# Kidney Susceptibility to Environmental Toxins: A Focus on Lead

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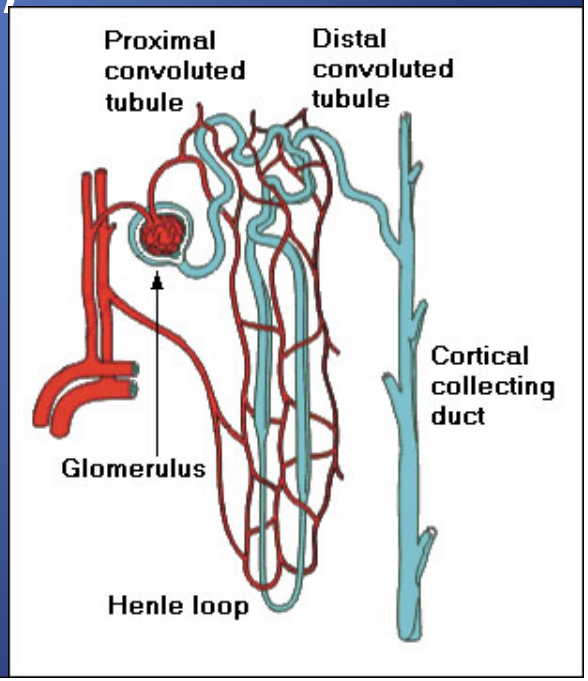
# Kidney Basics

- Kidneys in embryo produce urine by 12 weeks gestation
  - Role in fetal homeostasis minor compared to placenta
  - Fetal kidneys: ~2.5% cardiac output
    - Fetal hemodynamics/urine formation known to be affected by maternal factors (volume status, drugs, etc)
- Nephron: functional unit
- ~1 million/kidney
- Nephrogenesis complete 36 weeks gestation
  - Never reactivated in face of reduction functional kidney mass




http://www.pc.maricopa.edu/Biology/pfinkenstadt/BIO202/202LessonBuilder/Urinary/nephron.jpg

# The Kidney: A Likely "Target"?

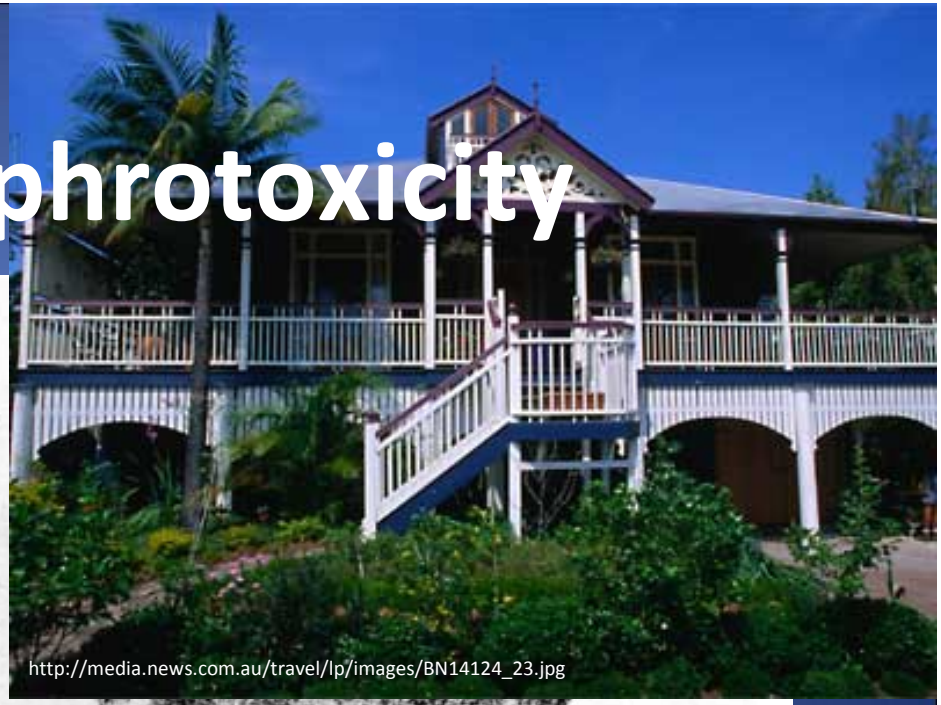
- 20% of cardiac output
- 180 liters of filtrate (water/solute: "early urine") produced daily
  - > 99% reabsorbed
  - Passive/active transport of solute
    - Highly metabolically active
    - Concentrate certain substances actively
    - Biotransformation of certain compounds
    - Reabsorbs organic metabolites that should not be lost
    - Excretes waste products and foreign organic substances to prevent accumulation

