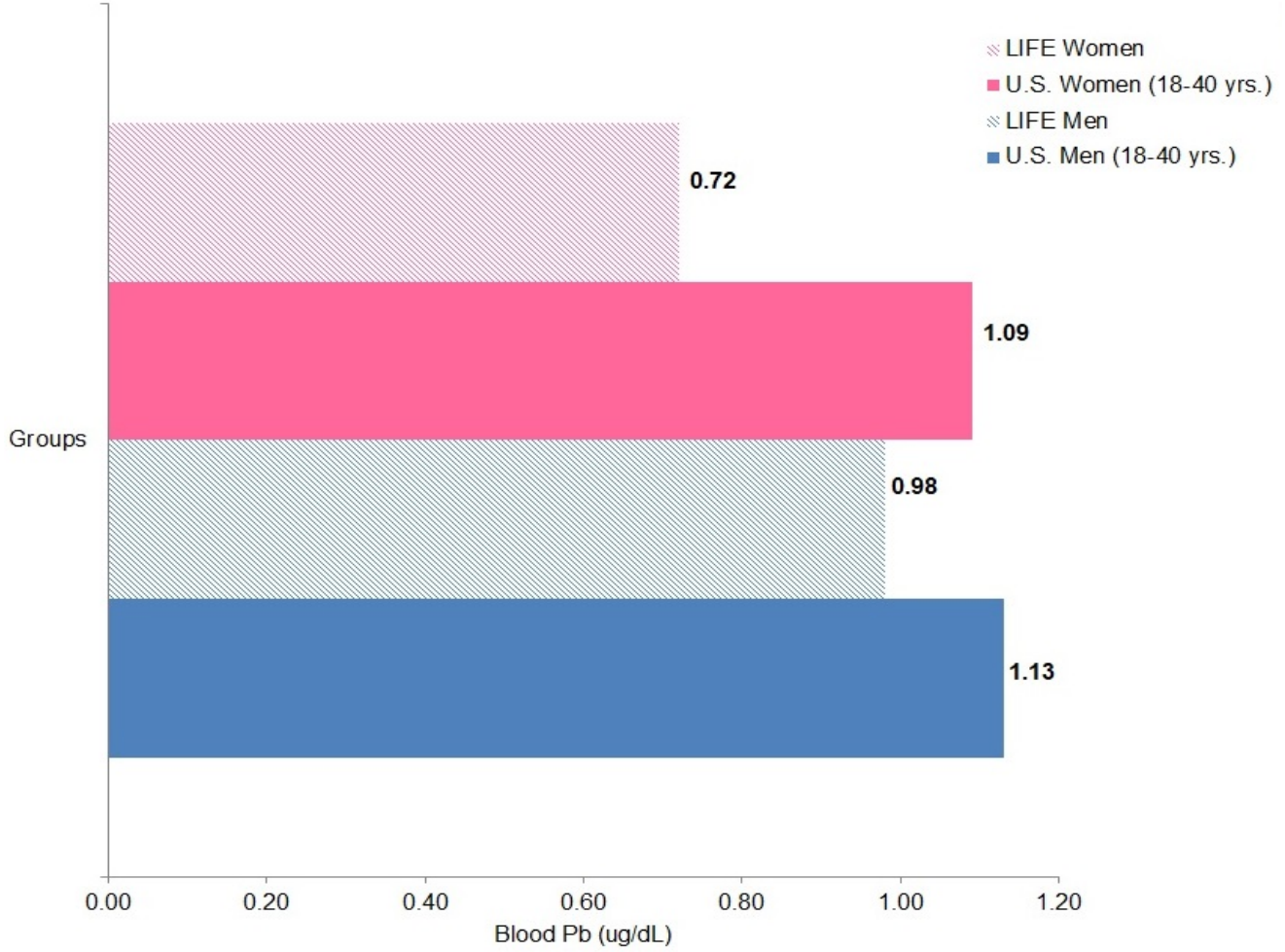
Longitudinal Investigation of Fertility and the Environment (LIFE)

- Prospective preconception pregnancy cohort with longitudinal data collection:
  - 501 couples planning a pregnancy in 2005-2009, Michigan & Texas (U.S.)
- Identify environmental influences on human reproduction



Louis et al., Paediatr Perinat Epidemiol 2011;25:413-424; https://www.nichd.nih.gov/about/org/diphr/od/research/longitudinal, accessed 10/30/18

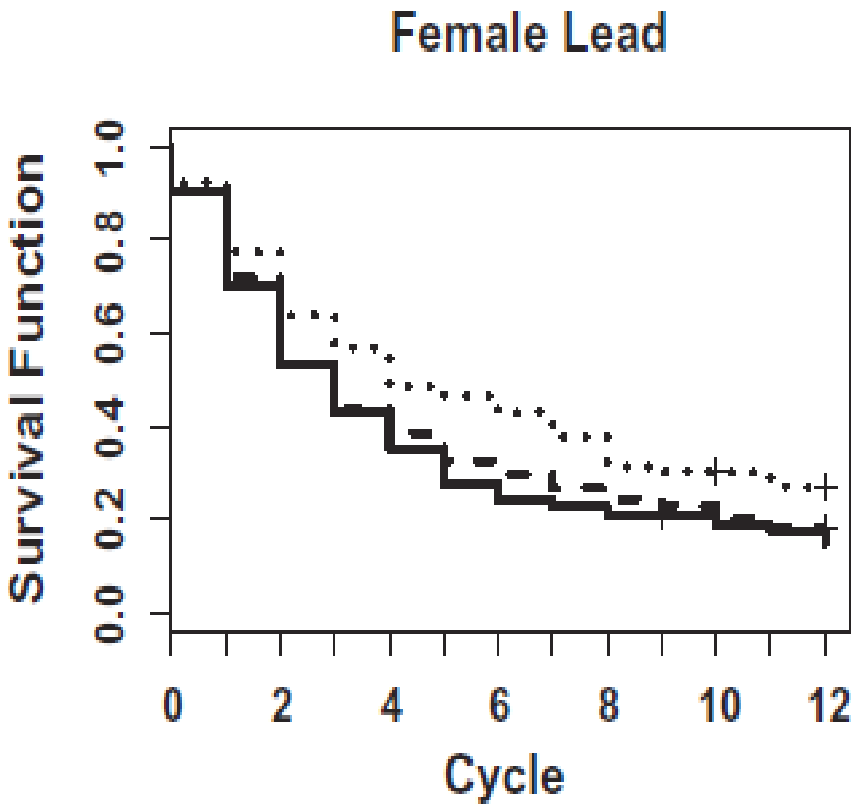
Median bld Pb for women (19-40 yrs) & men (19-51 yrs) vs U.S.

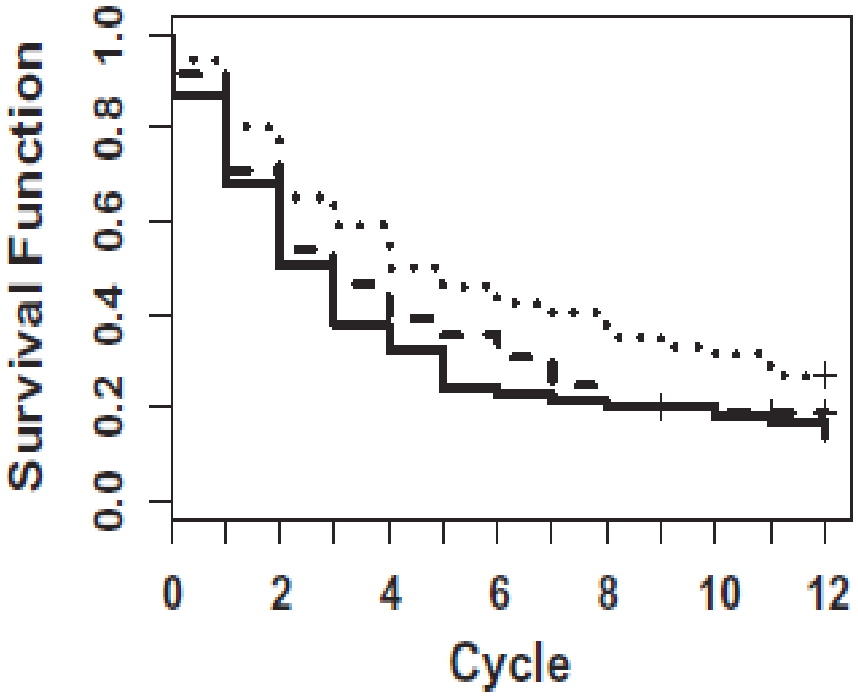


Bloom et al., Environ Res 2015;138:118-129; CDC, 2018 "Fourth National Report on Human Exposure to Environmental Chemicals - Updated Tables, March 2018"

