Ruprecht-Karls-Universität Heidelberg

Toxische Metalle – ein bisher unterschätzter Risikofaktor für Herzkreislauferkrankungen und Nierenerkrankungen

Prof. Dr. Berthold Hocher

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Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China

Central South University, Changsha , China

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Toxische Metalle – ein bisher unterschätzter Risikofaktor für Herzkreislauferkrankungen und Nierenerkrankungen

- ***Toxische Metallbelastung - Epidemiologische Daten aus Deutschland***

- **Toxische Metalle und Fetale Programmierung von Herzkreislauferkrankungen und Nierenerkrankungen**

- **Toxische Metalle und Nierenerkrankungen bei Erwachsenen**

- **Toxische Metalle und Herzkreislauferkrankungen bei Erwachsenen**

- **Was tun – Gibt es therapeutische Möglichkeiten?**

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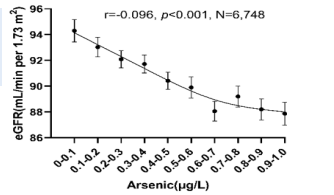
IMD - toxische Metall Studie – Design

Routine clinical laboratory parameters

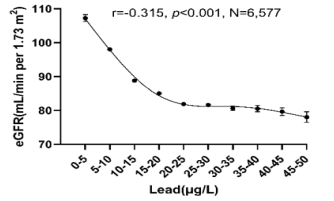
58,864 outpatients in Germany

eGFR

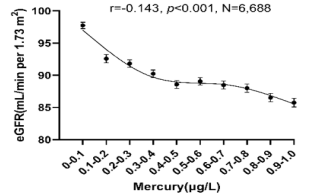
Metal analysis using ICP-MS



Correlation between Arsenic (0-1.0 µg/L) and eGFR



Correlation between Lead (0-50 µg/L) and eGFR



Correlation between Arsenic (0-1.0 µg/L) and eGFR

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IMD Labor Berlin-Potsdam

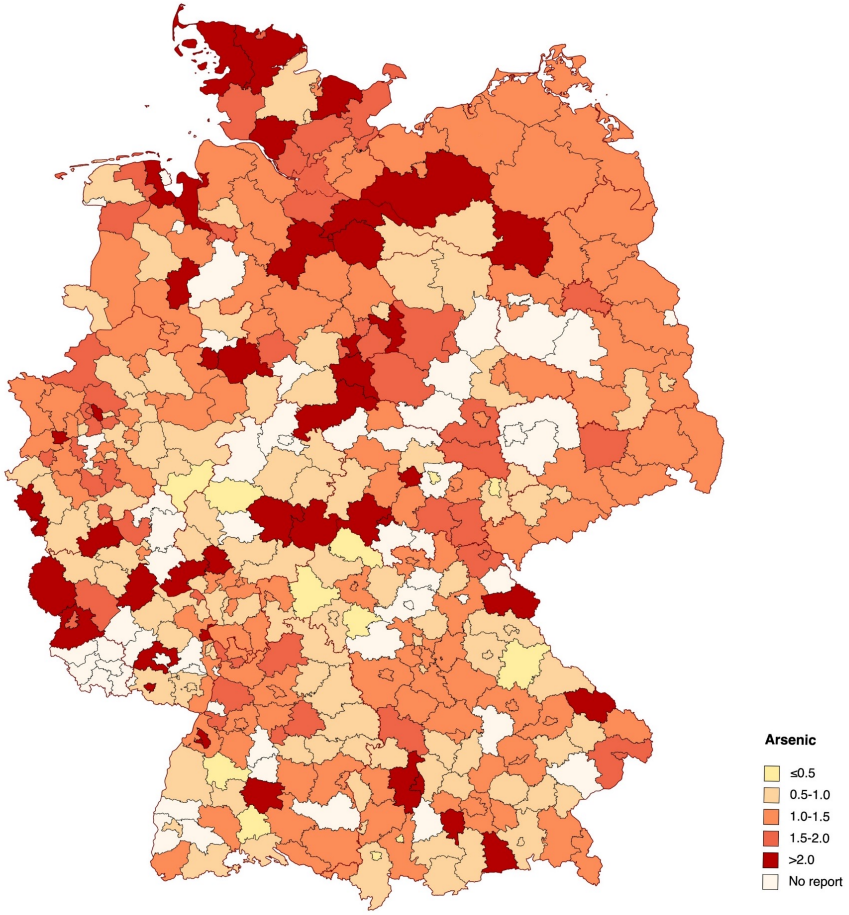
Ärztlicher Befundbericht

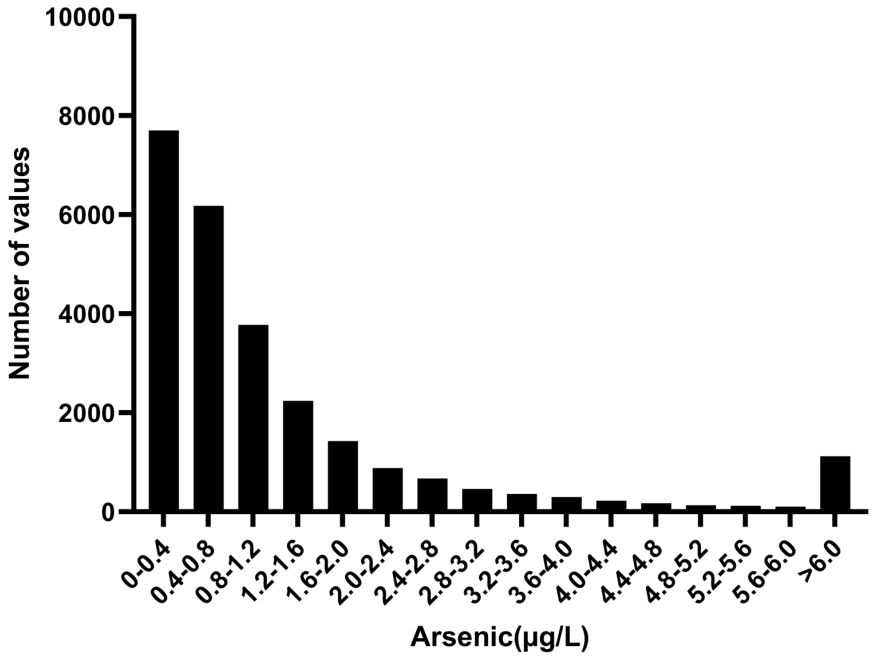
Mineralstoffanalyse im Vollblut - erweitertes Profil "11 + 6" (ICP-MS)

Die Analyse erfolgte im lysierten Heparin-Vollblut zur Bestimmung der intra- und extrazellulär lokalisierten Spurenelemente.

Analyt	Ergebnis		Referenzbereich	Abweichung vom Median
Magnesium	**35,1**	mg/l	30 - 40	**3** %
Selen	**102**	µg/l	90 - 230	**-5** %
Zink	**5,3**	mg/l	4,5 - 7,5	**-2** %
Calcium	**56**	mg/l	55 - 70	**-8** %
Kalium	**1708**	mg/l	1386 - 1950	**8** %
Natrium	**1567**	mg/l	1500 - 1850	**-4** %
Phosphor	**502**	mg/l	403 - 577	**16** %
Chrom	**0,32**	µg/l	0,14 - 0,52	**33** %
Kupfer	**0,87**	mg/l	0,70 - 1,39	**6** %
Mangan	**10,8**	µg/l	8,3 - 15,0	**-4** %
Molybdän	**0,2**	µg/l	0,3 - 1,3	**-60** %
Wechselwirkungen mit toxischen Metallen:				
Aluminium	**<10,0**	µg/l	< 11,4	
Arsen	**1,5**	µg/l	< 1,2	
Blei	**36,6**	µg/l	< 28	
Cadmium	**3,3**	µg/l	< 0,6	
Nickel	**0,2**	µg/l	< 3,8	
Quecksilber	**1,7**	µg/l	< 1,0	

Arsen





- The distribution of metals among the 374 districts in 16 federal states in Germany.
- The white part is no reported, and darker color means higher level of metals; the red color is the highest-level group.
- **Overlap highest area of arsenic and Cadmium: Eifel Kreis Bitburg- Prüm, Goslar, Wesemarsch , Frisland.**

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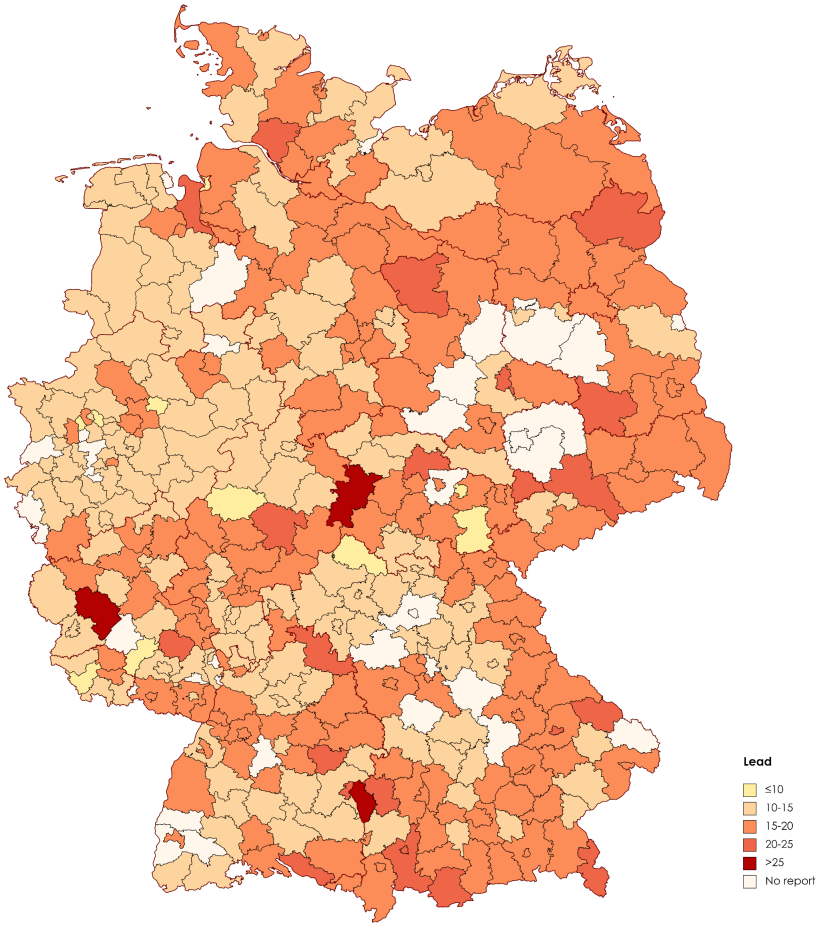
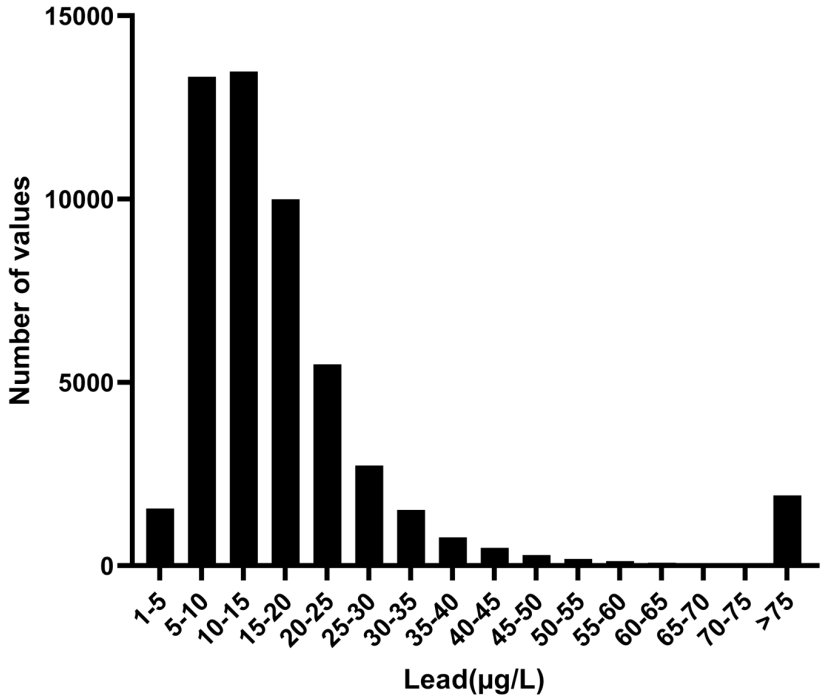
Blei





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- The white part is no reported, and darker color means higher level of metals; the red color is the highest-level group.
- **Highest area of Lead: Bernkastel-Wittlich, Neu-Ulm and Wartburgkreis.**

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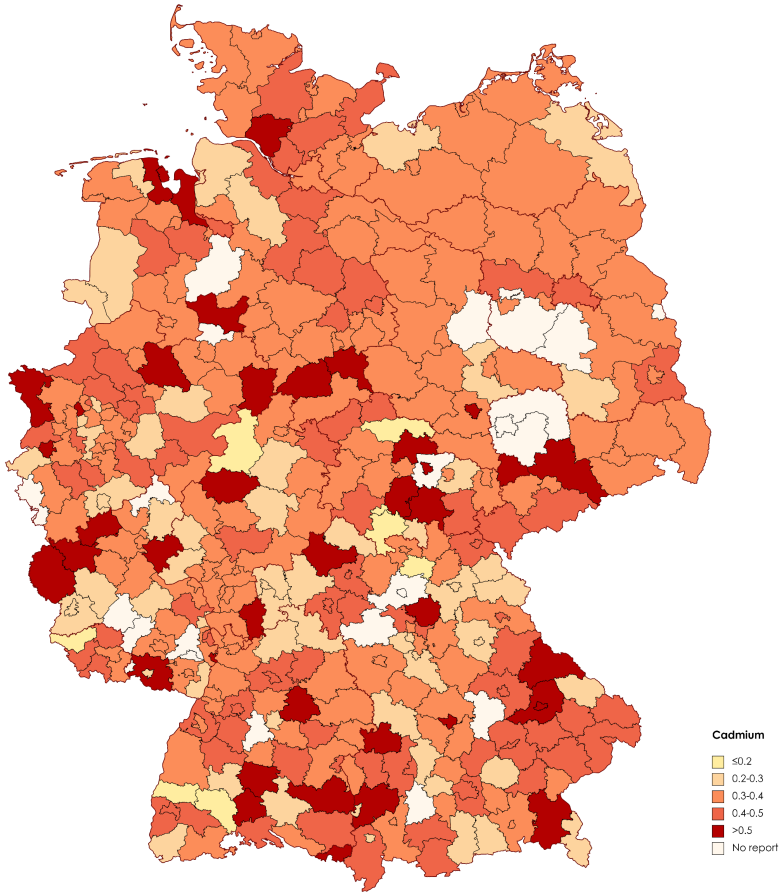
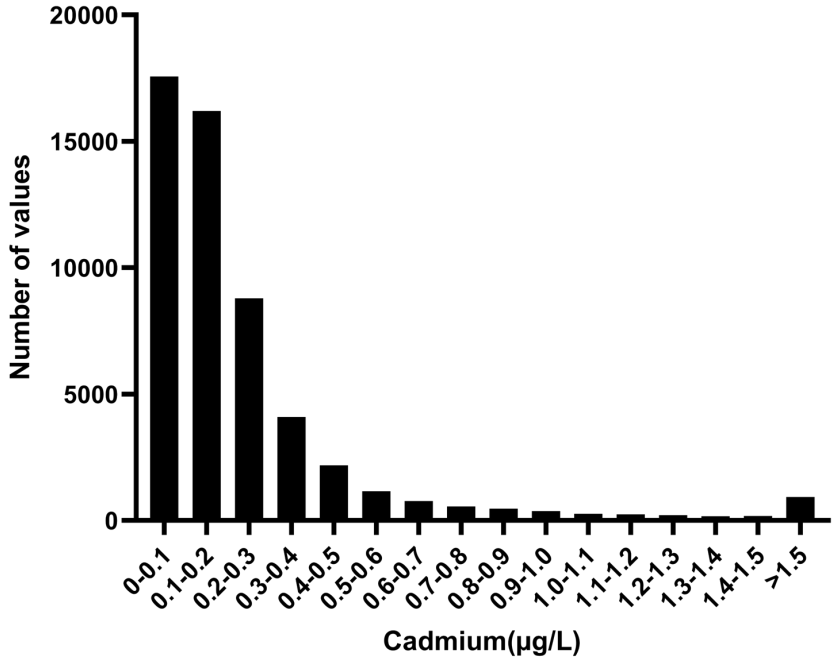
Cadmium