# Kidney Toxicants: Heavy Metals

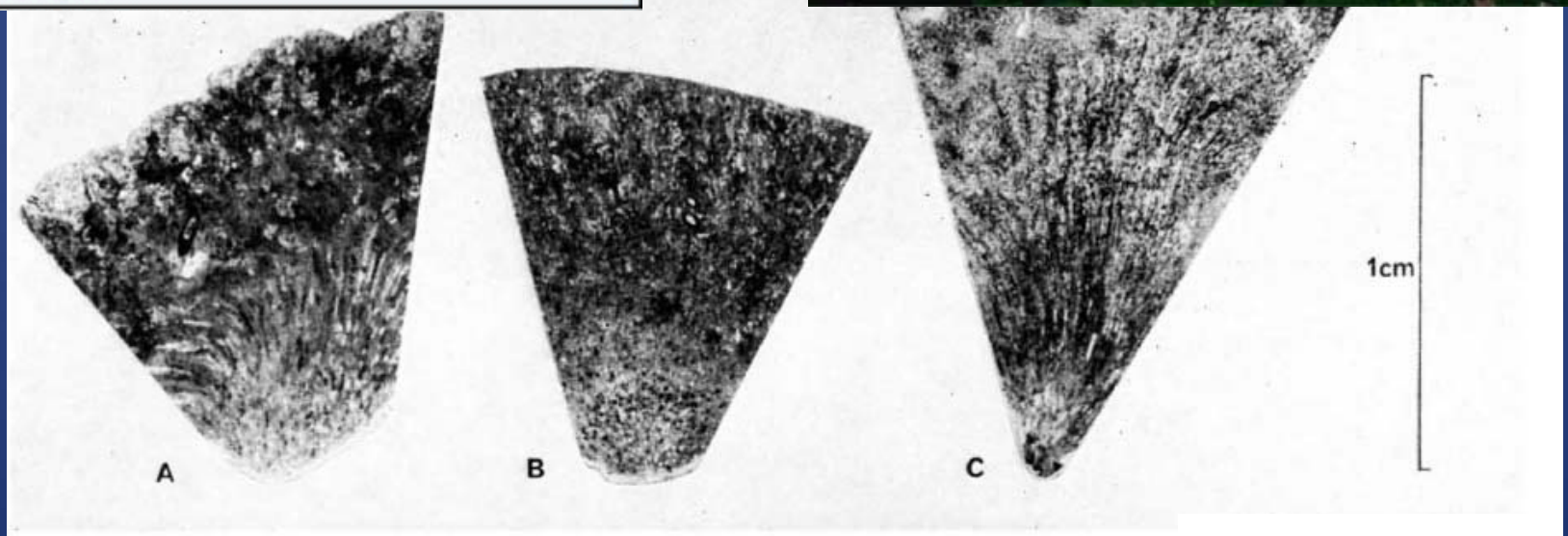
- Lead
- Cadmium
- Mercury
- Uranium
- Arsenic
- Chromium
- Copper