Associations for pre-conception bld Pb (1 SD) with fecundability

FOR=0.82 per SD higher paternal Pb (µg/dL)
(95% CI=0.68, 0.97)





- Adj partner bld Cd, Hg, parental ages, BMI, serum cotinine & lipids, parity & study site

Buck Louis et al., Chemosphere 2012;87:1201-1207

1st tertile solid line, 2nd tertile broken line, 3rd tertile dotted line

Associations for pre-conception bld Pb (tertiles) with birth outcomes

Parent	Tertile	HR for GA, wks. (n=195)	β for BW, g (n=232)	β for BL, cm (n=231)	β for HC, cm (n=182)
Maternal	2nd	0.78 (0.37, 1.62)	81.80 (-74.94, 238.55)	0.43 (-0.48, 1.35)	0.03 (-0.68, 0.74)
			-34.85 (-197.76, 128.06)	0.14 (-0.81, 1.09)	-0.33 (-1.04, 0.41)
			0.20	0.67	0.13
Paternal	2nd	1.18 (0.61, 2.31)	20.46 (-134.17, 175,09)	0.19 (-0.70, 1.08)	0.12 (-0.57, 0.80)
	3rd	1.05 (0.55, 2.01)	62.91 (-94.73, 220.55)	0.61 (-0.31, 1.53)	-0.03 (-0.72, 0.67)
	P-trend	0.89	0.88	0.42	0.97

Infant sex interaction (P=0.03):
HR=1.94 for boys (95% CI =1.06, 2.09)
HR=0.81 for girls (95% CI=0.52, 1.27)

- Adj partner Pb, parental ages, smoking, income, race & serum lipids

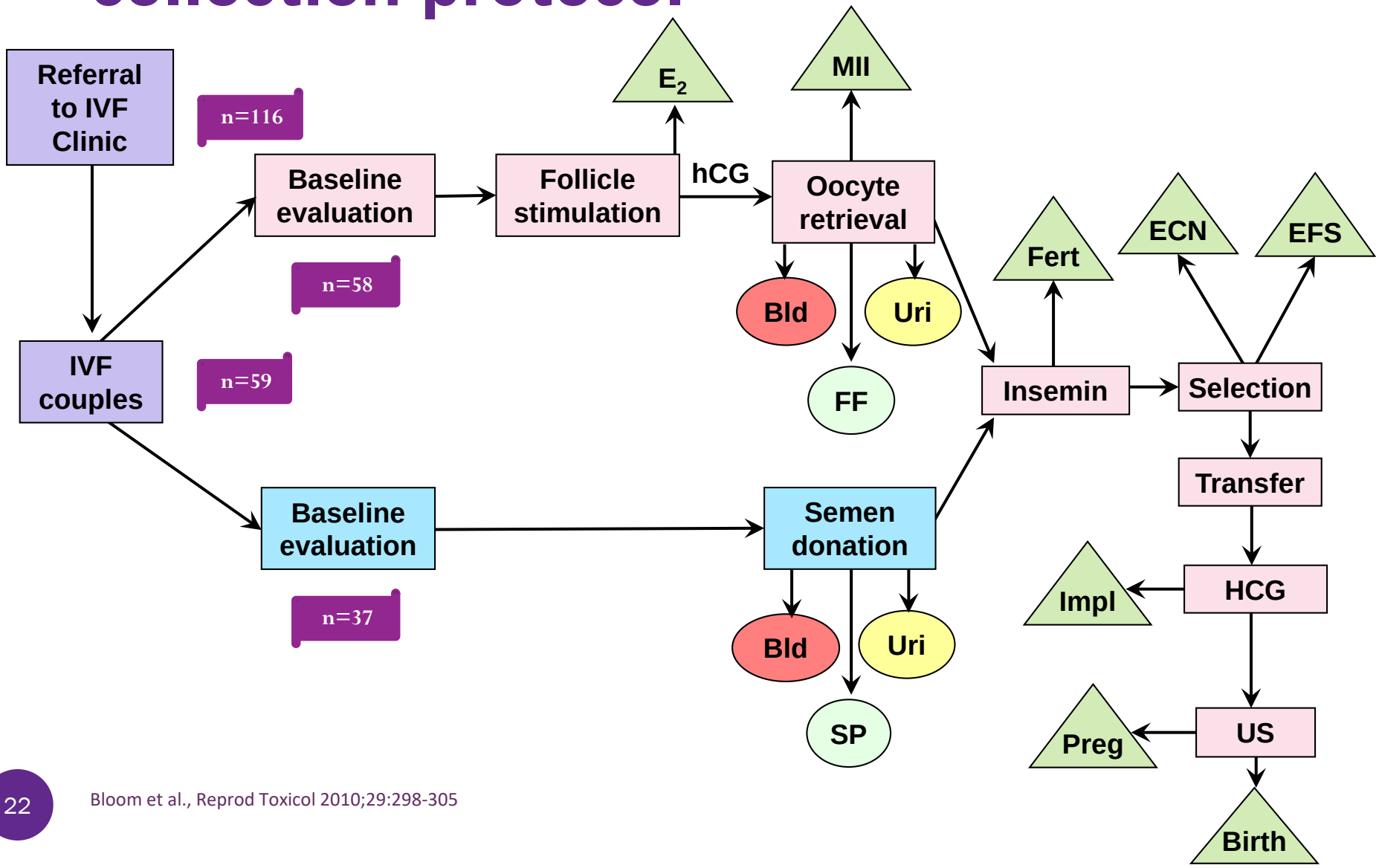
Bloom et al., Environ Res 2015;138:118-129; Environ Res 2015;142:760-761

Study of Metals & Assisted Reproductive Technologies (SMART)

- Prospective cohort of IVF couples using fresh, non-donor oocytes
- Initiated in response to the knowledge gap concerning environmental pollutants & periconceptual events
- Generate specific testable hypotheses concerning background exposures to toxic trace elements & IVF endpoints:
  - 2007-2008 – n=59 couples
  - 2015-2017 – n=65 couples