- The distribution of metals among the 374 districts in 16 federal states in Germany.
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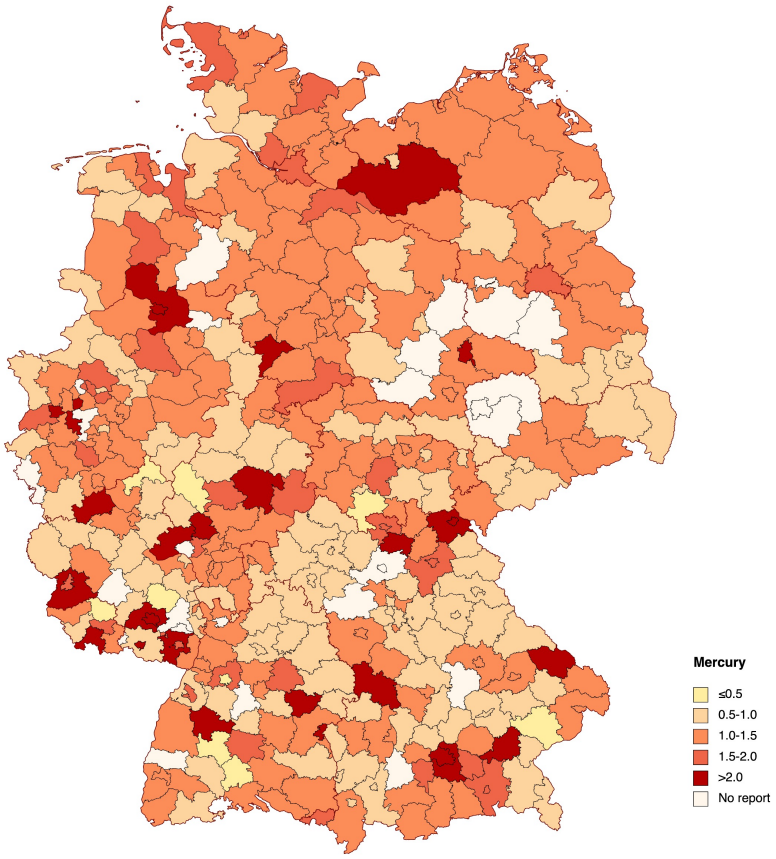
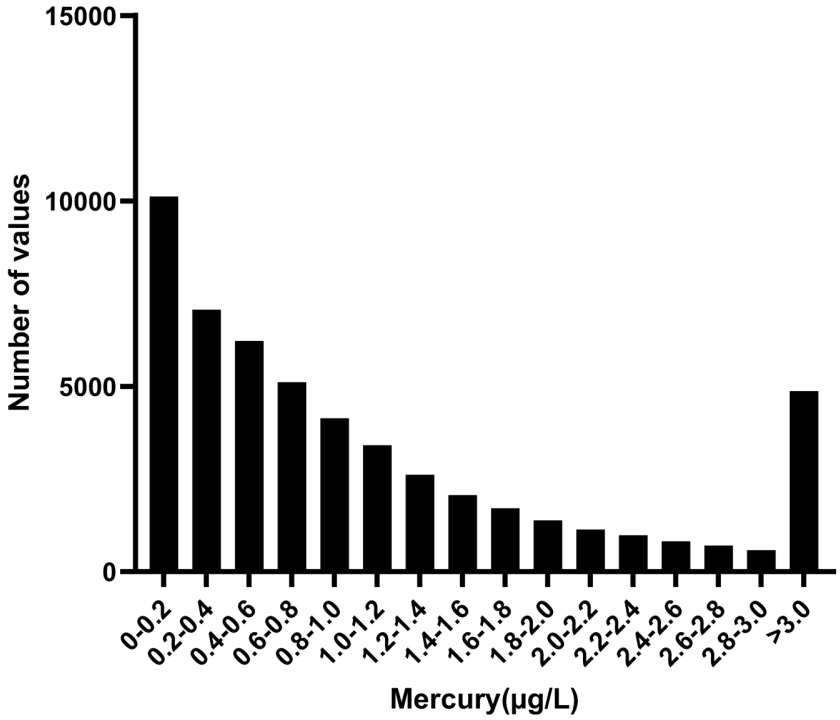
Quecksilber





- The distribution of metals among the 374 districts in 16 federal states in Germany.
- The white part is no reported, and darker color means higher level of metals; the red color is the highest-level group.
- **Overlap highest area of arsenic and mercury: Ludwigslust-Parchim.**
- **Overlap highest area of cadmium and mercury:Ahrweiler.**

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Schwermetallbelastung in Deutschland ist nicht homogen. Es gibt eine erhebliche Variabilität zwischen den Postleitzahlbezirken.

Das Verteilungsmuster für einzelne Schwermetalle unterscheidet sich deutlich in den Postleitzahlbezirken.

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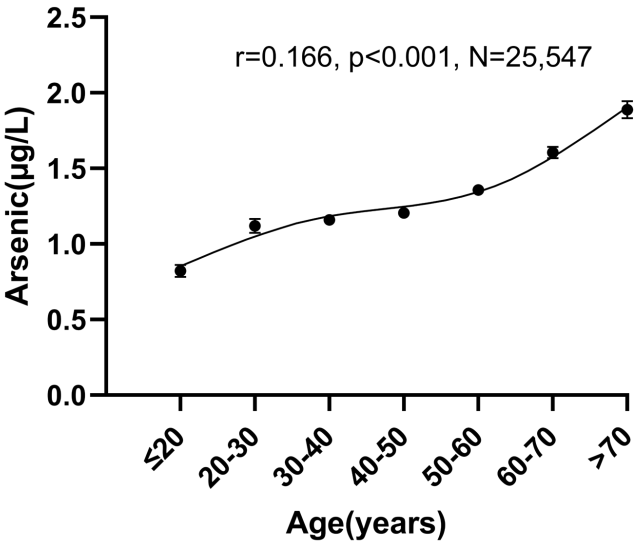
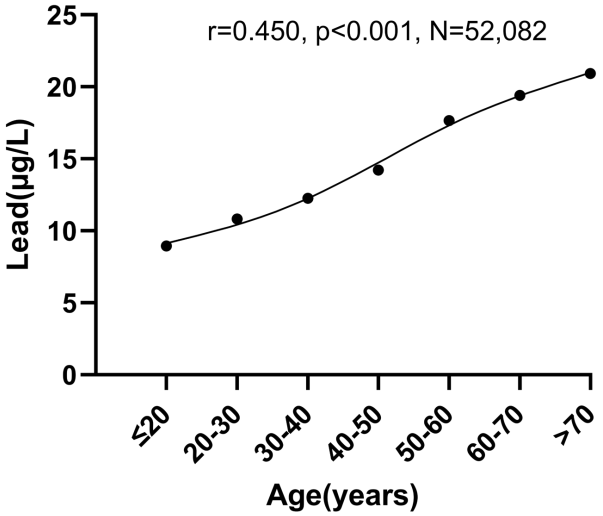
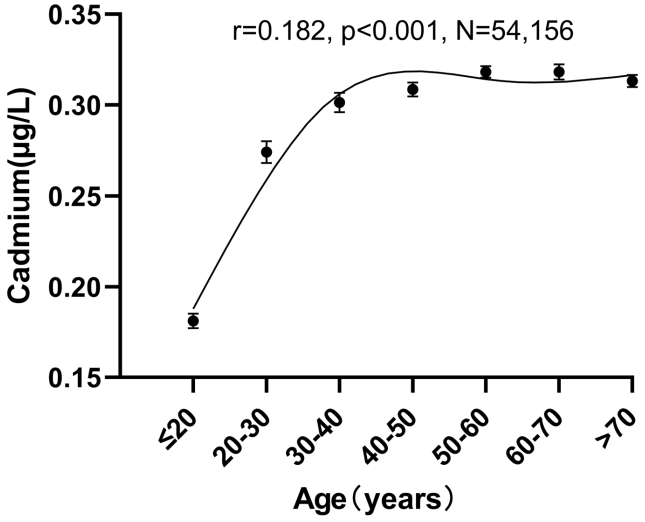
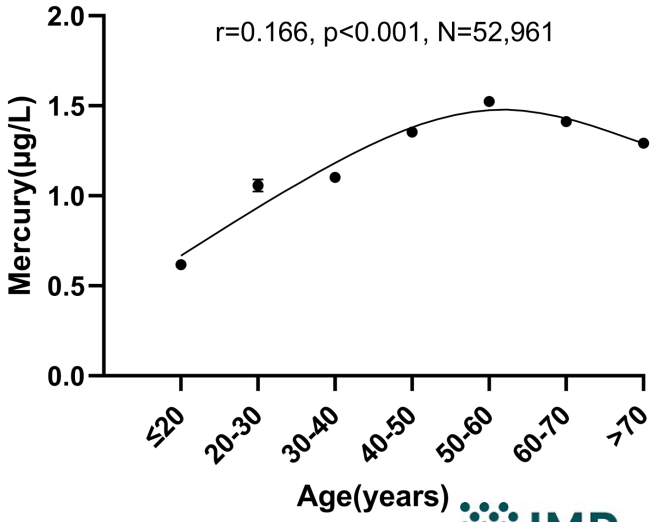
Altersabhängigkeit von Schwermetallen im Vollblut









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- Arsen- und Blei-Vollblukonzentrationen steigen lebenslang an
- Quecksilber und Cadmium steigen bis zum mittleren Lebensalten an und bleiben dann weitgehend konstant

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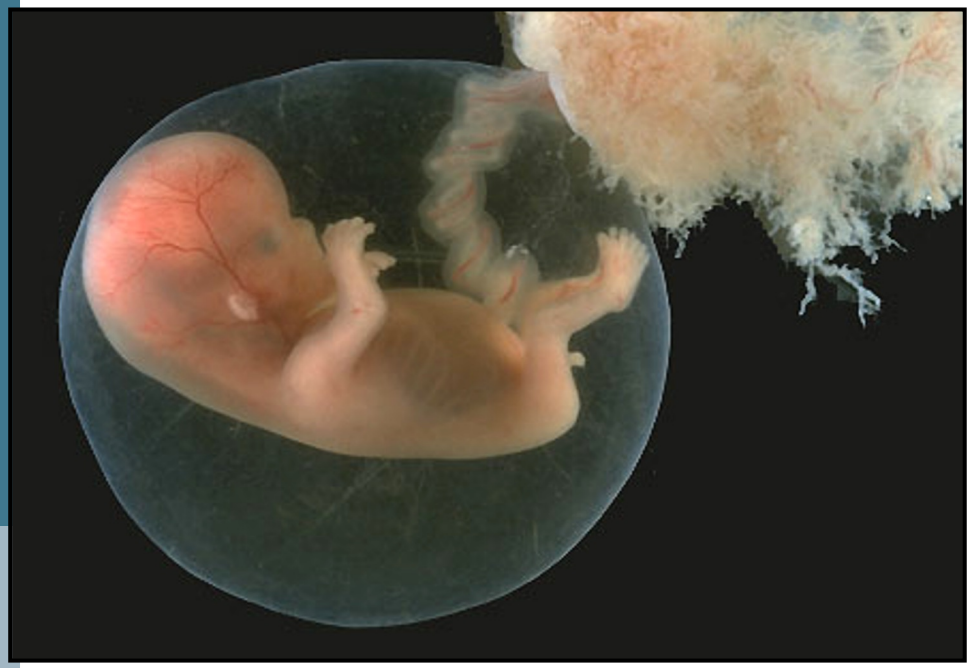
Fetal programming

David Barker



An event in a „critical", early – toxic metak exposure - period which permanently alters structure and function leading to cardiovascular diseases.