# Lead and Nephrotoxicity

http://www.instablogsimages.com/images/2009/06/29/queensland_lMfiX_24679.gif



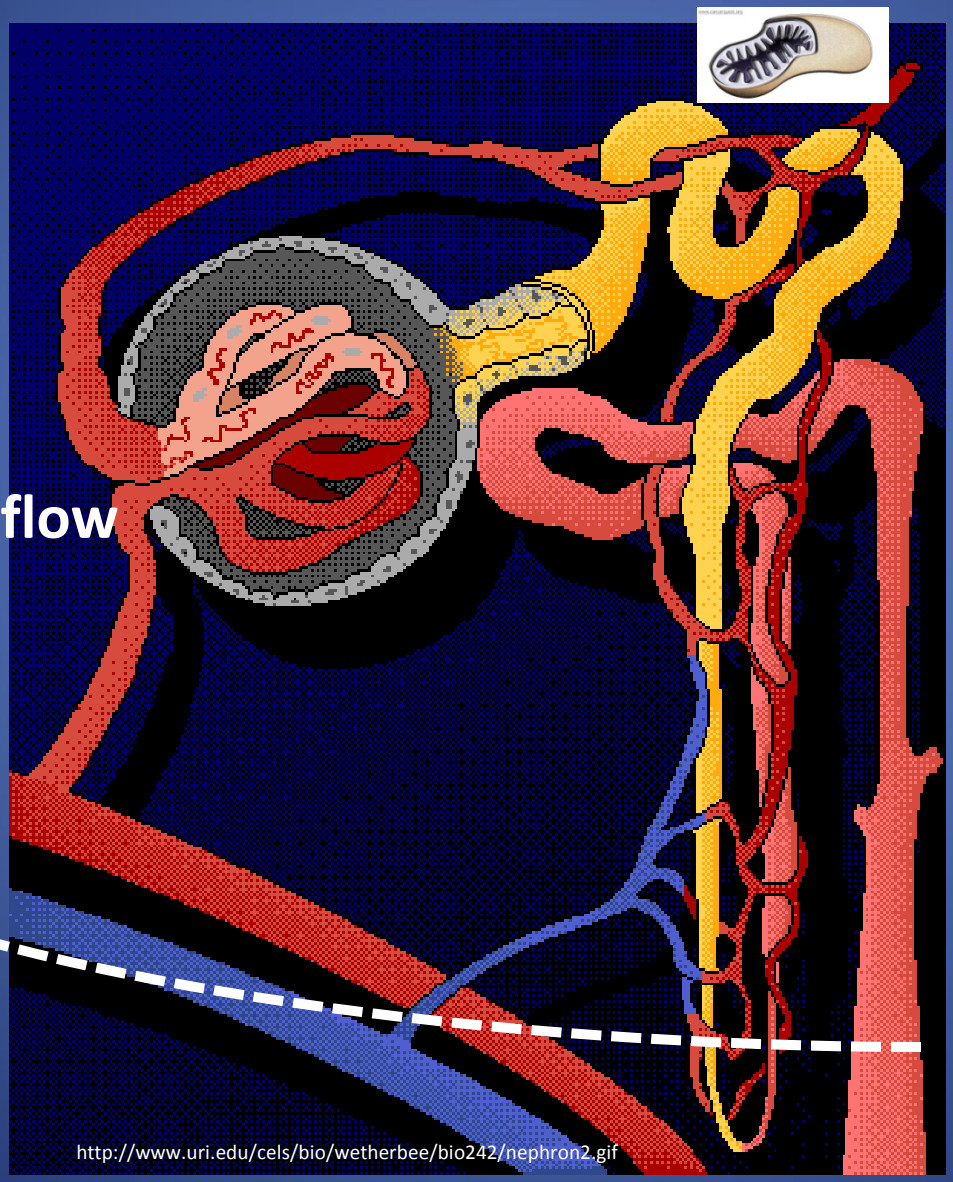
http://media.news.com.au/travel/lp/images/BN14124_23.jpg




*Kidney International, Vol. 4 (1973), p. 1–5*

**Fig. 2.** *A comparison between sections taken from cortex to papilla in the kidneys of (A) chronic lead nephropathy, (B) chronic glomerulonephritis and (C) a normal kidney (PAS stain × 3).* The lead nephritic kidney shows coarse granularity with gross cortical atrophy and interstitial fibrosis. The glomerulonephritic kidney shows large numbers of glomerular remnants, a uniform pattern of involvement and moderate cortical atrophy. [From Emmerson, 1967 [45] by permission of Blackwell Scientific Publications]

# Mechanisms of Toxicity




**Glomerulus**

↓ GFR

↓ Renal blood flow

**Proximal Tubule**

- Mitochondria:

-Impairments of oxidative metabolism

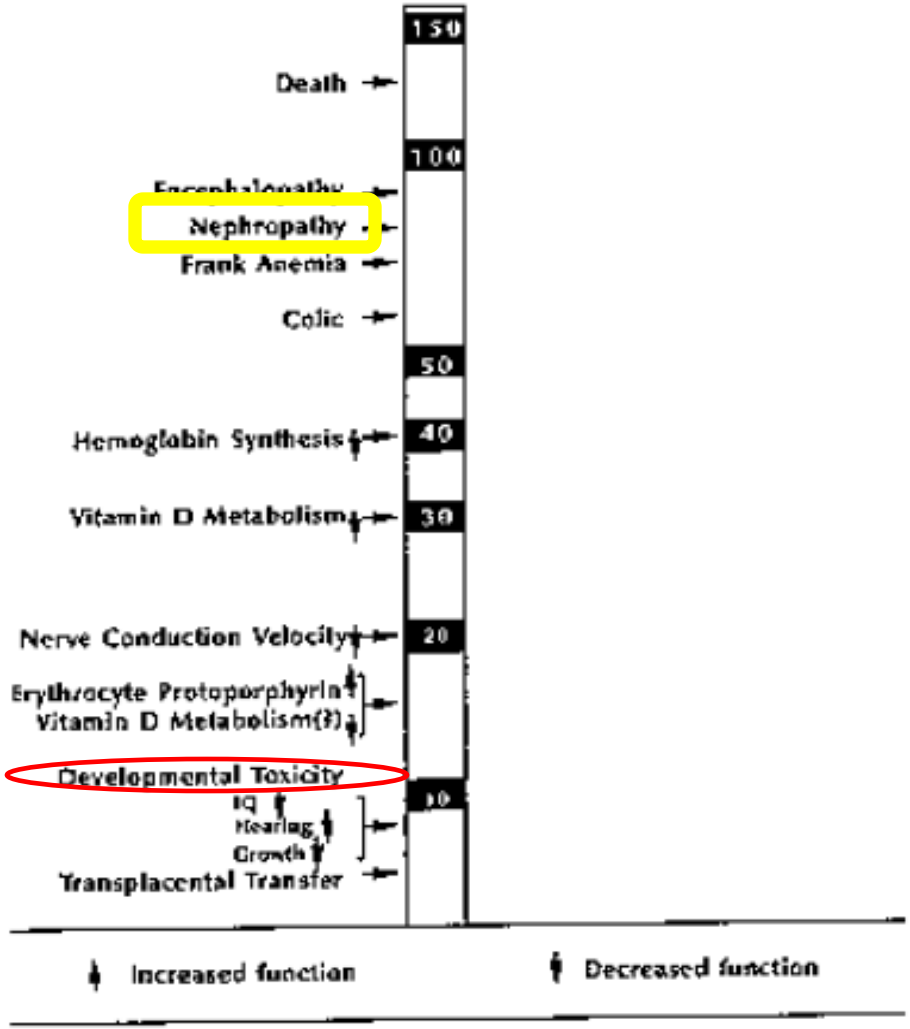
-↓ calcium uptake

-Interference with calcium-mediated or regulated intracellular events

- Oxidative stress: Depletion of NO

# Lead Toxicity: A Man-Made Disease

**Figure 2-1. Lowest observed effect levels of inorganic lead in children***




*Note: The levels in this diagram do not necessarily indicate the lowest levels at which lead exerts an effect. These are the levels at which studies have adequately demonstrated an effect.

Source: ATSDR, 1990.

**Trends in Blood Lead Levels and Blood Lead Testing Among US Children Aged 1 to 5 Years, 1988 2004**

Robert L. Jones, David M. Homa, Pamela A. Meyer, Debra J. Brody, Kathleen L. Caldwell, James L. Pirkle and Mary Jean Brown