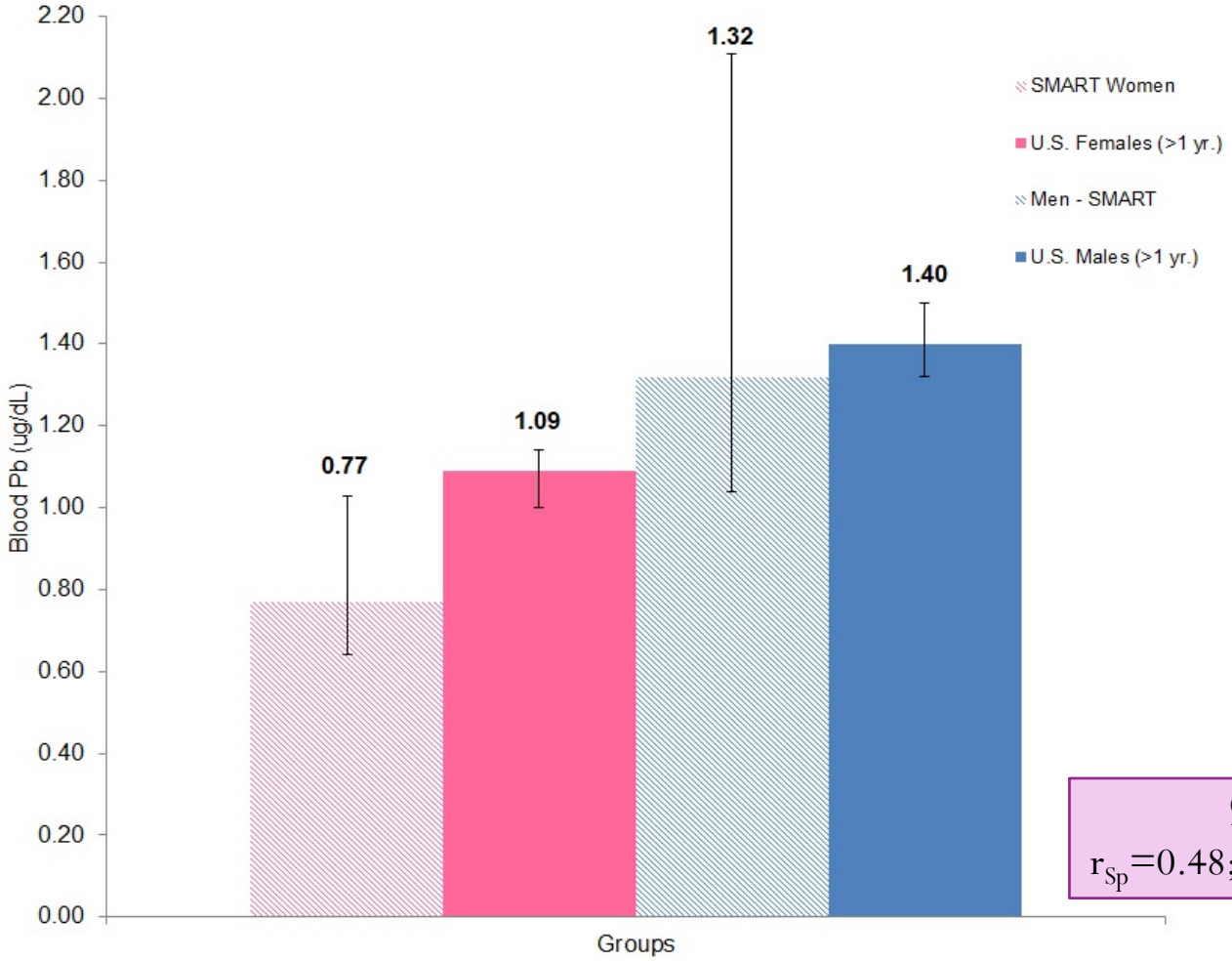
Bloom et al., Reprod Toxicol 2010;29:298-305

SMART enrollment & specimen collection protocol



Bloom et al., Reprod Toxicol 2010;29:298-305

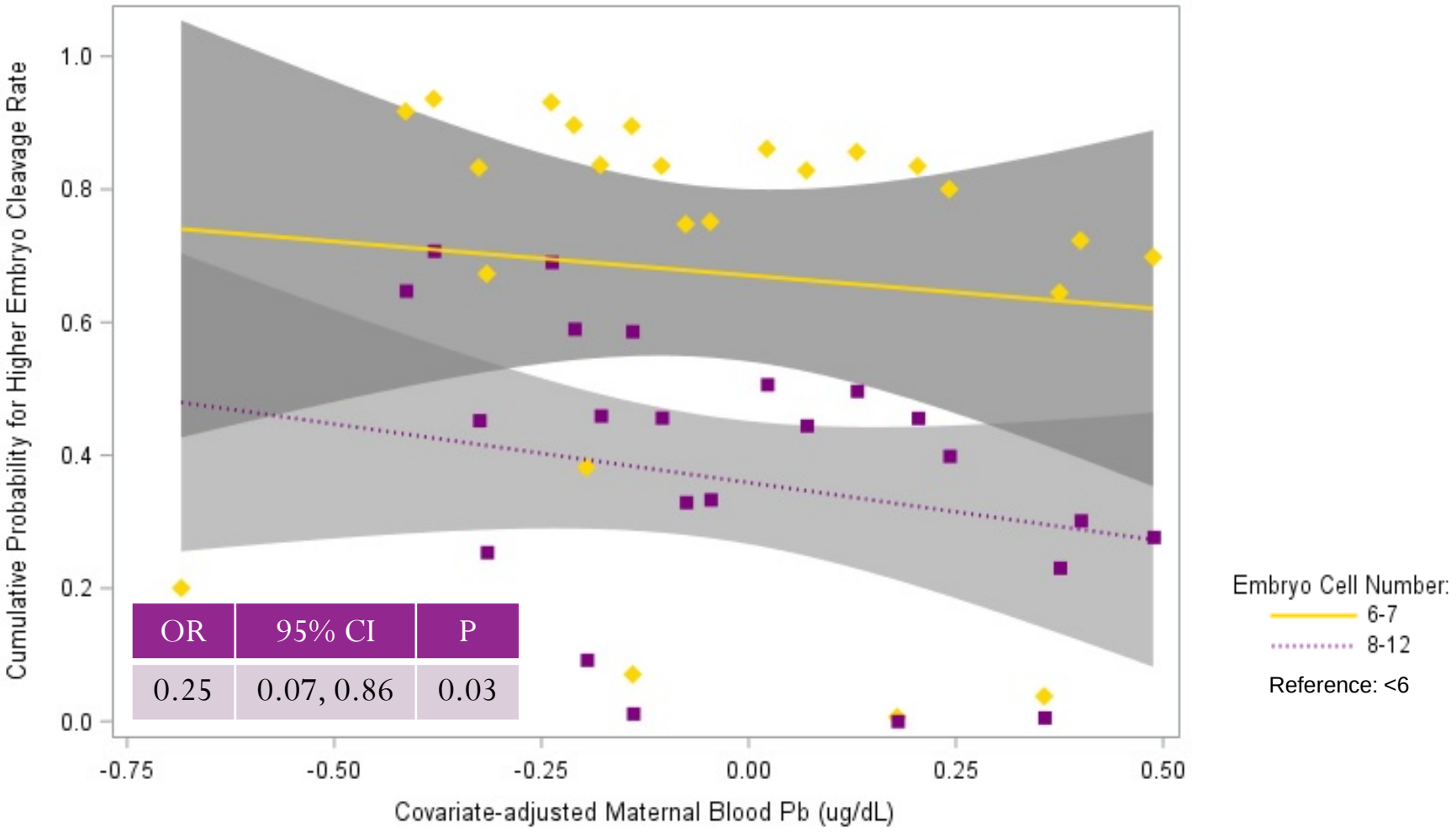
Median (95% CI) bld Pb for women (28-44 yrs) & men (31-48 yrs) vs U.S.