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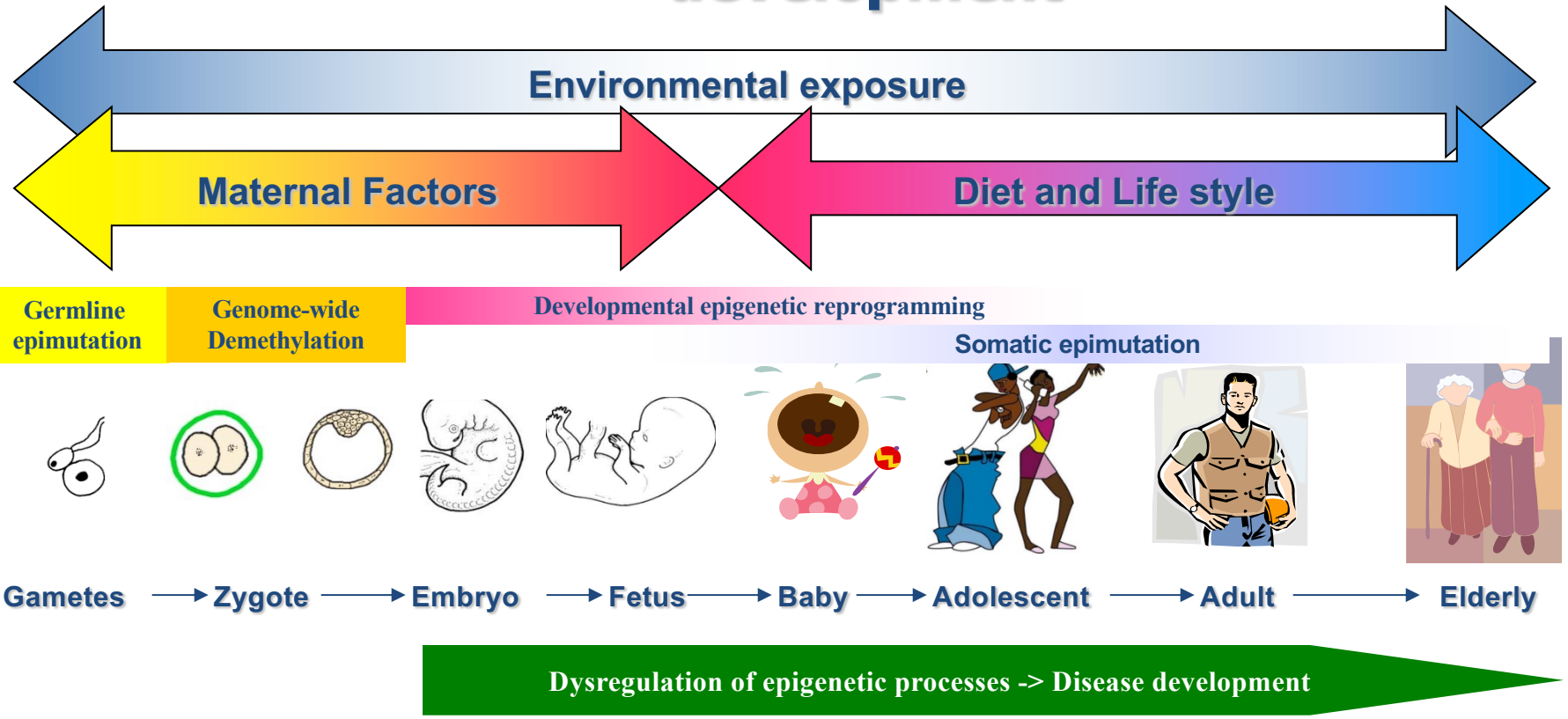
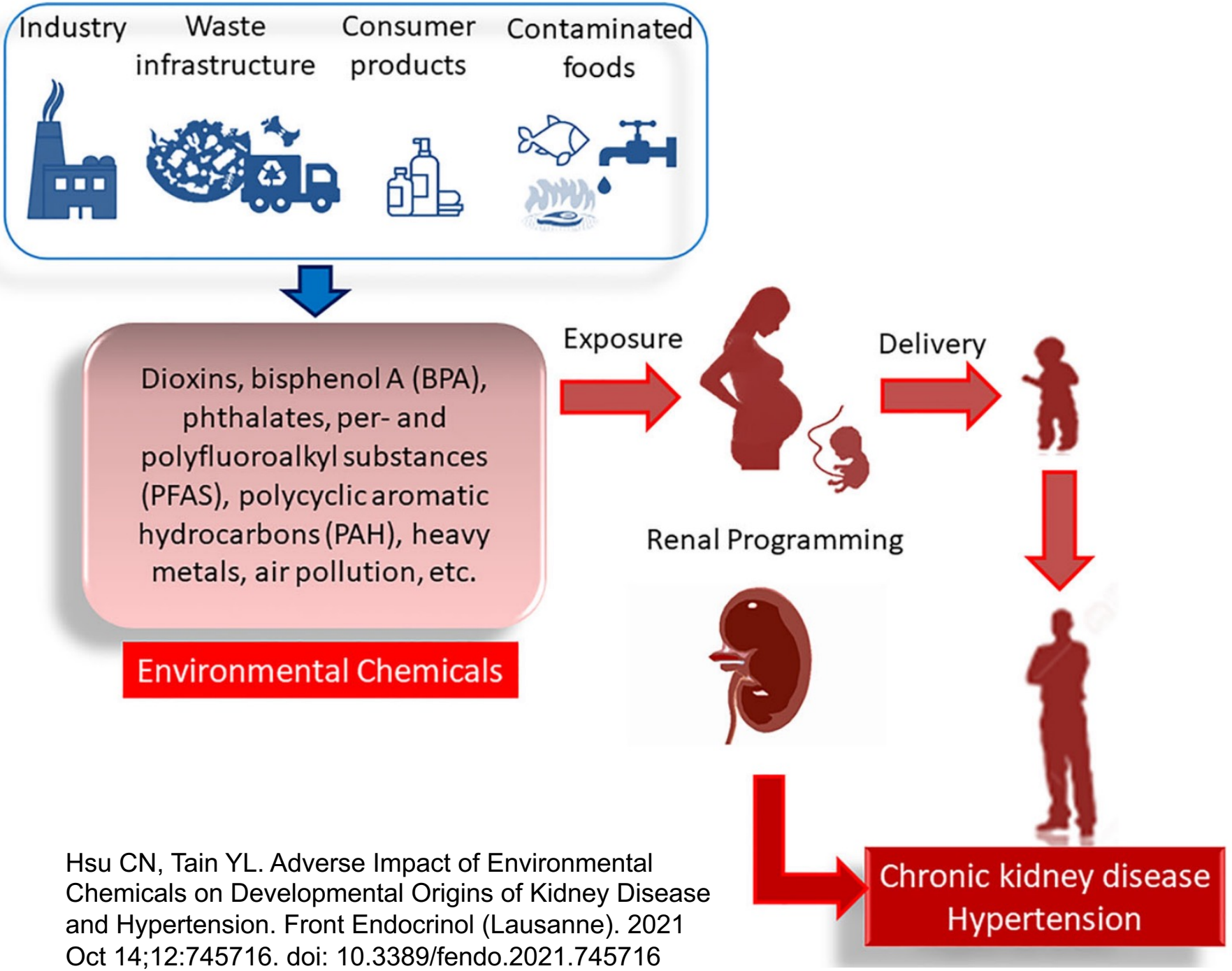
Environment – heavy metals - and development



Modified from Foley et al., 2008



Hsu CN, Tain YL. Adverse Impact of Environmental Chemicals on Developmental Origins of Kidney Disease and Hypertension. Front Endocrinol (Lausanne). 2021 Oct 14;12:745716. doi: 10.3389/fendo.2021.745716

Vergleich EDTA-Blut - Muttermilch

Toxische Metalle im EDTA-Vollblut (ICP-MS)

Analyt	Ergebnis		Referenzbereich
Aluminium	**28,4**	µg/l	< 11,4
Antimon	**<0,2**	µg/l	< 0,2
Arsen	**0,8**	µg/l	< 1,2
Barium	**5,2**	µg/l	< 2,7
Beryllium	**<0,2**	µg/l	< 0,2
Bismut	**<0,2**	µg/l	< 0,2
Blei	**13,4**	µg/l	< 28
Cadmium	**0,3**	µg/l	< 0,6
Cer	**0,02**	µg/l	< 0,04
Chrom	**0,4**	µg/l	0,14 - 0,52
Gold	**<2,0**	µg/l	< 2,0
Kobalt	**0,19**	µg/l	< 1,21
Kupfer	**0,78**	mg/l	0,70 - 1,39
Mangan	**10,9**	µg/l	7,5 - 20
Molybdän	**0,8**	µg/l	0,3 - 1,3
Nickel	**2,0**	µg/l	< 3,8
Palladium	**<2,0**	µg/l	< 2,0
Platin	**<0,2**	µg/l	< 0,2
Quecksilber	**0,6**	µg/l	< 1,0
Silber	**<0,2**	µg/l	< 0,2
Thallium	**<0,2**	µg/l	< 0,2
Titan	**13,0**	µg/l	< 105
Vanadium	**<0,2**	µg/l	< 0,2
Zink	**3,7**	mg/l	4,5 - 7,5
Zinn	**<0,2**	µg/l	< 0,4
Zirkonium	**<2,0**	µg/l	< 2,0

Toxische Metalle Nativmaterial

Die Analyse erfolgt mittels ICP-MS.

Analyt	Ergebnis	
Aluminium	**< NWG**	µg/l
Antimon	**< NWG**	µg/l
Arsen	**< NWG**	µg/l
Barium	**3,8**	µg/l
Beryllium	**< NWG**	µg/l
Bismut	**< NWG**	µg/l
Blei	**< NWG**	µg/l
Cadmium	**< NWG**	µg/l
Cer	**< NWG**	µg/l
Chrom	**0,7**	µg/l
Gold	**< NWG**	µg/l
Kobalt	**< NWG**	µg/l
Kupfer	**524**	µg/l
Mangan	**3,8**	µg/l
Molybdän	**9,3**	µg/l
Nickel	**< NWG**	µg/l
Palladium	**< NWG**	µg/l
Platin	**< NWG**	µg/l
Quecksilber	**< NWG**	µg/l
Silber	**< NWG**	µg/l
Thallium	**< NWG**	µg/l
Titan	**< NWG**	µg/l
Vanadium	**< NWG**	µg/l
Zink	**4305**	µg/l
Zinn	**< NWG**	µg/l
Zirkon	**< NWG**	µg/l

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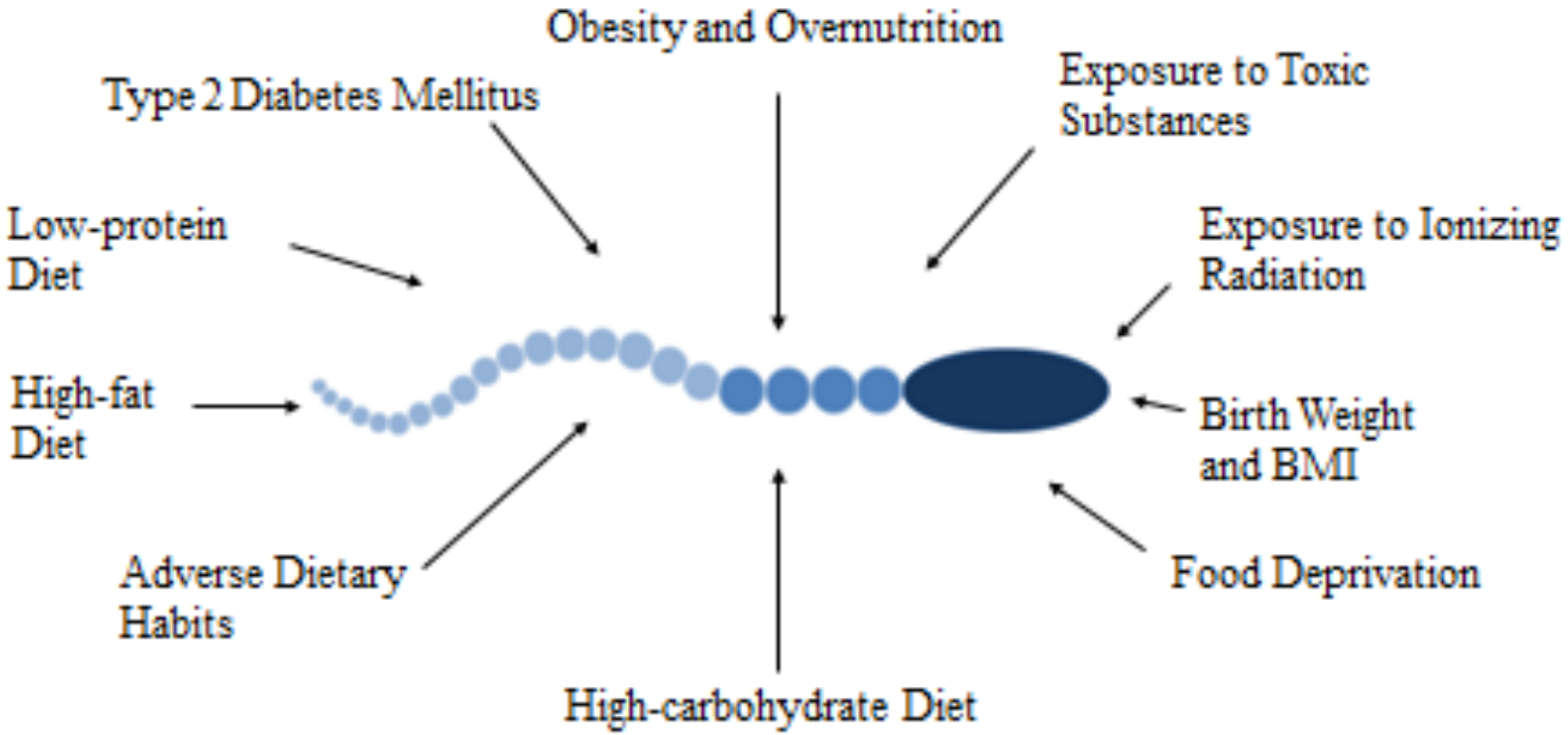
Paternale Programmierung kardio-metabolischer Erkrankungen – Einfluss von Umweltfaktoren auf Sperma



Li, Tsuprykov, Yang, Hocher, J. Hypertension 2016

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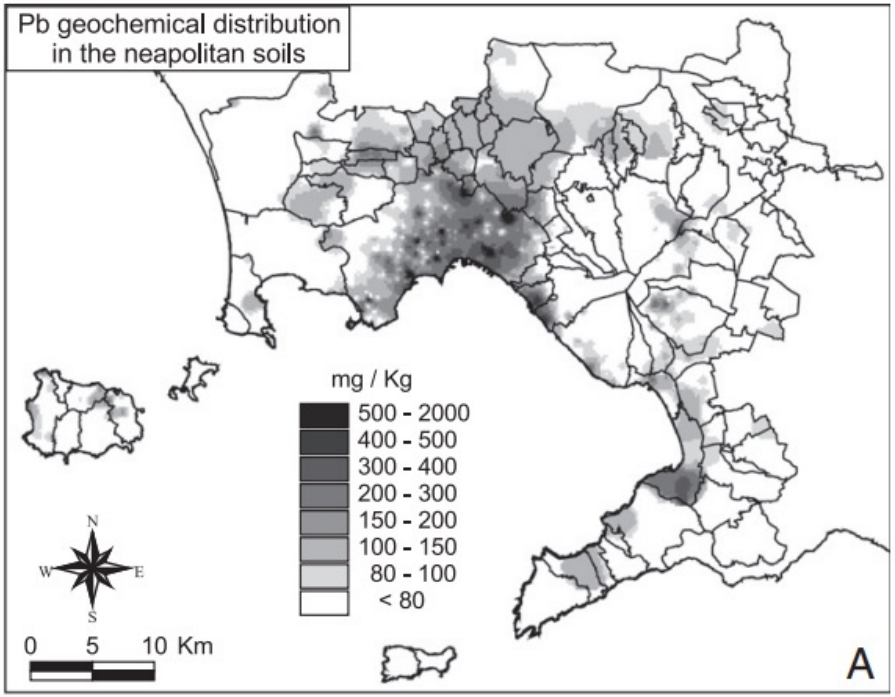