*Pediatrics* 2009;123;e376-e385
DOI: 10.1542/peds.2007-3608

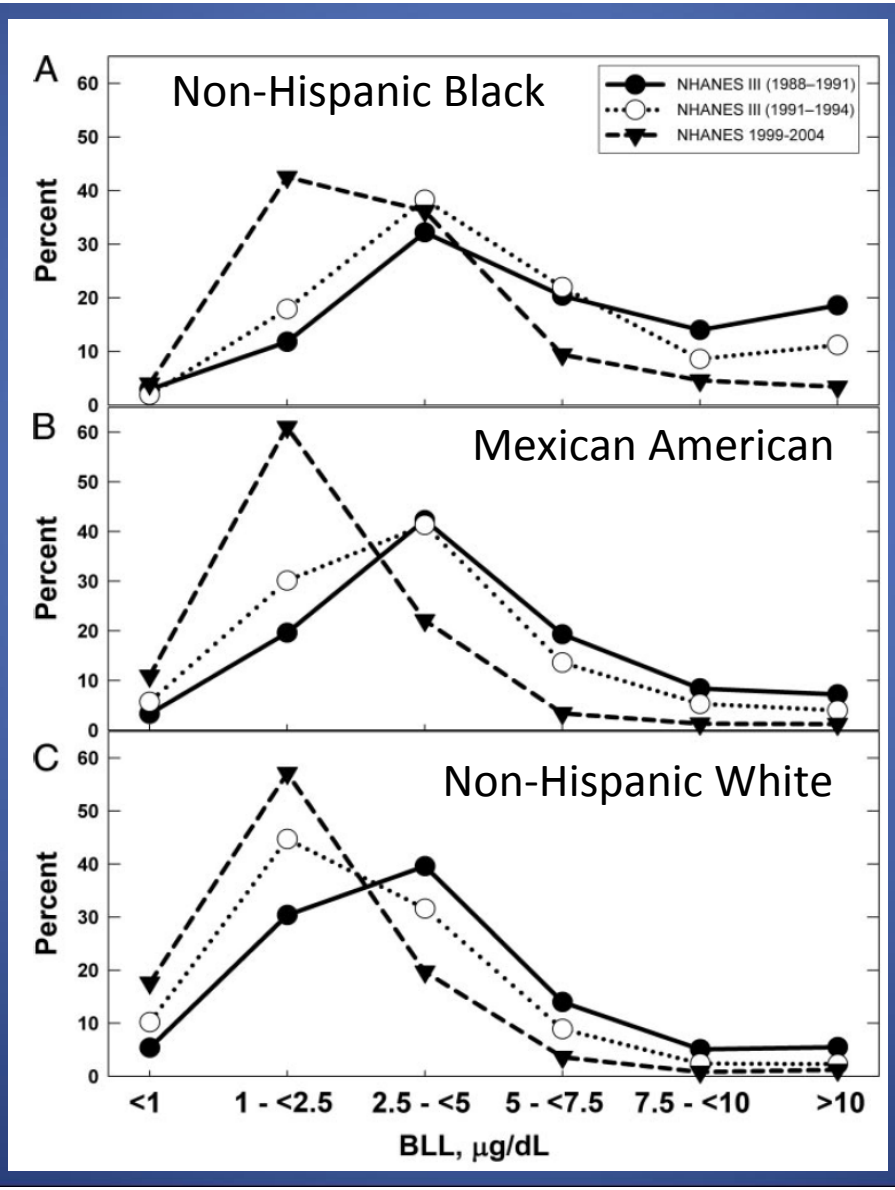


**Table C1.** Review of studies examining low-level environmental **lead** exposure and effects on kidney function in adults and children.

**STUDIES IN ADULTS**

| First Author | Year | Country | Population | Design | N | Outcome | Assess-ment | Average Lead Levels | Effect/Comparison |
|---|---|---|---|---|---|---|---|---|---|
| Yu(4) | 2004 | Taiwan | Male + Female with CKD, 25-82 yr | Prospective Cohort | 121 | Decline in GFR | BLL[1] | (Means) High-normal 4.9 µg/dL, Low-normal 3.4 µg/dL | -4.0 mL/min/1.73 $m^2$ (p=0.015) [per 1 µg/dL increment, over 48 month observation period] |
| Munter (68) | 2003 | USA | M + F ≥20 yr with hypertension | Cross-sectional | 4813 | Elevated creatinine[2] | BLL | Quartiles (range, µg/dL): 1 (0.7-2.4), 2 (2.5-3.8), 3 (3.9-5.9), 4 (6.0-56) | Adjusted odds ratio (95% CI) [$4^{th}$ vs $1^{st}$ quartile]: 2.07 (1.26, 3.40) |
| Lin (5) | 2003 | Taiwan | M + F with CKD, 18-80 yr | Prospective Cohort | 202 | 1.5x increase baseline creatinine | BLB[3] | Range 80- 596 µg | Adjusted relative risk (95% CI): 1.00 (1.00, 1.01) [per 1 µg increment |
| Lin(5) | 2003 | Taiwan | M + F with CKD, 18-80 yr | Single-blind, randomized clinical trial[4] | 64 | Change in GFR | BLL | (Means) Chelation group 6.1 ± 2.5 µg/dL, placebo 5.9 ± 3.0 µg/dL | Chelation group: +2.1 ± 5.7 mL/min/1.73$m^2$; Placebo -6.0 ± 5.8 mL/min/1.73$m^2$ (p<0.001) |
| Lin(69) | 2001 | Taiwan | M + F with CKD, 34-70 yr | Prospective Cohort | 110 | 1.5x increase baseline creatinine | BLL | (Means) High-normal 3.6 µg/dL, low-normal 2.1 µg/dL | Adjusted relative risk (95% CI): 41.5 (3.9, 440.8) |
| Kim(2) | 1996 | USA | Normative Aging Study, M, 38-88 yrs | Retrospective Cohort | 459 | Change in serum creatinine | BLL | (Mean) 9.9 µg/dL | 0.05 mg/dL (95% CI: -0.01, 0.10) change in creatinine between study visits [per 10-fold increase in BLL] |
| Payton(70) | 1994 | USA | Normative Aging Study, M, 43-90 yrs | Cross-sectional | 744 | Change in creatinine clearance | BLL | (Mean) 8.1 µg/dL | -10.4 mL/min [per 10 µg/dL increment] |