♀ & ♂
r_{Sp}=0.48; P=0.09; n=14

Bloom et al., Reprod Toxicol 2010;29:298-305; CDC, 2018 "Fourth National Report on Human Exposure to Environmental Chemicals - Updated Tables, March 2018"

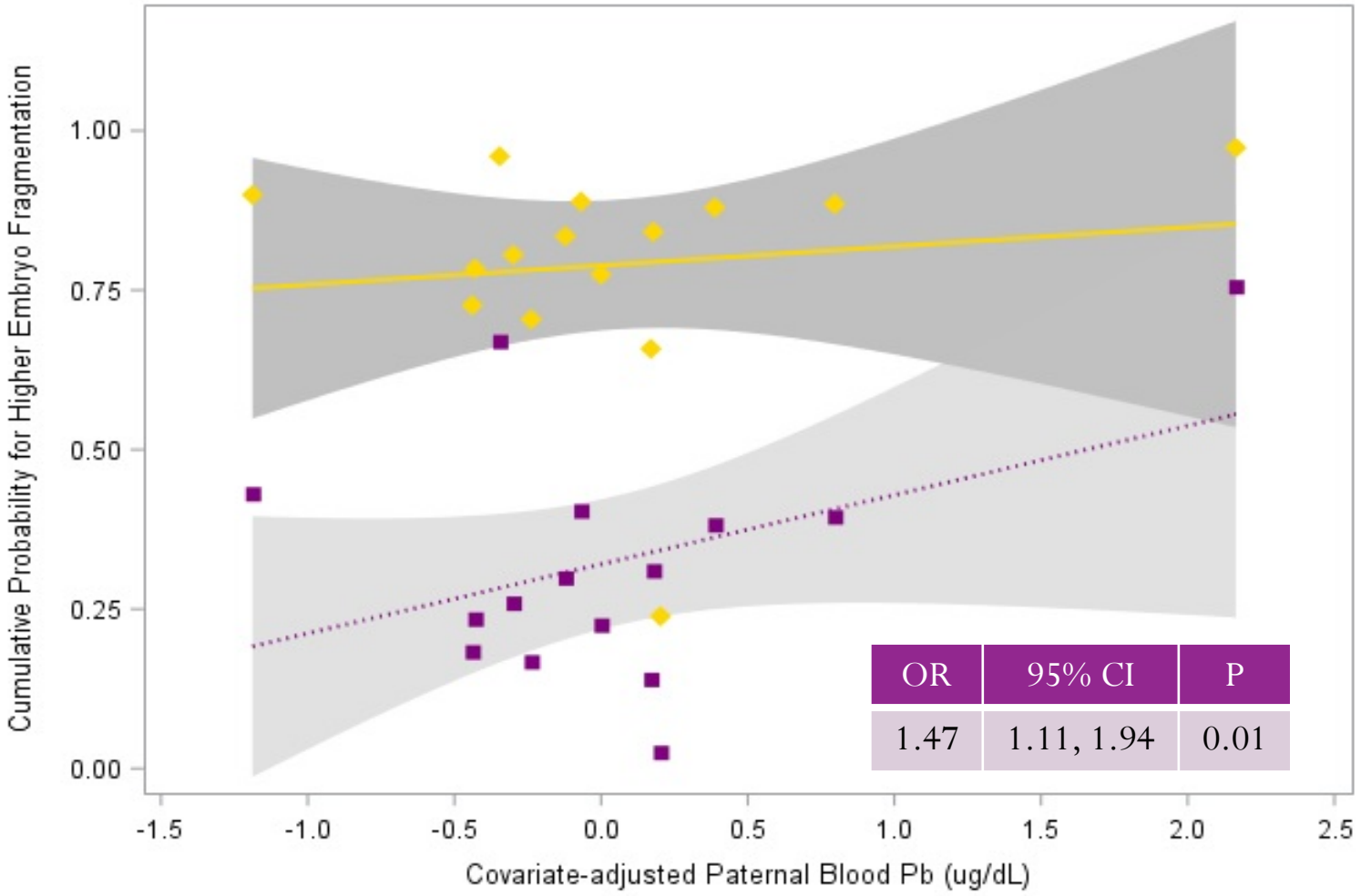
Odds for higher maternal bld Pb (1 µg/dL) with embryo quality (n=24:190)



Bloom et al., Reprod Toxicol 2011;31:164-170

Adj bld Hg, urine Cd & creatinine, age, race, smoking & day of transfer

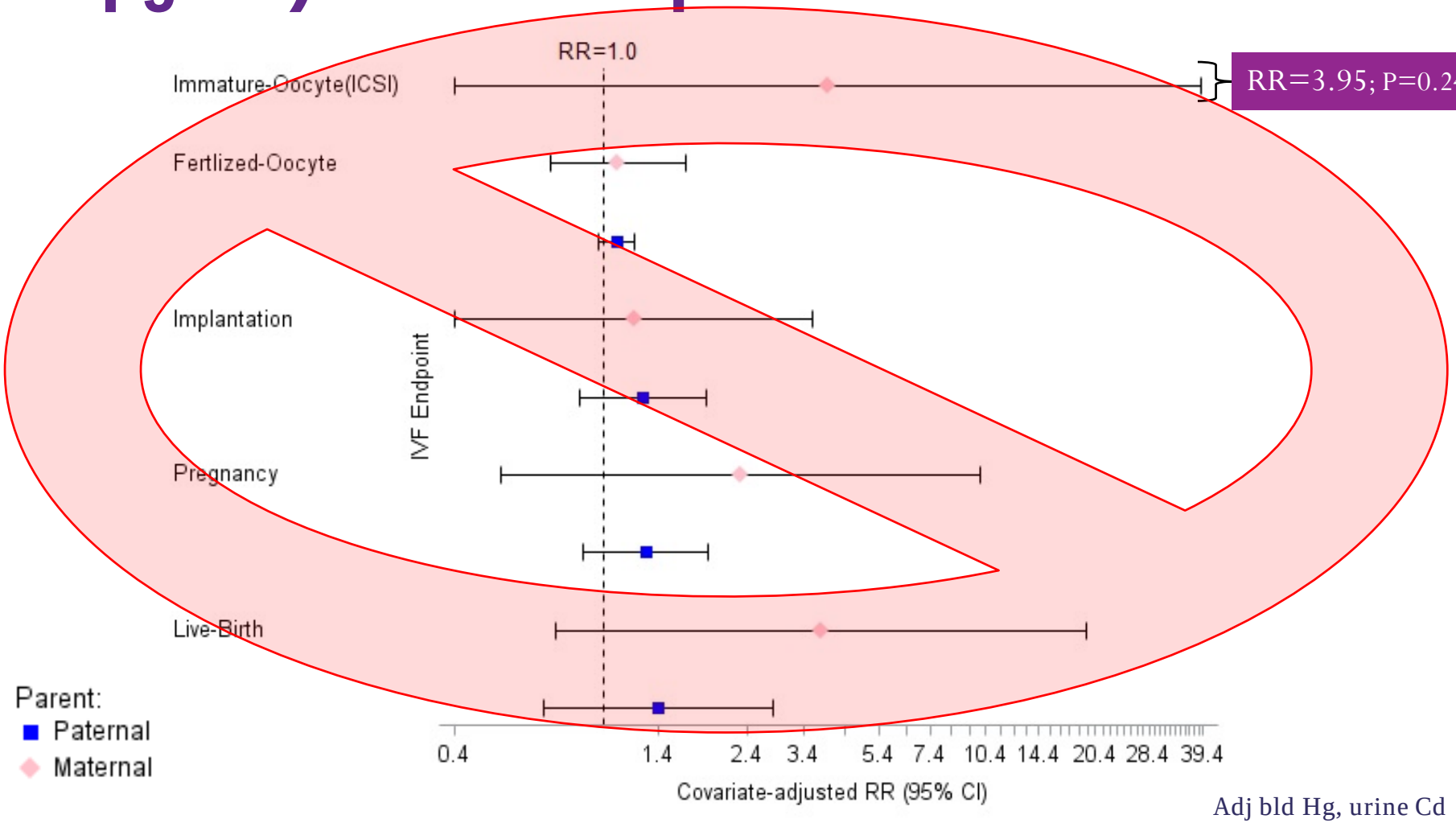
Odds for higher paternal bld Pb (1 µg/dL) with embryo quality (n=15:123)