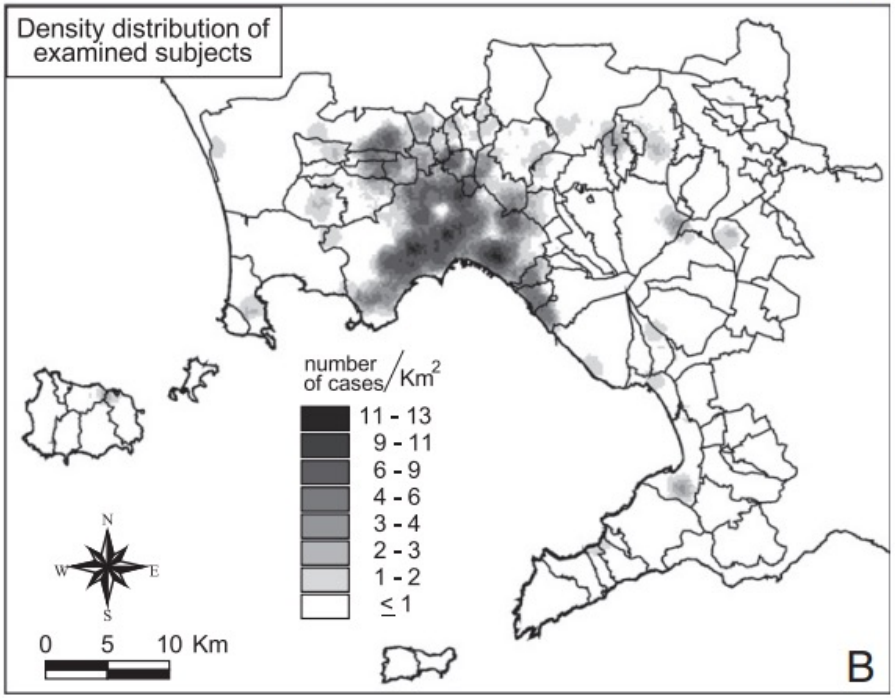

Contents lists available at SciVerse ScienceDirect

Journal of Geochemical Exploration

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

Does heavy metals pollution affects semen quality in men? A case of study in the metropolitan area of Naples (Italy)

L. Giaccio [a,b], D. Cicchella [a,*], B. De Vivo [b], G. Lombardi [c], M. De Rosa [c]

[a] Department of Science for Biology, Geology and Environment, University of Sannio, Via dei Mulini 59/A, 82100 Benevento, Italy
[b] Dipartimento di Scienze della Terra, University of Naples "Federico II", Via Mezzocannone 8, 80134 Naples, Italy
[c] Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II', via S. Pansini 5, 80131 Naples, Italy

A) Bleibelastung in unterschiedlichen Wohngebieten im Großraum Neapel

B) Spermienqualität in unterschiedlichen Wohngebieten im Großraum Neapel

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PLOS ONE

RESEARCH ARTICLE

Reproductive effects of cadmium on sperm function and early embryonic development *in vitro*

Li-lin Zhao[1☯], Yan-fei Ru[1☯], Miao Liu[1], Jia-nan Tang[1], Ju-fen Zheng[1], Bin Wu[1], Yi-hua Gu[1]*, Hui-juan Shi[1,2]*

Table 1. Effects of cadmium on mouse sperm fertilization capability in the IVF procedure and on subsequent embryonic development.

Category	No. of oocytes (replicates)	No. with pronuclei formation (%)[a]	No. of 2-cell embryos (%)[b]	No. of 4-cell embryos (%)[b]	No. of 8-cell embryos (%)[b]	No. of morulae (%)[b]	No. of blastocysts (%)[b]
Control	199 (5)	186 (92.8)	181 (96.6)	176 (94.7)	176 (94.7)	176 (94.7)	159 (86.8)
2.5μg/ml	179 (5)	131 (71.9)**	129 (98.3)	124 (94.8)	124 (94.8)	122 (93.2)	117 (88.4)
5μg/ml	214 (5)	121 (53.9)***,##	115 (95.8)	115 (95.8)	115 (95.8)	114 (95.1)	108 (88.6)
10μg/ml	113 (5)	15 (13.3)***,###,$$$	15 (100.0)	14 (97.1)	14 (97.1)	14 (94.1)	12 (84.3)

[a]Based on total oocytes.

[b]Based on total pronuclear embryos.

**, ##p<0.01,

***, ###, $$$p<0.001, comparisons were made between the control group and each treated group, between the 2.5 μg/ml group and the other two concentration groups, and between the 5 μg/ml and 10 μg/ml concentration groups, respectively.

Künstliche Befruchtung

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ORIGINAL ARTICLE
Nephrology

JKMS

http://dx.doi.org/10.3346/jkms.2015.30.3.272 • J Korean Med Sci 2015; 30: 272-277

Environmental Heavy Metal Exposure and Chronic Kidney Disease in the General Population

Nam Hee Kim,[1] Young Youl Hyun,[1] Kyu-Beck Lee,[1] Yoosoo Chang,[2] Seungho Rhu,[2] Kook-Hwan Oh,[3] and Curie Ahn[3]

[1]Department of Nephrology, and [2]Department of Occupational Medicine, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul; [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

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Lead (Pb), mercury (Hg), and cadmium (Cd) are common heavy metal toxins and cause toxicological renal effects at high levels, but the relevance of low-level environmental exposures in the general population is controversial. A total of 1,797 adults who participated in the KNHANES (a cross-sectional nationally representative survey in Korea) were examined, and 128 of them (7.1%) had chronic kidney disease (CKD). Our study assessed the association between Pb, Hg, Cd exposure, and CKD. Blood Pb and Cd levels were correlated with CKD in univariate logistic regression model. However, these environmental heavy metals were not associated with CKD after adjustment for age, sex, BMI, smoking, hyperlipidemia, hypertension, diabetes, and these metals in multivariate logistic regression models. We stratified the analysis according to hypertension or diabetes. In the adults with hypertension or diabetes, CKD had a significant association with elevated blood Cd after adjustment, but no association was present with blood Pb and Hg. The corresponding odds ratio [OR] of Cd for CKD were 1.52 (95% confidence interval [CI], 1.05-2.19, $P = 0.026$) in adults with hypertension and 1.92 (95% CI, 1.14-3.25, $P = 0.014$) in adults with diabetes. Environmental low level of Pb, Hg, Cd exposure in the general population was not associated with CKD. However, Cd exposure was associated with CKD, especially in adults with hypertension or diabetes. This finding suggests that environmental low Cd exposure may be a contributor to the risk of CKD in adults with hypertension or diabetes.

Die Cd-Exposition in der Normalbevölkerung, insbesondere bei Erwachsenen mit Bluthochdruck oder Diabetes, ist mit dem Auftreten einer chronischen Nierenerkrankung (eGFR < 60) assocciert. .
Dieses Ergebnis legt nahe, dass eine niedrige Cd-Exposition in der Umwelt zum CKD-Risiko bei Erwachsenen mit Bluthochdruck oder Diabetes beitragen kann.

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End-stage renal disease and low level exposure to lead, cadmium and mercury; a population-based, prospective nested case-referent study in Sweden

Johan Nilsson Sommar[1*], Maria K Svensson[2], Bodil M Björ[1], Sölve I Elmståhl[3], Göran Hallmans[4], Thomas Lundh[5], Staffan MI Schön[6], Staffan Skerfving[5] and Ingvar A Bergdahl[1]

Abstract

Background: Cadmium (Cd), lead (Pb), and mercury (Hg) cause toxicological renal effects, but the clinical relevance at low-level exposures in general populations is unclear. The objective of this study is to assess the risk of developing end-stage renal disease in relation to Cd, Pb, and Hg exposure.

Methods: A total of 118 cases who later in life developed end-stage renal disease, and 378 matched (sex, age, area, and time of blood sampling) referents were identified among participants in two population-based prospective cohorts (130,000 individuals). Cd, Pb, and Hg concentrations were determined in prospectively collected samples.

Results: Erythrocyte lead was associated with an increased risk of developing end-stage renal disease (mean in cases 76 µg/L; odds ratio (OR) 1.54 for an interquartile range increase, 95% confidence interval (CI) 1.18-2.00), while erythrocyte mercury was negatively associated (2.4 µg/L; OR 0.75 for an interquartile range increase, CI 0.56-0.99). For erythrocyte cadmium, the OR of developing end-stage renal disease was 1.15 for an interquartile range increase (CI 0.99-1.34; mean Ery-Cd among cases: 1.3 µg/L). The associations for erythrocyte lead and erythrocyte mercury, but not for erythrocyte cadmium, remained after adjusting for the other two metals, smoking, BMI, diabetes, and hypertension. Gender-specific analyses showed that men carried almost all of the erythrocyte lead and erythrocyte cadmium associated risks.

Conclusions: Erythrocyte lead is associated with end-stage renal disease but further studies are needed to evaluate causality. Gender-specific analyses suggest potential differences in susceptibility or in exposure biomarker reliability.

Keywords: Biobank, Cadmium, Case-referent, End-stage renal disease, Lead, Mercury

Erythrozyten-Blei wird mit Nierenerkrankungen im Endstadium in Verbindung gebracht, doch sind weitere Studien erforderlich, um die Kausalität zu bewerten.

IMD Labor Berlin

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Toxic metals and chronic kidney disease: A systematic review of recent literature

Emily C. Moody[1], **Steven G. Coca**[2], and **Alison P. Sanders**[1,3]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[2]Department of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[3]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Abstract

Purpose of Review—Arsenic (As), cadmium (Cd), and lead (Pb) are ubiquitous toxicants with evidence of adverse kidney impacts at high exposure levels. There is less evidence whether environmental exposure to As, Cd, or Pb plays a role in development of chronic kidney disease (CKD). We conducted a systematic review to summarize the recent epidemiologic literature examining the relationship between As, Cd, or Pb with CKD.

Recent Findings—We included peer-reviewed studies published in English between January 2013 and April 2018 for As and Cd, and all dates prior to April 2018 for Pb. We imposed temporality requirements for both the definition of CKD (as per NKF-KDOQI guidelines) and environmental exposures prior to disease diagnosis. Our assessment included cohort, case-control or cross-sectional study designs that satisfied 5 inclusion criteria. We included a total of 8 articles of which 3, 2, and 4 studies examined the effects of As, Cd, or Pb, respectively.

Summary—Studies of As exposure consistently reported negative impacts on CKD incidence; studies of Pb exposure were mixed. We found little evidence of effects of Cd exposure with CKD. Additional well-designed prospective cohort studies are needed and we present recommendations for future studies.

Studien zur As-Exposition berichteten durchweg über negative Auswirkungen auf die CKD-Inzidenz; Studien zur Pb-Exposition waren uneinheitlich. Wir fanden wenig Hinweise auf Auswirkungen der Cd-Exposition auf CKD.

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Offene Fragen

- Beeinflussen Schwermetalle (As, Pb, Hg, Cd) die Nierenfunktion auch bei Patienten ohne CKD ?
- Gibt es Konzentrationen von Schwermetallen (As, Pb, Hg, Cd), die die Nierenfunktion nicht beinflussen – also sicher sind ?,

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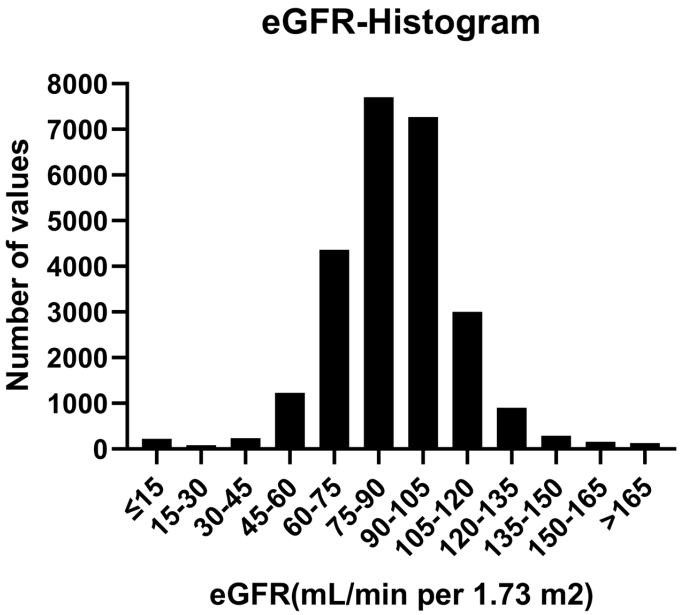
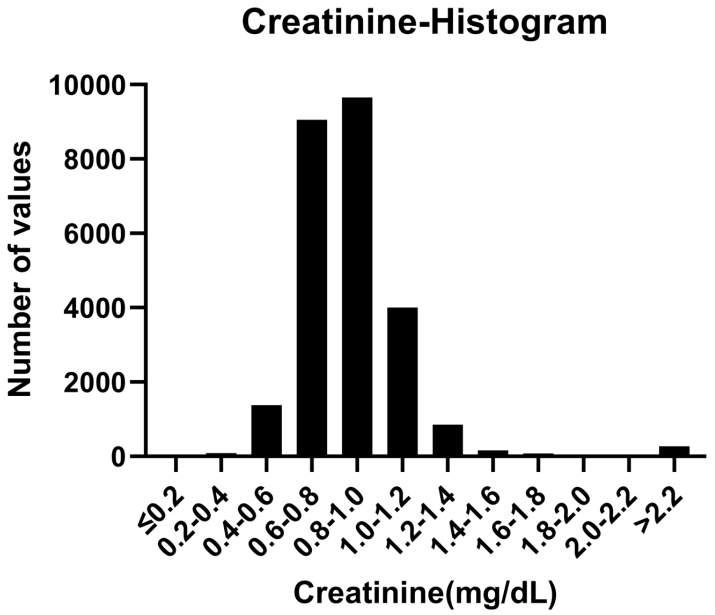
eGFR & Creatinine Distribution





CKD-EPI Formel: eGFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

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Kein Cadmium Effekt nachweisbar

Table 2c. Multivariate Linear Regression – Cadmium (Dependent Variable: eGFR)

Variables	**Multivariate Linear Regression**	
	β Coefficient / 95%CI	***p* Value**
Constant	130.63(128.492~132.769)	<0.001
Age	-0.822(-0.843~-0.801)	<0.001
Sex	-0.268(-0.925~0.389)	0.424
CRP	-0.044(-0.079~-0.010)	0.011
Glucose	0.012(-0.004~0.028)	0.137
Cadmium	0.607(-0.153~1.366)	0.118

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Der Effekt von Arsen ist unabhängig vom Alter, Geschlecht CrP und Blutzucker

Table 2a. Multivariate Linear Regression – Arsenic (Dependent Variable: eGFR)

Variables	**Multivariate Linear Regression**	
	β Coefficient / 95%CI	***p* Value**
Constant	132.826(129.996~135.655)	<0.001
Age	-0.788(-0.818~0.759)	<0.001
Sex	-1.133(-2.016~-0.249)	0.012
CRP	-0.073(-0.113~-0.034)	<0.001
Glucose	-0.0001(-0.021~0.02)	0.990
Arsenic	-0.22(-0.405~-0.035)	0.020

- To minimize the effect of confounding factors, we chose to include in the multifactorial regression analysis several influencing variables that most affect renal function in the normal population (IDF Diabetes Atlas 2020 estimates that 15.3% of the German population had diabetes, so we included blood glucose in the multivariate regression analysis).