Bloom et al., Reprod Toxicol 2011;31:164-170

Adj bld Hg, urine Cd & creatinine, age, race & smoking

Associations for higher bld Pb (1 ln µg/dL) & IVF endpoints



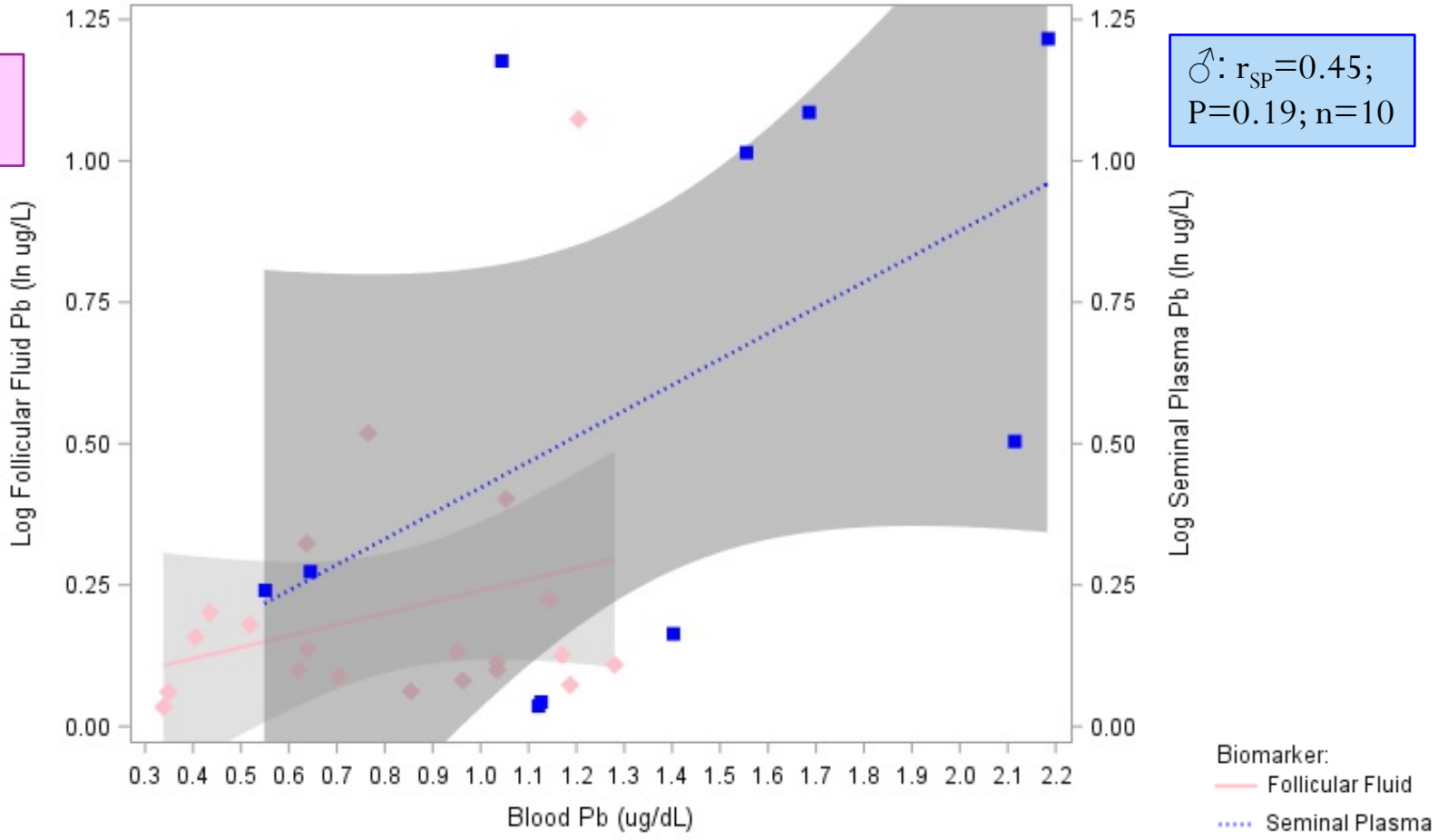
Adj bld Hg, urine Cd & creatinine, age, race & smoking

Bloom et al., Reprod Toxicol 2012;34:471-481; Reprod Toxicol 2012;33:126; Reprod Toxicol 2010;29:298-305

Association for bld Pb with FF Pb & SP Pb

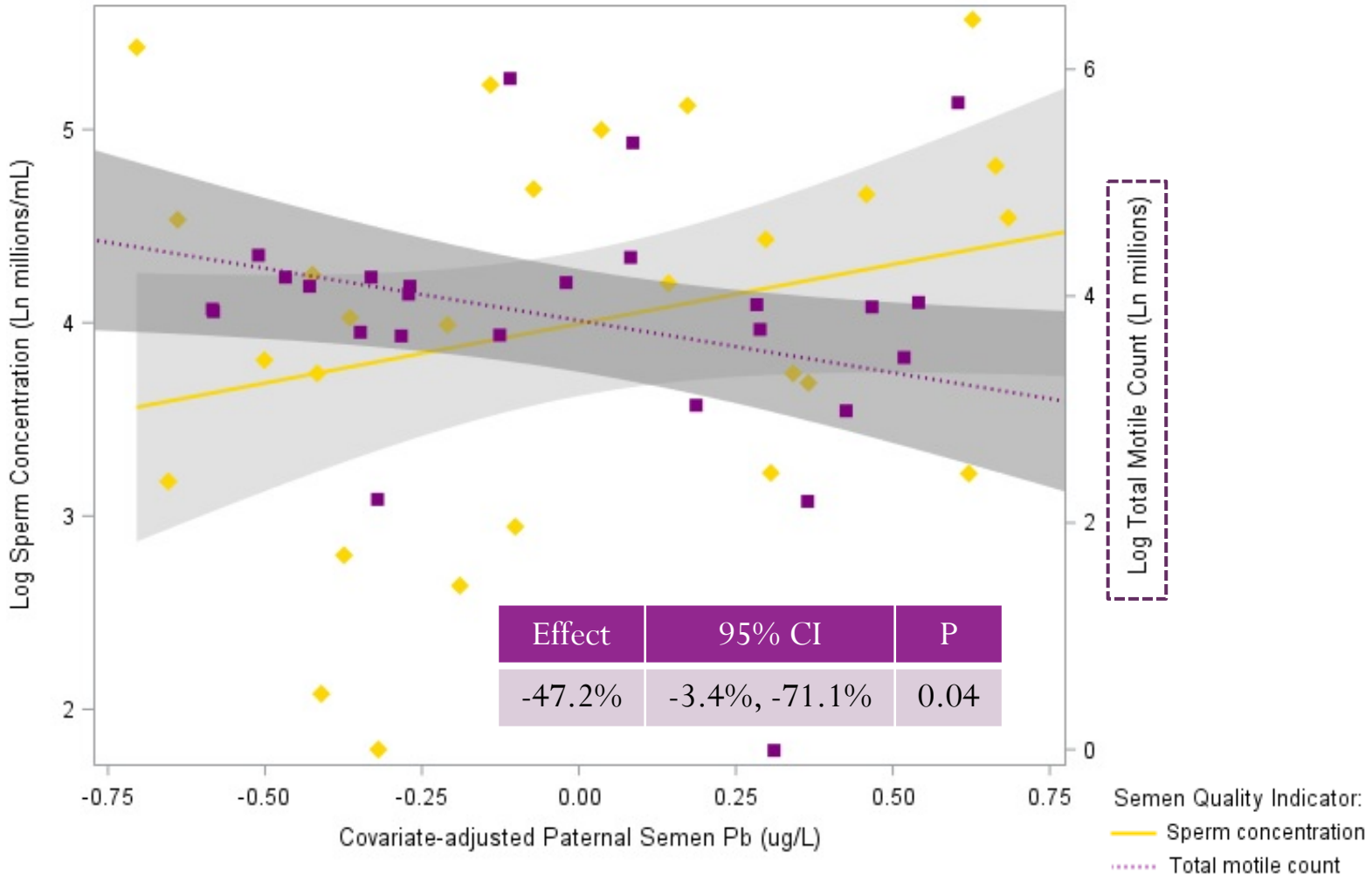
♀: r_{SP}=0.19; P=0.40; n=21

♂: r_{SP}=0.45; P=0.19; n=10



Bloom et al., J Assist Reprod Genet 2012;29:1369-1379

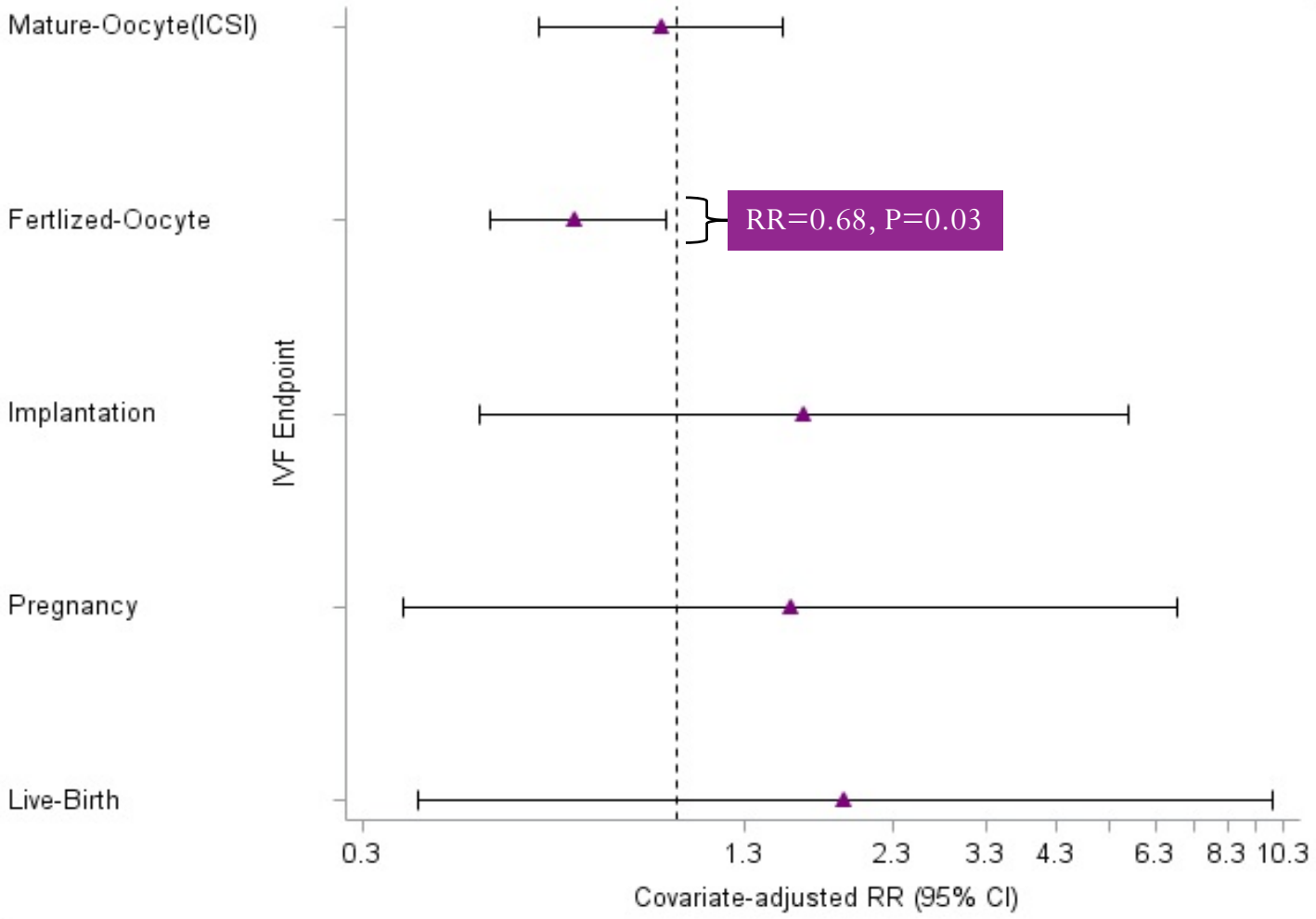
Associations for SP Pb (1 µg/L) with semen quality (n=30)



Kim et al., Environ Res 2014;133:334-337

Adj bld Hg, urine Cd & creatinine, age, race & smoking

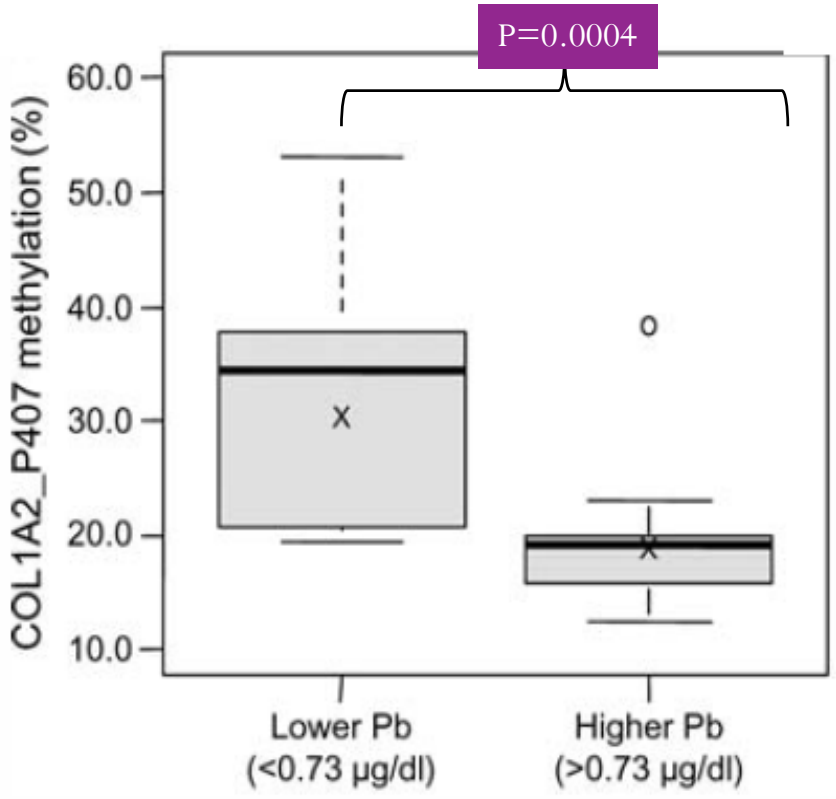
Associations for FF Pb (1 √µg/L) & IVF outcomes (n=46)

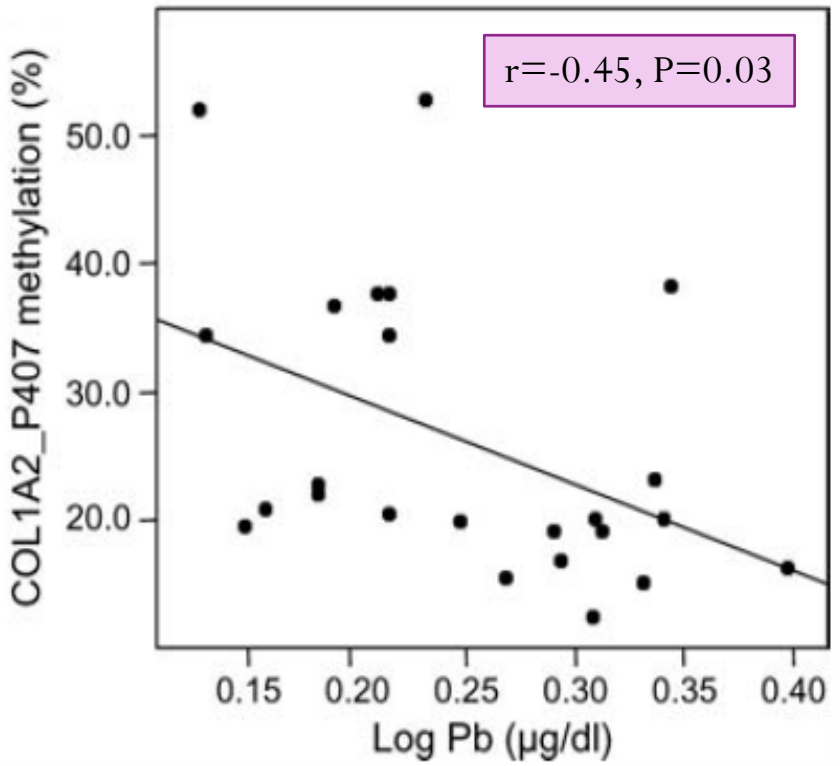


Bloom et al., J Assist Reprod Genet 2012;29:1369-1379

Adj FF Hg, Cd, age, race & smoking

Association between women's bld Pb & COL1A2_P407 % methylation (n=24)