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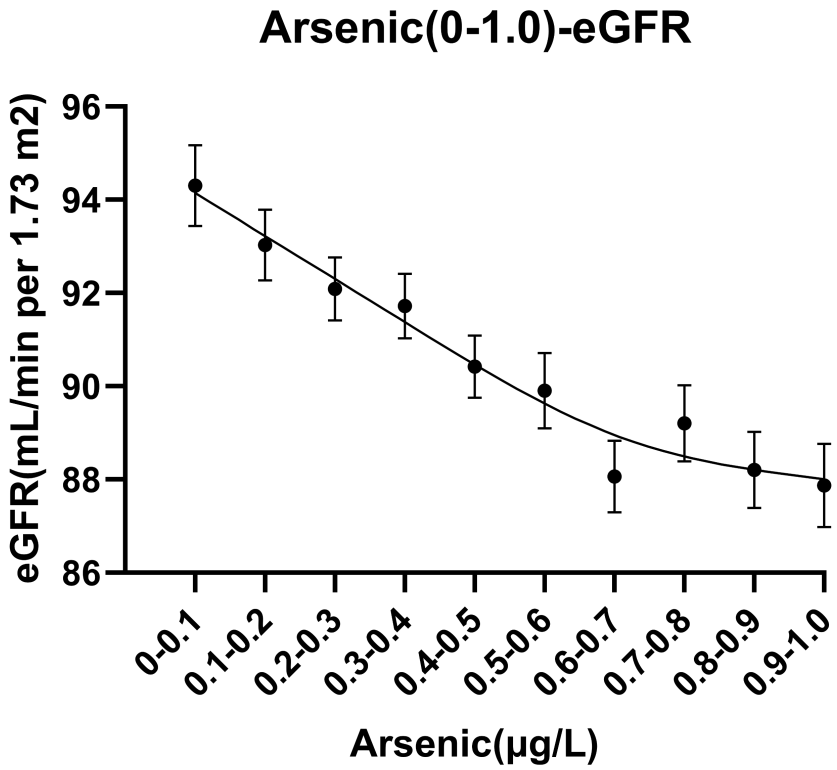

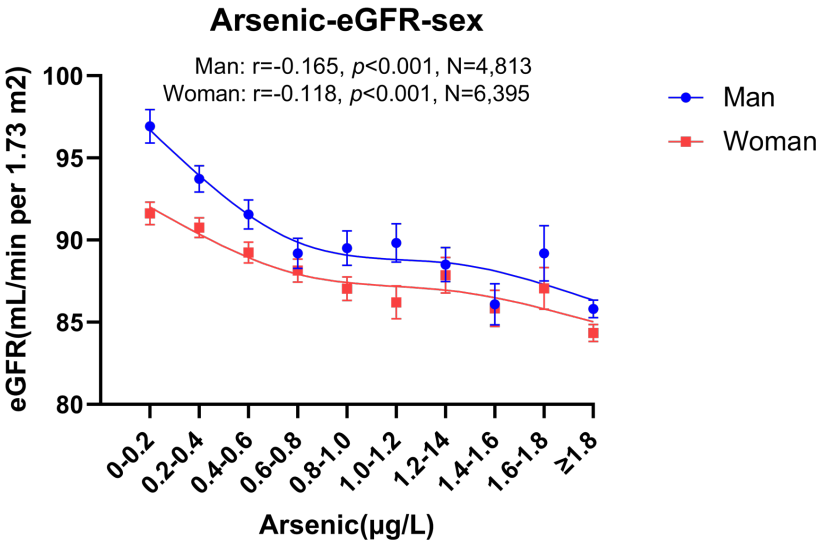

Kein sicherer unterer Grenzwert für Arsen

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Der Effekt von Blei ist unabhängig vom Alter, Geschlecht CrP und Blutzucker

Table 2b. Multivariate Linear Regression – Lead (Dependent Variable: eGFR)

Variables	**Multivariate Linear Regression**	
	β Coefficient / 95%CI	***p* Value**
Constant	130.815(128.688~132.941)	<0.001
Age	-0.791(-0.813~-0.769)	<0.001
Sex	-0.425(-1.074~0.225)	0.200
CRP	-0.055(-0.088~-0.022)	0.001
Glucose	0.005(-0.010~0.021)	0.512
Lead	-0.050(-0.078~-0.022)	<0.001

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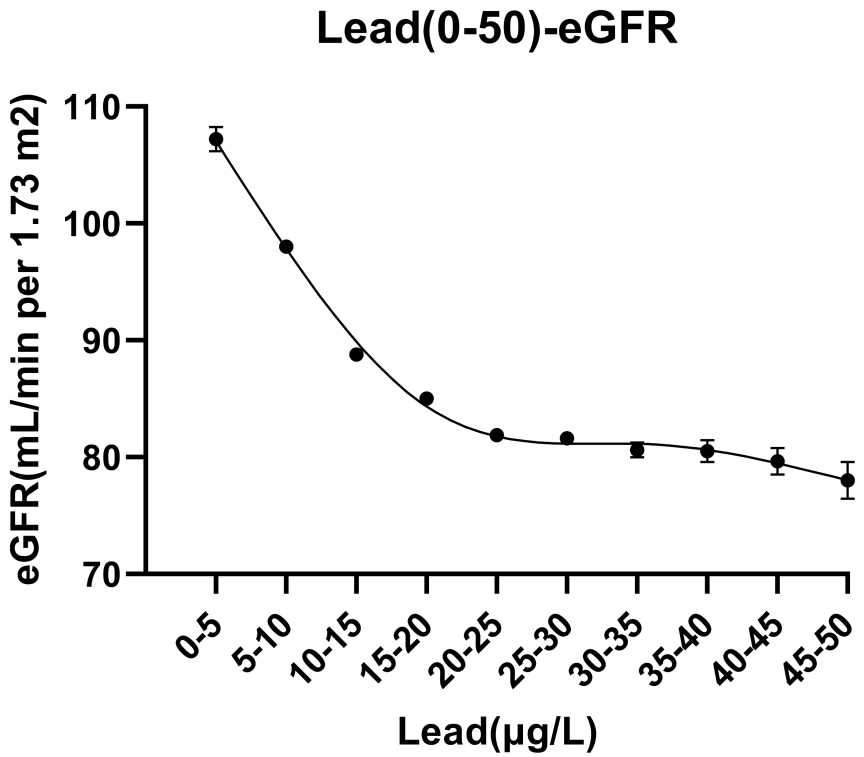

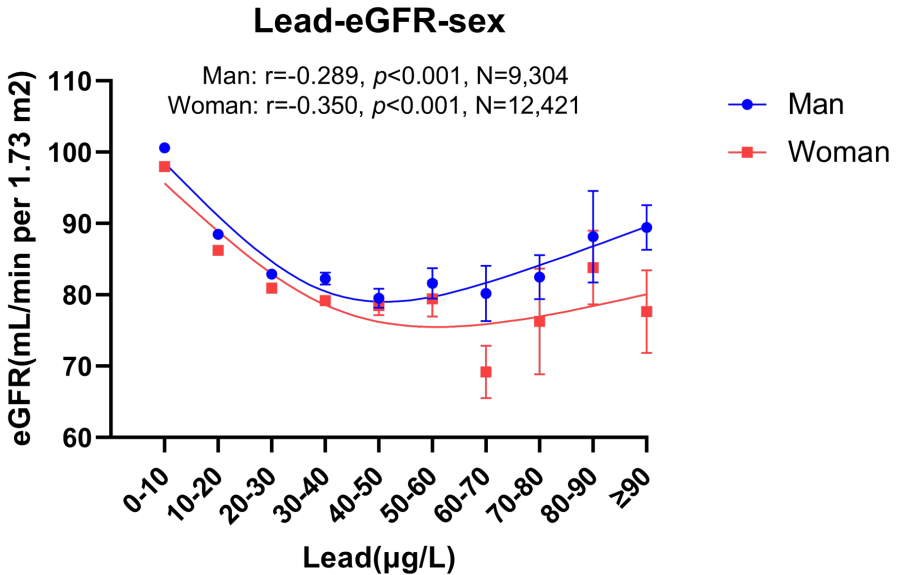

Kein sicherer unterer Grenzwert für Blei

IMD Labor Berlin

Der Effekt von Quecksilber ist unabhängig vom Alter, Geschlecht, CrP und Blutzucker

Table 2d. Multivariate Linear Regression – Mercury (Dependent Variable: eGFR)

Variables	**Multivariate Linear Regression**	
	β Coefficient / 95%CI	***p* Value**
Constant	131.778(129.64~133.917)	<0.001
Age	-0.805(-0.826~-0.784)	<0.001
Sex	-0.673(-1.321~-0.026)	0.042
CRP	-0.043(-0.076~-0.010)	0.011
Glucose	0.005(-0.011~0.020)	0.542
Mercury	-0.306(-0.417~-0.196)	<0.001

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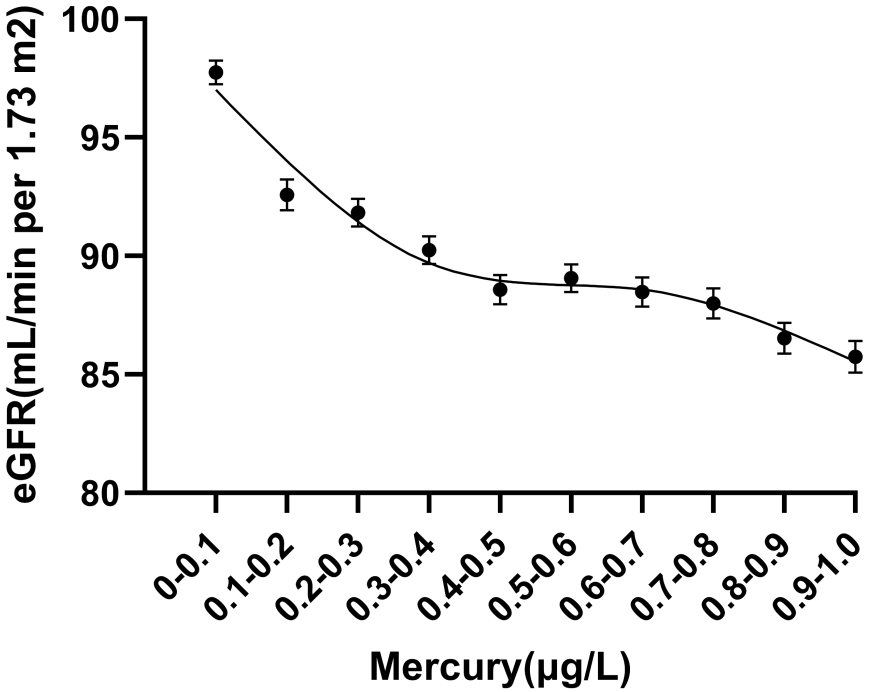
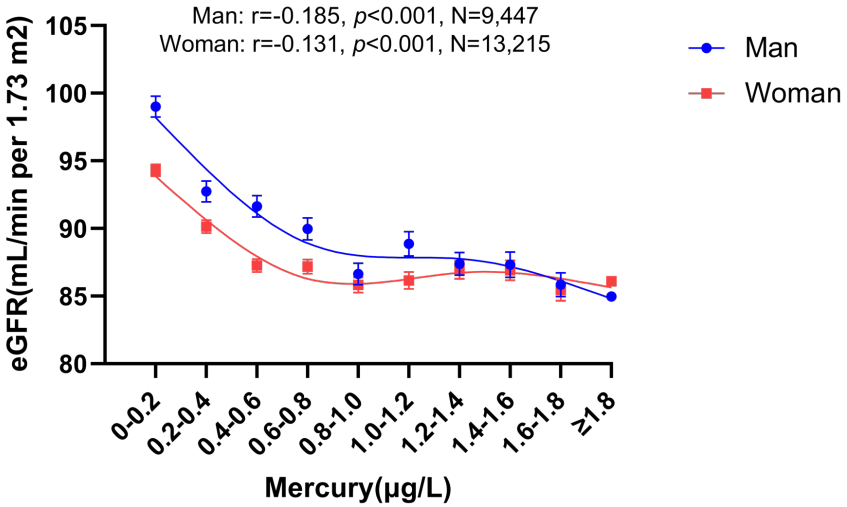
Mercury(0-1.0)-eGFR



Mercury-eGFR-sex



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- Die Association von **Pb**, Hg und As mit eGFR ist unabhängig von Risikofaktoren wie Alter, Geschlecht, CrP und Nüchternzucker
- Ein **sicherer unterer Grenzwert** für die Effekte von Pb, Hg und As auf die eGFR ist nicht nachweisbar

IMD Labor Berlin

Toxische Metalle – ein bisher unterschätzter Risikofaktor für Herzkreislauferkrankungen und Nierenerkrankungen

- ***Toxische Metallbelastung- Epidemiologische Daten aus Deutschland***
- **Toxische Metalle und Fetale Programmierung von Herzkreislauferkrankungen und Nierenerkrankungen**
- **Toxische Metalle und Nierenerkrankungen bei Erwachsenen**
- **Toxische Metalle und Herzkreislauferkrankungen bei Erwachsenen**
- **Was tun – Gibt es therapeutische Möglichkeiten**