- Illumina GoldenGate Methylation Cancer Panel (1505 CpG sites) confirmed with pyrosequencing
  - Col1A2 product is a component of **collagen/connective tissue**

Hanna et al., Hum Reprod 2012;27:1401-1410

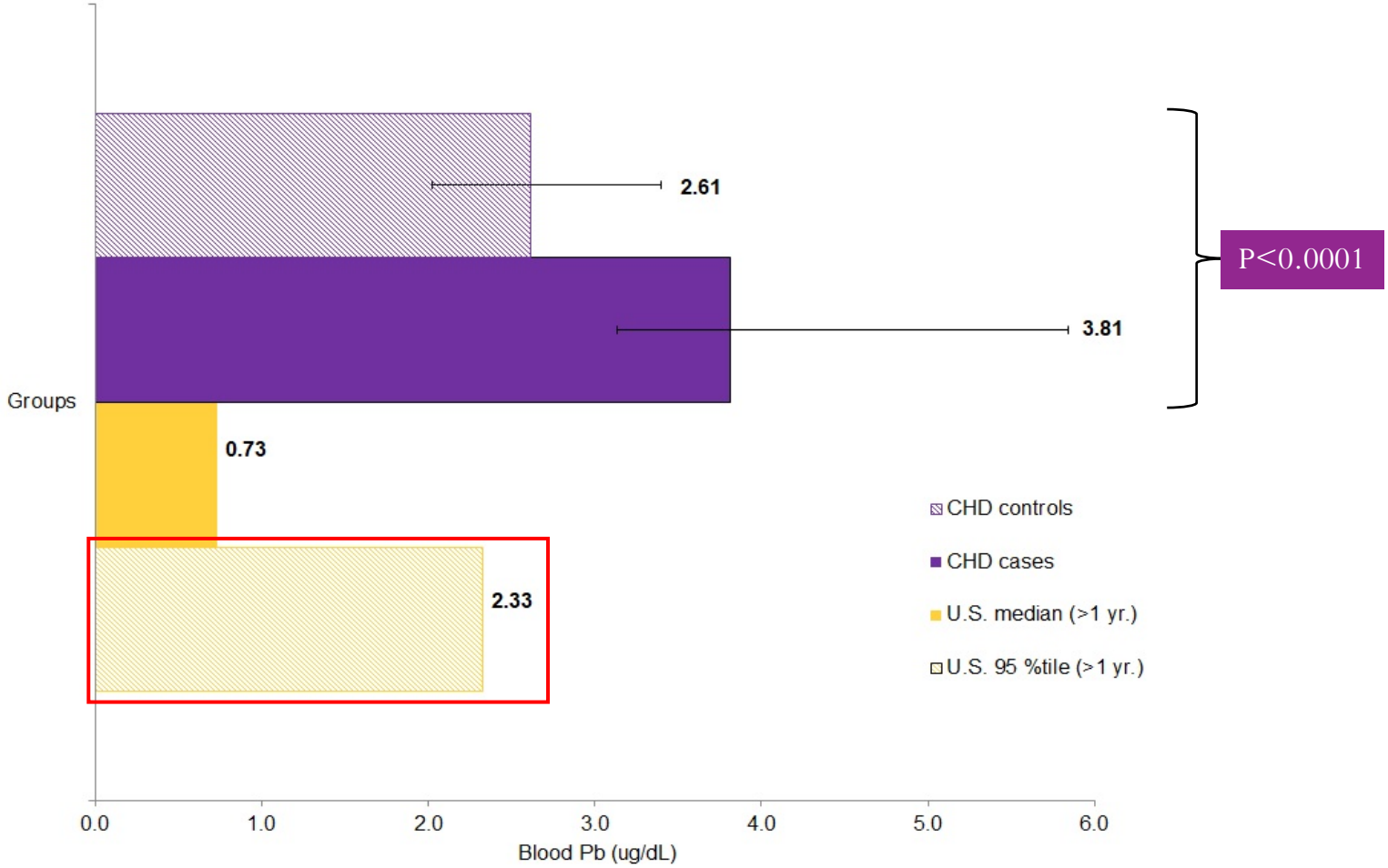
Environment & Congenital Heart Defects Study

- Guangdong Cardiovascular Institute, Guangzhou, China
- Hospital-based case-control study (2013-2014):
  - n=120 cases of ultrasound -& clinically confirmed CHDs
  - n=108 controls
- Maternal bld at 17-40 wks gestation
- Assess associations between bld Pb & CHDs