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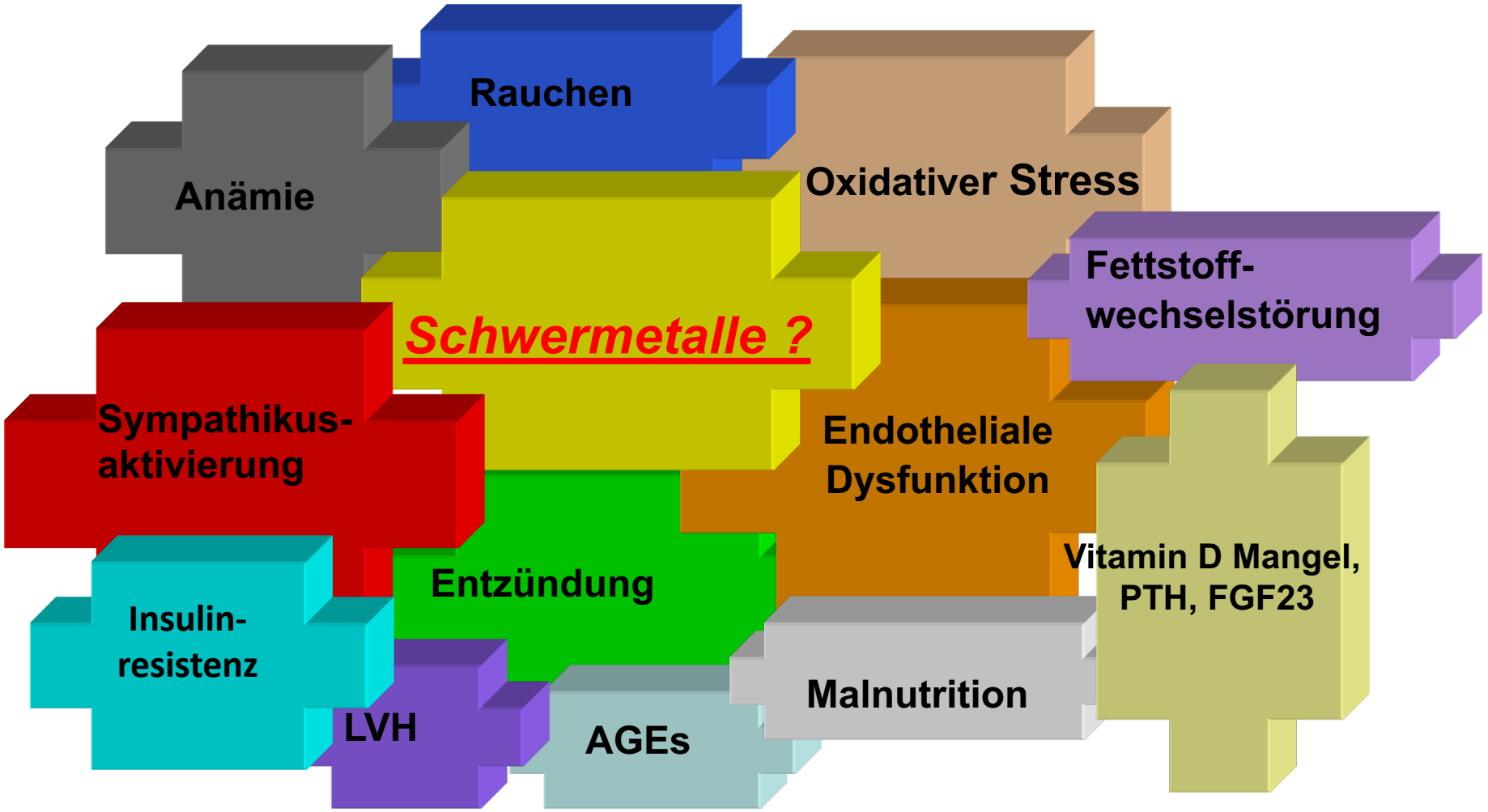
Ursachen der Herzkreislauferkrankungen und CKD-Progression bei CKD – ein kompliziertes Puzzle



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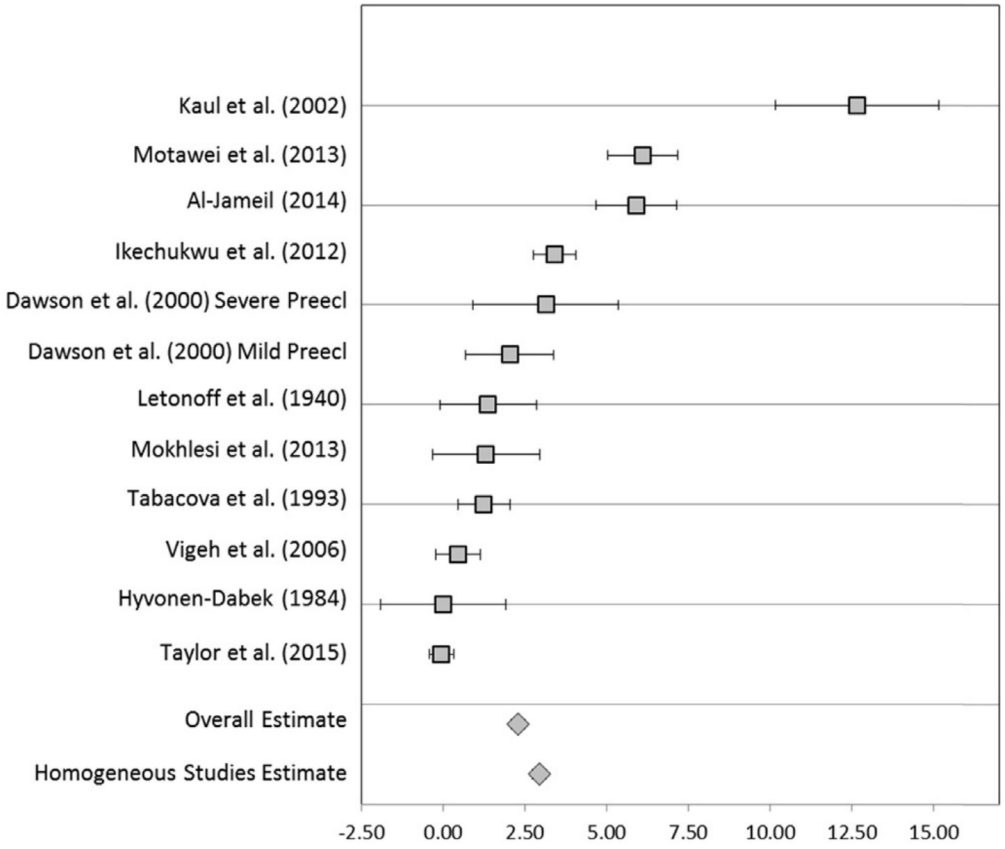
Blood lead and preeclampsia: A meta-analysis and review of implications☆



Die Bleikonzentration im Blut schwangerer Frauen ist ein wichtiger Risikofaktor für Präeklampsie, wobei ein Anstieg um 1 µg/dL ist mit einer um 1,6 % erhöhten Wahrscheinlichkeit einer Präeklampsie verbunden

Forest plot der log Odds Ratios und der zugehörigen Konfidenzintervalle für jede Studie, geordnet nach Größenordnung, zusammen mit den log Odds Ratios für die meta-analytischen Schätzungen auf der Grundlage aller Studien (die Gesamtschätzung) und nur der homogenen Studien

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Environmental Research 212 (2022) 113231

Contents lists available at ScienceDirect

Environmental Research

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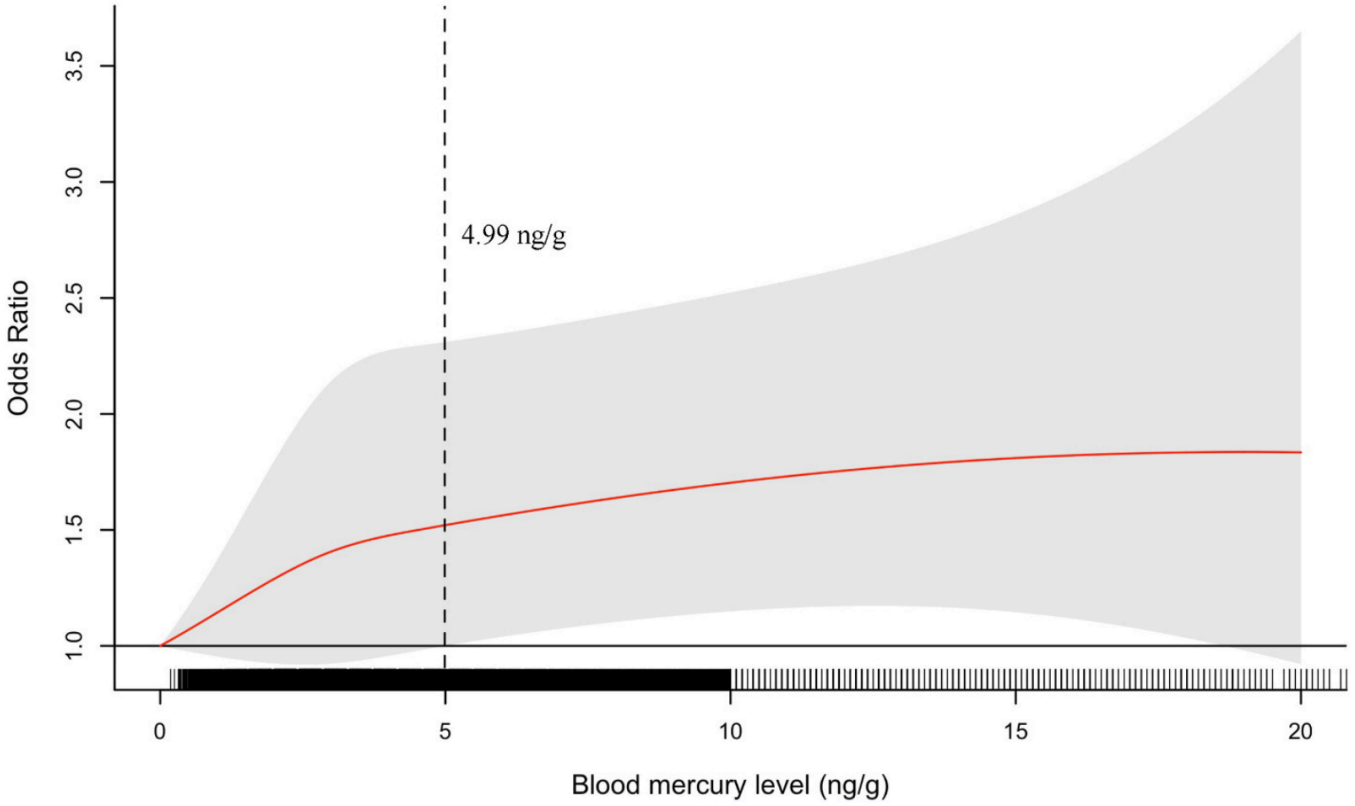
Association between whole blood metallic elements concentrations and gestational diabetes mellitus in Japanese women: The Japan environment and Children's study



Dosis-Wirkungs-Beziehung zwischen Hg und dem Risiko für Schwangerschafts-diabetes mellitus.

n=78 964 Schwangere

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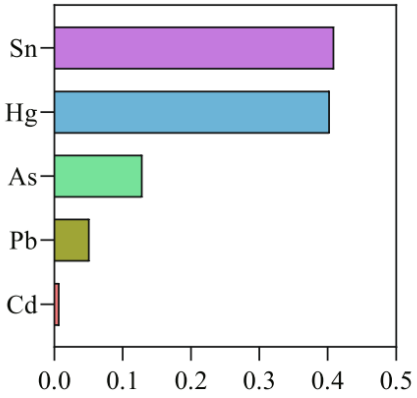
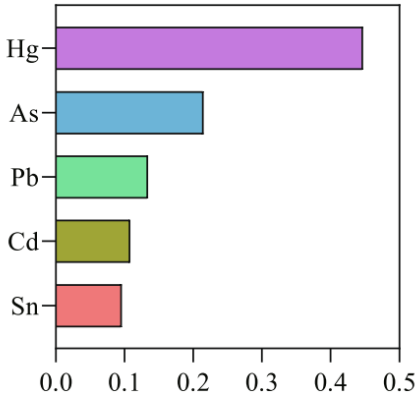
Assoziation von toxischen Metallen mit Glukosestoffwechsel

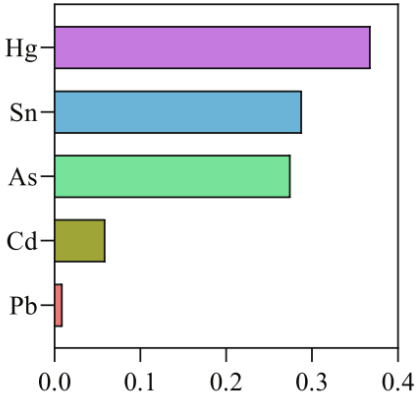
Schwangerschafts-diabetes mellitus



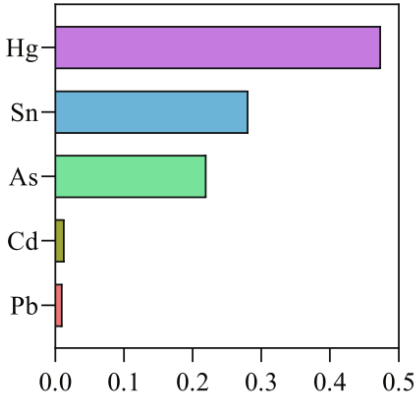
Nüchternblutzucker



1-h-Blutglukose



2-h-Blutglukose



Zhang et al., Associations between endocrine-disrupting heavy metals in maternal hair and gestational diabetes mellitus: A nested case-control study in China. Environ Int 2021; 157: 106770

IMD Labor Berlin

IMD Labor Berlin-Potsdam

Ärztlicher Befundbericht

Untersuchung	Ergebnis	Einheit	Referenzbereich
Klinische Chemie			
Glucose (nüchtern) i. cNaF-Pl.(enz.)	**124**	mg/dl	< 100
Hämoglobin A1c i. EDTA-Blut	**7.2**	%	< 5.7
Hämoglobin A1c i. EDTA-Blut	**55**	mmol/mol	< 39

Screening auf Diabetes mellitus:
<5.7% (<39 mmol/mol) - Kein Hinweis auf Diabetes mellitus.
5.7-6.4% (39-47 mmol/mol) - Grenzbereich, weitere Abklärung über Nüchternglukose und evtl. oGTT angezeigt.
>6.4% (>47 mmol/mol) - Wert spricht für Diabetes mellitus.
Therapieverlaufskontrolle bei Diabetes mellitus:
Zielbereich 6.5-7.5% (48-58 mmol/mol)

Hormone					
Insulin i.S.	(CMIA)	9.7	µU/ml	2.0	- 23.0

> 12 Std. Fasten < 6.0 µU/ml

HOMA-INDEX	2.97		

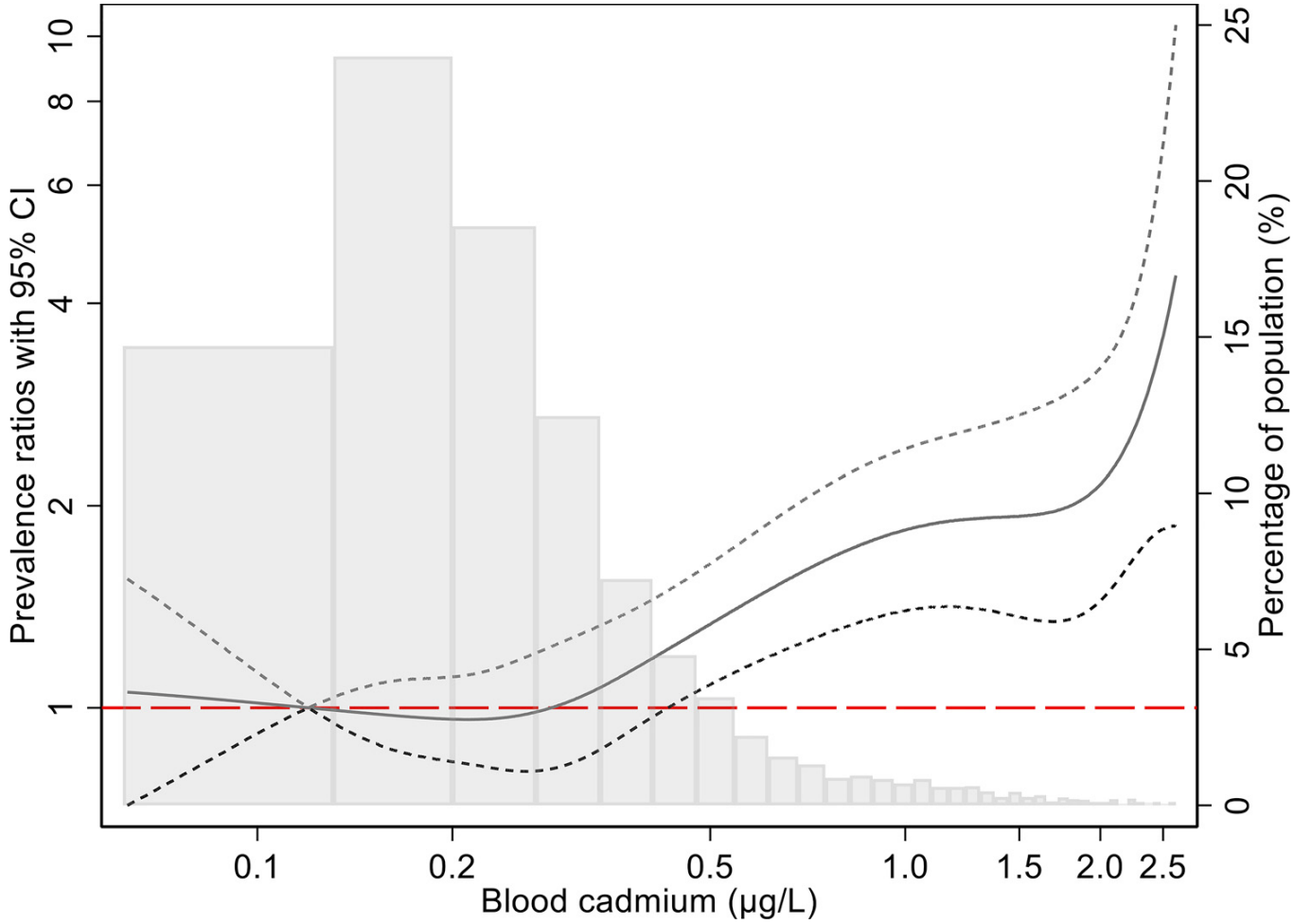
Berechnung erfolgt aus Nüchternglucose und Insulin.
bis 1.0 - normal;
> 2.0 - Hinweis auf eine Insulinresistenz;
> 2.5 - Insulinresistenz sehr wahrscheinlich;
> 5.0 - Durchschnittswert bei Typ II-Diabetikern;

Wechselwirkungen mit toxischen Metallen:

Aluminium	**<10,0**	µg/l	< 11,4	
Arsen	**1,5**	µg/l	< 1,2	
Blei	**36,6**	µg/l	< 28	
Cadmium	**3,3**	µg/l	< 0,6	
Nickel	**0,2**	µg/l	< 3,8	
Quecksilber	**1,7**	µg/l	< 1,0	

Cadmium Exposure and Coronary Artery Atherosclerosis: A Cross-Sectional Population-Based Study of Swedish Middle-Aged Adults

Lars Barregard,[1] Gerd Sallsten,[1] Florencia Harari,[1] Eva M. Andersson,[1] Niklas Forsgard,[2] Ola Hjelmgren,[3,4] Oskar Angerå, Erika Fagman,[6] Margaretha Persson,[7] Thomas Lundh,[8] Yan Borné,[7] Björn Fagerberg,[3] Gunnar Engström,[7] and Göran Bergström[3,4]



https://doi.org/10.1289/EHP8523

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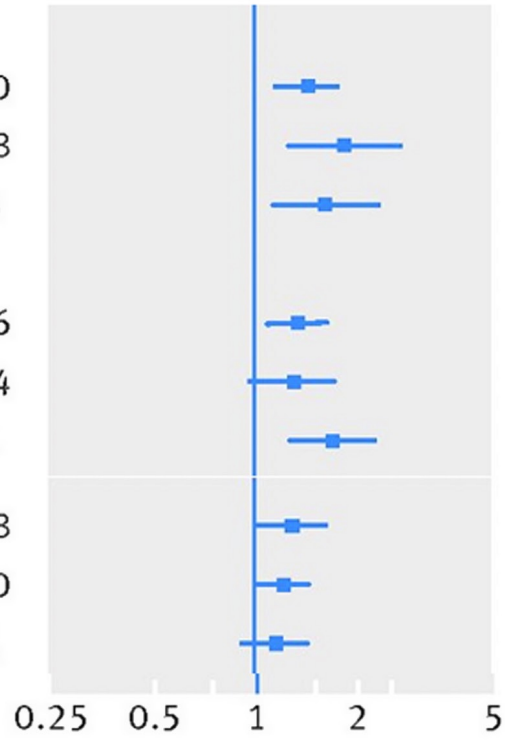
Metals as Cardiovascular Risk Factors: A Scientific Statement From the American Heart Association.

J Am Heart Assoc. 2023 Jul 4;12(13):e029852. doi: 10.1161/JAHA.123.029852.

Metals	No. studies	No. participants	No. events	Relative risk (95% CI)
Lead				
Cardiovascular disease	10	110 382	4970	1.43 (1.16–1.76)
Coronary heart disease	8	91 779	2228	1.85 (1.27–2.69)
Stroke	6	89 494	518	1.63 (1.14–2.34)
Cadmium				
Cardiovascular disease	6	50 674	3756	1.33 (1.09–1.64)
Coronary heart disease	5	32 070	1654	1.29 (0.98–1.71)
Stroke	3	9123	601	1.72 (1.29–2.28)
Arsenic				
Cardiovascular disease	7	135 943	3208	1.30 (1.04–1.63)
Coronary heart disease	8	190 816	4640	1.23 (1.04–1.45)
Stroke	4	134 526	961	1.15 (0.92–1.43)



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Journal of the American Heart Association

AHA SCIENTIFIC STATEMENT

Contaminant Metals as Cardiovascular Risk Factors: A Scientific Statement From the American Heart Association

Gervasio A. Lamas, MD, FAHA, Chair; Aruni Bhatnagar, PhD, FAHA; Miranda R. Jones, MHS, PhD; Koren K. Mann, PhD; Khurram Nasir, MD, MPH, FAHA; Maria Tellez-Plaza, MD, PhD; Francisco Ujueta, MD, MS; Ana Navas-Acien, MD, PhD, Vice Chair; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Council on the Kidney in Cardiovascular Disease

…… Public health measures reducing metal exposure are associated with reductions in cardiovascular disease death. ……

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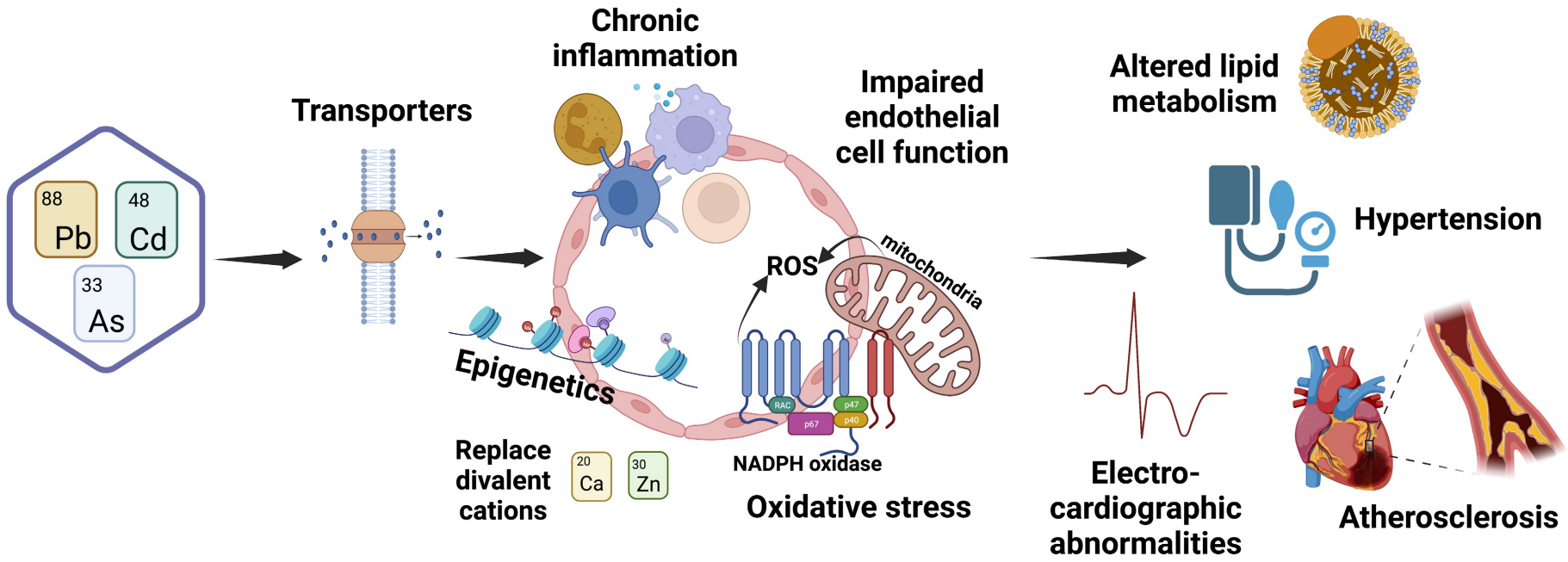

Pharmacokinetics and relevant mechanisms for the subclinical and clinical effects of lead (Pb), cadmium (Cd), and arsenic (As). Figure created with Biore nder.com. This is not a complete figure on mechanisms. For example, evidence on metals and hyperglycemia and thrombosis also exists. Ca: calcium; ROS, reactive oxygen species; and Zn, zinc.

Metals as Cardiovascular Risk Factors: A Scientific Statement From the American Heart Association.

J Am Heart Assoc. 2023 Jul 4;12(13):e029852. doi: 10.1161/JAHA.123.029852.

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Toxische Metalle – ein bisher unterschätzter Risikofaktor für Herzkreislauferkrankungen und Nierenerkrankungen

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- **Was tun – Gibt es therapeutische Möglichkeiten**

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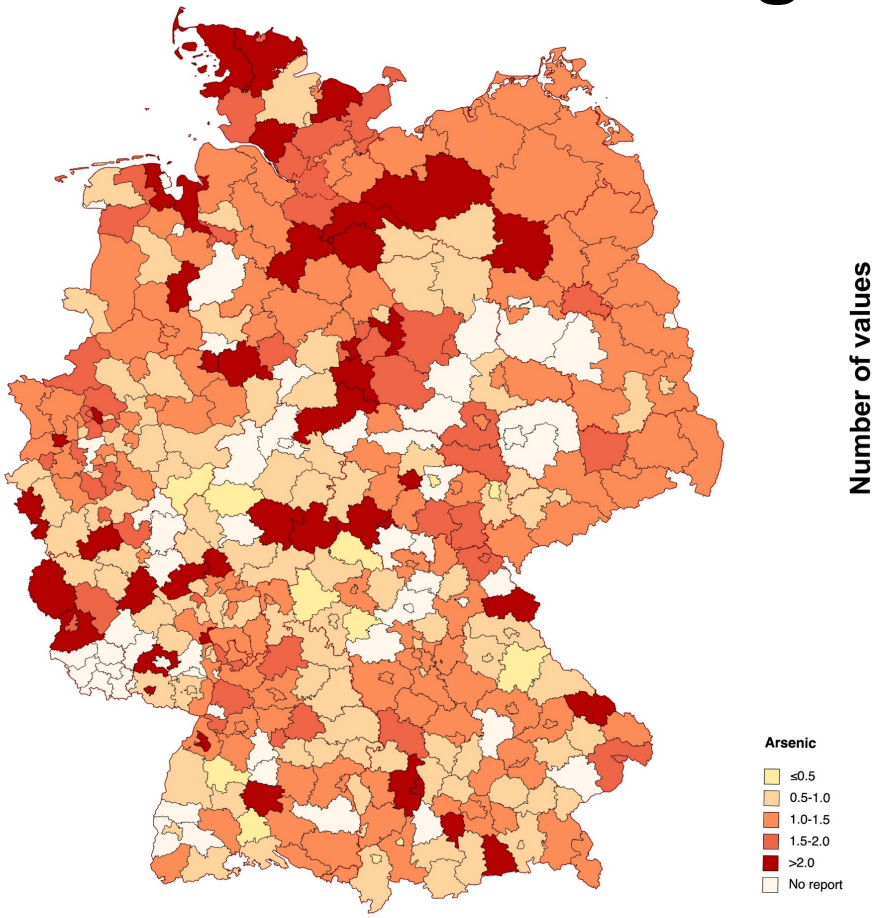
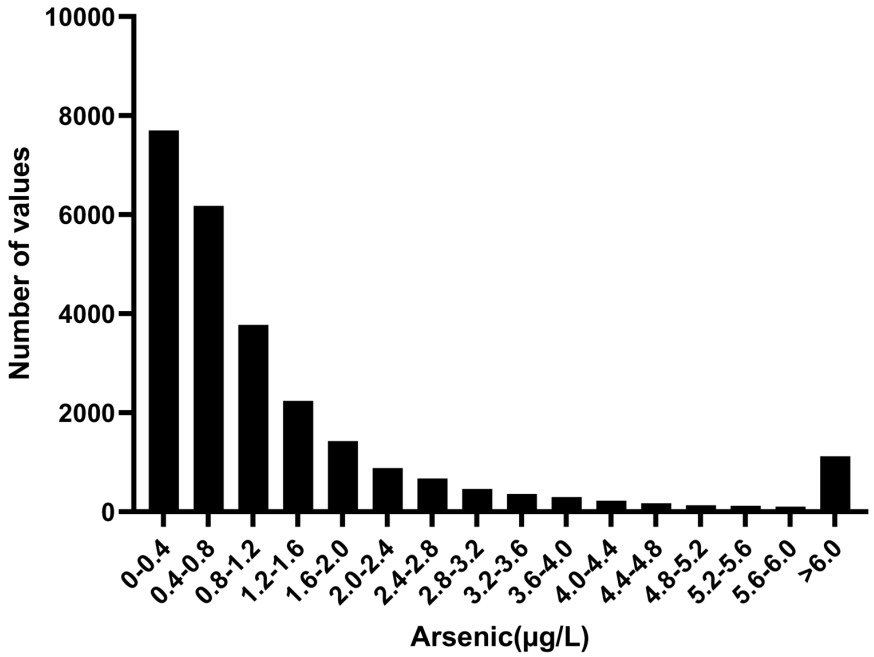
Analyse lokaler Faktoren ist wichtig





Arsen in Deutschland

- The distribution of metals among the 374 districts in 16 federal states in Germany.
- The white part is no reported, and darker color means higher level of metals; the red color is the highest-level group.
- **Overlap highest area of arsenic and Cadmium: Eifel Kreis Bitburg- Prüm, Goslar, Wesemarsch , Frisland.**

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Wasserfilter

IMD Labor Berlin

Kidney and heavy metals - The role of environmental exposure (Review).