Canton Tower, Guangzhou, China

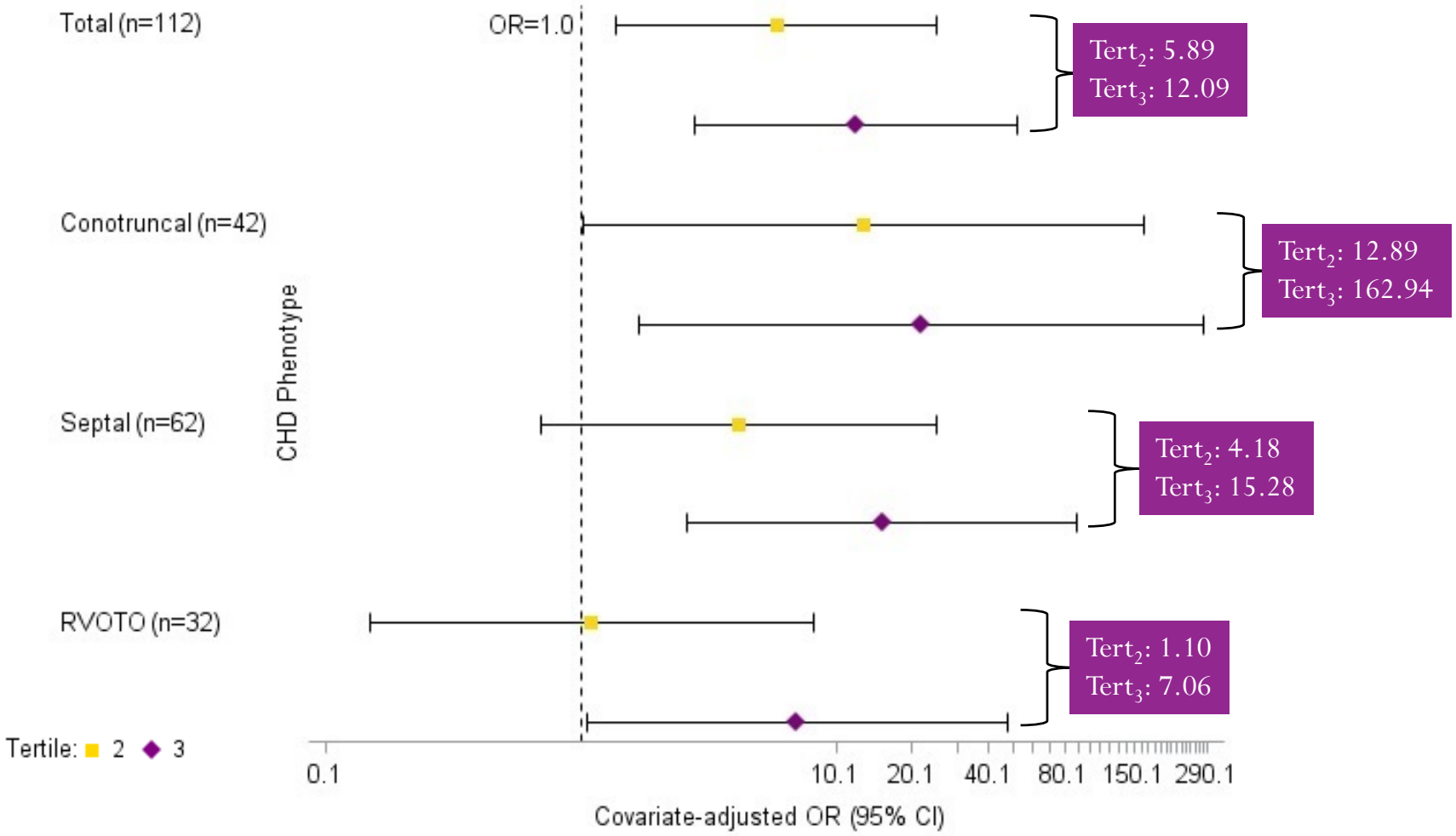
Ou et al., Environ Int 2017;106:127-134

Median (IQR) bld Pb for women (19-43 yrs) vs U.S.



CDC, 2018 "Fourth National Report on Human Exposure to Environmental Chemicals - Updated Tables, March 2018"; Ou et al., Environ Int 2017;106:127-134

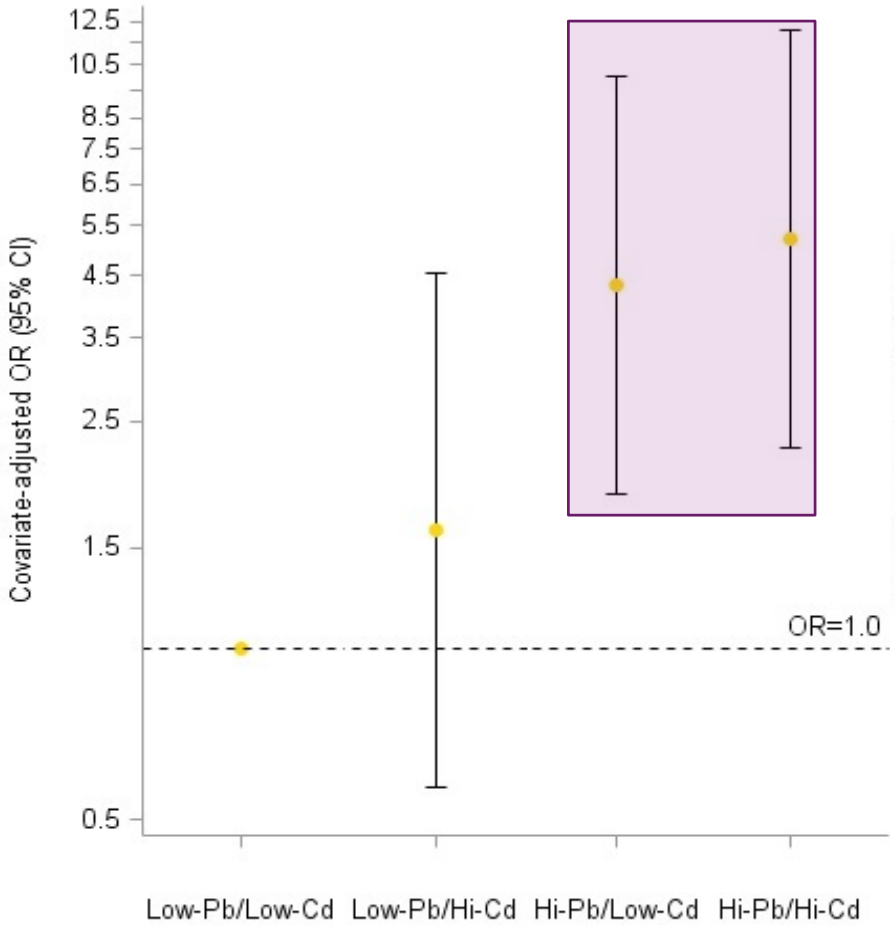
Risk for CHDs with maternal blood Pb (n=219)

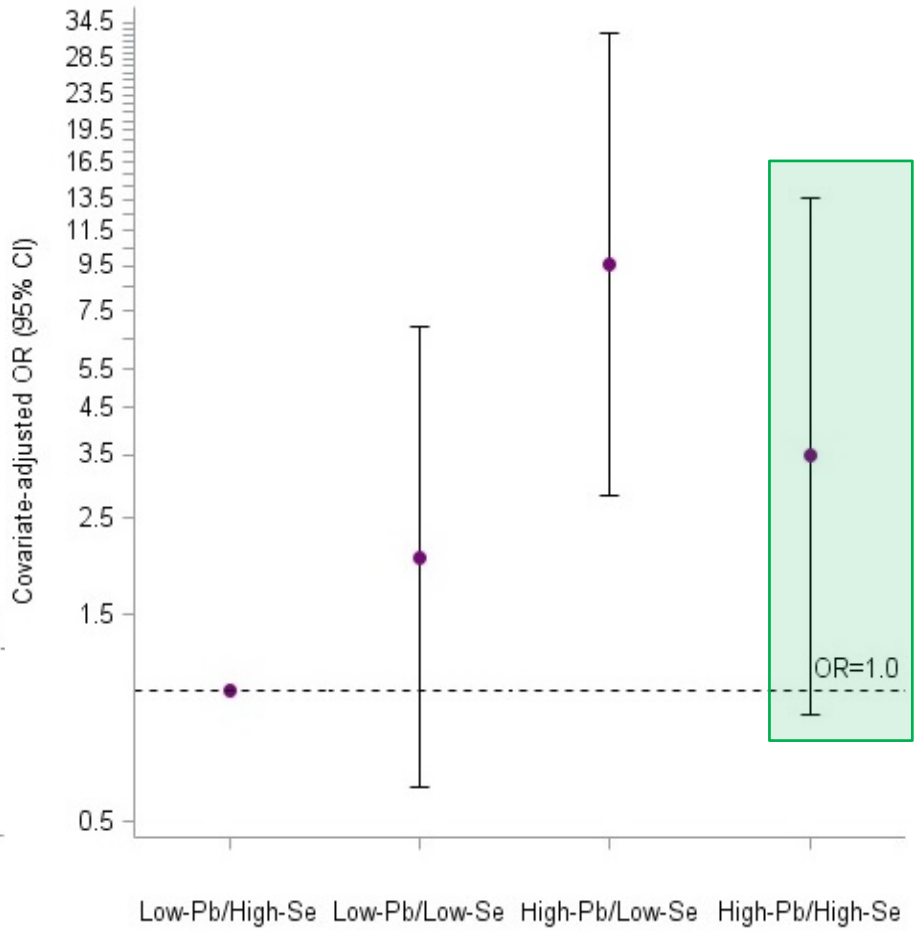


Ou et al., Environ Int 2017;106:127-134

Adj bld Cd, Cr, Cu, Hg, Se, maternal age, BMI, education, smoking, migrant & folic acid/multivitamin use, infant sex & time of collection

Interactions among blood Pb, Cd & Se on total CHDs risk (n=219)





Ou et al., Environ Int 2017;106:127-134

Adj bld. Cd, Cr, Cu, Hg, Se, maternal age, BMI, education, smoking, migrant & folic acid/multivitamin use, infant sex & time of collection

Three for the road…

1. Impact of low level (<10 µg/dL), "background" Pb exposure unclear
   - Vulnerable populations?
2. Mixtures of low-level Pb, other trace elements, other pollutants
3. Critical windows & timing for biologic effects & for measuring exposure to investigate human health effects

Restored Roman Roadway, Alba Iulia, Romania

Thank you for your time this morning!

University at Albany,
Main Fountain, Albany, NY

Questions, Comments, Concerns?