Mol Med Rep. 2017 May;15(5):3413-3419. doi: 10.3892/mmr.2017.6389.

Table I. Therapeutic approaches in acute heavy metal toxicity [adapted from Lentini *et al* (11)].

Metal	HD	PD	CVVH	CVVHDF	TPE	HMP	Chelators
Arsenic	HD+DMSA or HD+BAL	PD+DMSA or PD+BAL	Unknown	Unknown	Unknown	Unknown	BAL, DMSA, D-penicillamine
Cadmium	No	No	No	No	No	No	Calcium-EDTA
Copper	HD+ D-penicillamine	Unknown	Unknown	CVVHDF+ D-penicillamine	No	Yes	D-penicillamine, BAL
Lead	No	No	No	No	Unknown	No	Calcium-sodium EDTA, BAL, DMSA
Lithium	Yes	Yes	Yes	Yes	No	No	No
Mercury	No	No	No	CVVHDF+DMPS	Unknown	No	BAL, DMSA, DMPS (inorganic only)
Platin	Yes	Yes	Unknown	Unknown	Yes	No	No

HD, hemodialysis; PD, peritoneal dialysis; CVVH, continuous venous-venous hemofiltration; CVVHDF, continuous venous-venous hemodiafiltration; TPE, therapeutic plasma exchange; HMP, hemoperfusion; DMSA, dimercaptosuccinic acid; BAL, dimercaprol; EDTA, ethylenediaminetetraacetic acid; DMPS, dimercapto-1-propane sulfonate.

Chelationen haben unterschiedliche Eliminationskapazität auf einzelne tox. Metalle

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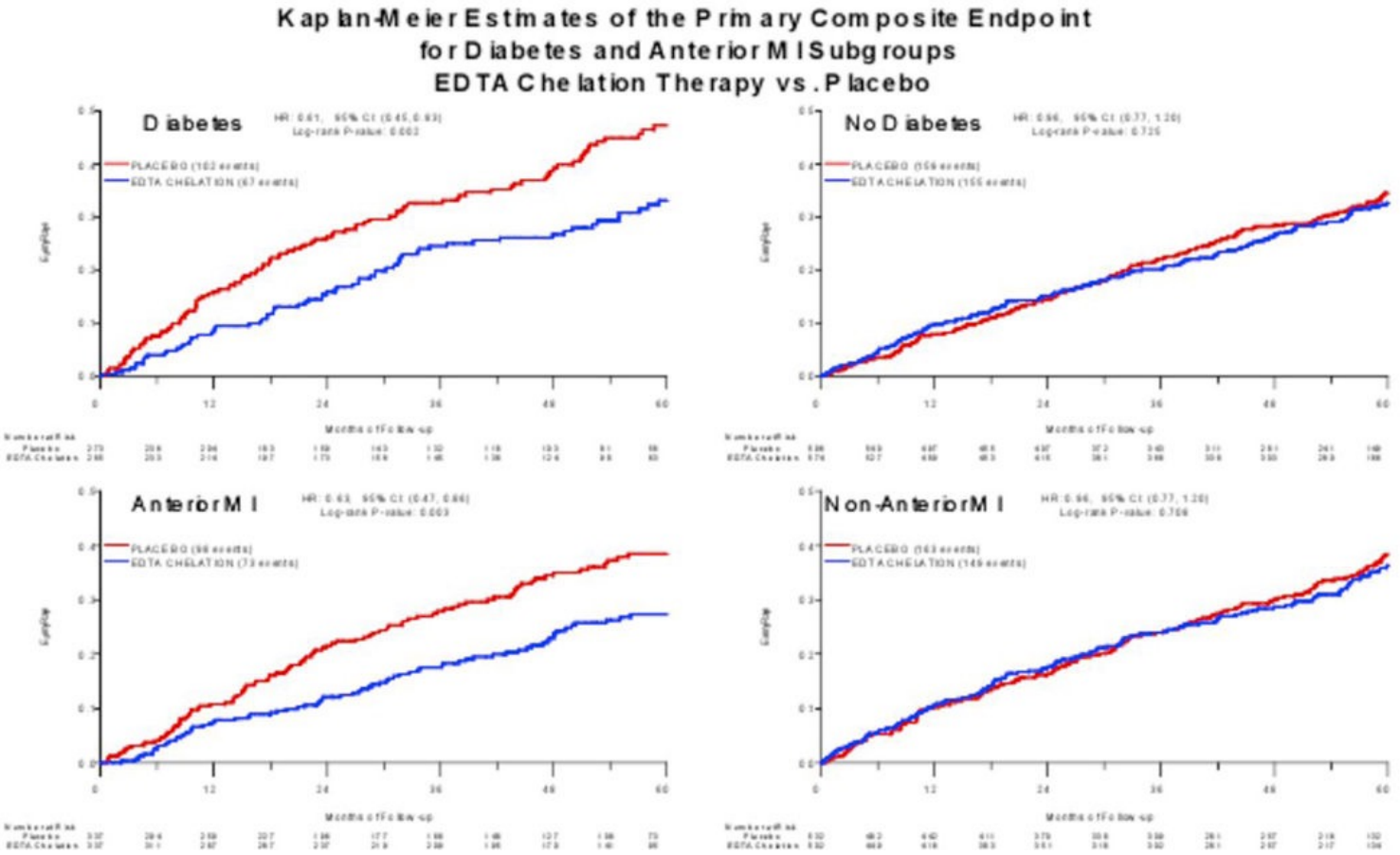
Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: The TACT Randomized Trial

JAMA. 2013 March 27; 309(12): 1241–1250. doi:10.1001/jama.2013.2107



Kaplan-Meier Estimates of the Primary Composite Endpoint for Diabetes and Anterior MISubgroups EDTA Chelation Therapy vs. Placebo

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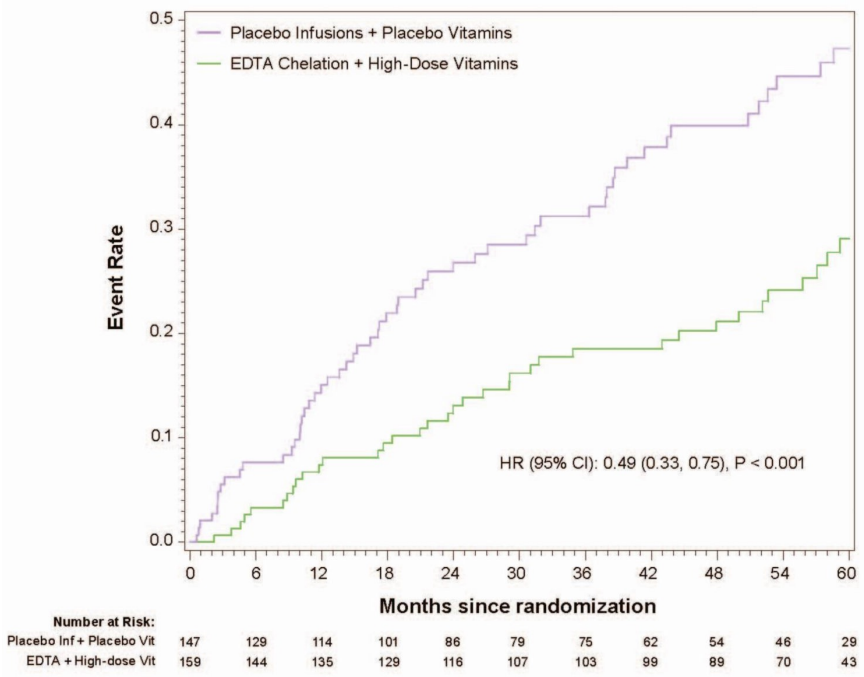
EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: The factorial group results of the Trial to Assess Chelation Therapy.

Am Heart J. 2014 Jul;168(1):37-44.e5. doi: 10.1016/j.ahj.2014.02.012.



Conclusions: In stable post-MI patients on evidence-based medical therapy, the combination of oral high-dose vitamins and chelation therapy compared with double placebo reduced clinically important cardiovascular events to an extent that was both statistically significant and of potential clinical relevance.

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The trial to assess chelation therapy 2 (TACT2): Rationale and design

Gervasio A. Lamas, MD[a], Kevin J. Anstrom, PhD[b], Ana Navas-Acien, MD, PhD[c], Robin Boineau, MD, MA[d], Hwasoon Kim, PhD[c], Yves Rosenberg, MD[f], Mario Stylianou, PhD[f], Teresa L.Z. Jones, MD[g], Bonnie R. Joubert, PhD[h], Regina M. Santella, PhD[c], Esteban Escolar, MD[a], Y. Wady Aude, MD[i], Vivian Fonseca, MD[j], Thomas Elliott, MBBS[k], Eldrin F. Lewis, MD, MPH[l], Michael E. Farkouh, MD, MSc[m], David M. Nathan, MD[n], Ana C. Mon, MPH[a], Leigh Gosnell[c], Jonathan D. Newman, MD, MPH[o], and Daniel B. Mark, MD, MPH[c], for the TACT2 Investigators , *Miami Beach, FL, Chapel Hill, NC, New York, NY, Bethesda, MD, Durham, NC, McAllen, TX, New Orleans, LA, Vancouver, BC, Palo Alto, CA, Boston, MA, New York, NY*

Abstract

Background Intravenous edetate disodium-based infusions reduced cardiovascular events in a prior clinical trial. The Trial to Assess Chelation Therapy 2 (TACT2) will replicate the initial study design.

Methods TACT2 is an NIH-sponsored, randomized, 2x2 factorial, double masked, placebo-controlled, multicenter clinical trial testing 40 weekly infusions of a multi-component edetate disodium (disodium ethylenediamine tetra-acetic acid, or Na_2EDTA)-based chelation solution and twice daily oral, high-dose multivitamin and mineral supplements in patients with diabetes and a prior myocardial infarction (MI). TACT2 completed enrollment of 1000 subjects in December 2020, and infusions in December 2021. Subjects are followed for 2.5 to 5 years. The primary endpoint is time to first occurrence of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina. The trial has >;85% power to detect a 30% relative reduction in the primary endpoint. TACT2 also includes a Trace Metals and Biorepository Core Lab, to test whether benefits of treatment, if present, are due to chelation of lead and cadmium from patients. Design features of TACT2 were chosen to replicate selected features of the first TACT, which demonstrated a significant reduction in cardiovascular outcomes in the EDTA chelation arm compared with placebo among patients with a prior MI, with the largest effect in patients with diabetes.

Results Results are expected in 2024.

Conclusion TACT2 may provide definitive evidence of the benefit of edetate disodiumbased chelation on cardiovascular outcomes, as well as the clinical importance of longitudinal changes in toxic metal levels of participants. (Am Heart J 2022;252:1–11.)

2x2 factorial, double masked, placebo-controlled, multicenter clin-ical trial testing 40 weekly infusions of a multi-component edetate disodium (disodium ethylenediamine tetra-acetic acid, or Na 2 EDTA)-based chelation solution and twice daily oral, high-dose multivitamin and mineral supplements in patients with diabetes and a prior myocardial infarction

2024 wird spannend

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Was hat Hocher gesagt

- **Toxische Metalle als Risikofaktor**:
  - Toxische Metalle wie **Arsen, Blei, Cadmium und Quecksilber sind unterschätzte Risikofaktoren für Herz-Kreislauf-Erkrankungen (CHD) und chronische Nierenerkrankungen (CKD) -> Analyse von tox. Metalled sollten Bestandteil der Laboranalytik bei V. a. KHK oder CKD sein.**
- **Epidemiologische Daten aus Deutschland**:
  - Studien zeigen eine **erhebliche Variabilität der Schwermetallbelastung** zwischen den verschiedenen Postleitzahlbezirken in Deutschland.
  - **Arsen und Blei-Konzentrationen im Vollblut steigen lebenslang an, *während* Quecksilber und Cadmium bis zum mittleren Lebensalter ansteigen** und dann konstant bleiben.
  - **Es gibt *keinen sicheren unteren Grenzwert* für Arsen, Blei und Quecksilber in Bezug auf ihre Auswirkungen auf die Nierenfunktion.**

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Fetale Programmierung und maternale Erkrankungen :

- Toxische Metalle können während **kritischer Entwicklungsphasen zu dauerhaften strukturellen und funktionalen Veränderungen** führen, die das Risiko für Herz-Kreislauf- und Nierenerkrankungen der Nachkommen erhöhen.
- Blei im Blut schwangerer Frauen ist ein signifikanter Risikofaktor für Präeklampsie.
- toxischen Metallen erhöhen das Risikp für Schwangerschaftsdiabetes
- **Analyse tox. Metalle bei Kinderwunsch bei Mutter und Vater**

Therapeutische Möglichkeiten:

- Die Variabilität der Schwermetallbelastung in Deutschland erfordert die Analyse **lokaler Faktoren.**
- **Wasserfilter** könnten eine Lösung zur Reduzierung der Metallbelastung sein, deren Wirksamkeit jedoch nachgewiesen werden muss.
- **Chelat-Therapie mit EDTA** könnte bei bestimmten Subgruppen (z.B. **Diabetiker oder Patienten nach einem Myokardinfarkt**) wirksam sein, insbesondere in Kombination mit Spurenelementen und Vitamin-Substitution
- TACT2-Studiendaten ???

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Vielen Dank!

Fragen ?

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