**STUDIES IN CHILDREN**

| First Author | Year | Country | Population | Design | N | Outcome | Assess-ment | Average Lead Levels | Effect/Comparison |
|---|---|---|---|---|---|---|---|---|---|
| de Burbure (9) | 2006 | France, Czech Republic, Poland | M + F, mean age ~10 yrs, living near smelters | Cross-sectional | 800 | Comparison of serum/urinary markers of kidney function | BLL | (Means) Exposed 3.6-6.5 µg/dL, non-exposed 2.8-3.8 µg/dL | Serum creatinine, cystatin C, and β2-microglobulin negatively correlated with BLL (statistically significant) |
| Oktem(71) | 2004 | Turkey | M auto-shop workers, 15-19 yrs | Cross-sectional | 150 | Comparison of urinary markers of tubular damage and serum creatinine | BLL | (Means) Exposed 7.8 µg/dL, non-exposed 1.6 µg/dL | Urinary NAG[5] (U/g creatinine): exposed 2.5, non-exposed 1.4 (p<0.05); serum creatinine: no difference |
| Sonmez (72) | 2002 | Turkey | M auto-shop workers, 12-19 yrs | Cross-sectional | 68 | Comparison of urinary markers of tubular damage and serum creatinine | BLL | (Means) Exposed 8.1 µg/dL, non-exposed 3.5 µg/dL | Urinary NAG (U/g creatinine): exposed 4.7, non-exposed 3.1 (p<0.01); serum creatinine: no difference |
| Fels (73) | 1998 | Poland | M +F living near lead smelter, mean age 9 yrs | Cross-sectional | 112 | Comparison of urinary and serum markers of tubular function | BLL | (Means) Exposed 13.3 µg/dL, non-exposed 3.9 µg/dL | Exposed: significant increase excretion of prostaglandins, thromboxane B2, EGF[6], β2-microglobulin, Clara cell protein |
| Verberk (8) | 1996 | Romania | M + F, daycare varying distance from lead smelter, 3-6 yrs | Cross-sectional | 151 | Comparison of urinary markers of tubular damage | BLL | (Means) Highest exposure group 43.8 µg/dL, lowest exposure group 15.5 µg/dL | 14% increase in urinary NAG (90 % CI: 7,20) per 10 µg/dL increase; no difference: albumin, RBP, AAP, A1M[7] |
| Bernard (7) | 1995 | Czech Republic | M + F living near lead smelter, 12-15 yrs | Cross-sectional | 195 | Comparison of urinary markers of tubular damage | BLL | (Means) Highest exposure group [girls, boys] 12.9, 14.9 µg/dL, non-exposed 8.4, 8.7 µg/dL | Urinary RBP (µg/g creatinine): highest exposure 117.8, non-exposed 73.8 ("significant difference") |

1 BLL- blood lead level
2 As calculated by Modification of Diet in Renal Disease Formula (MDRD)
3 BLB- body lead burden
4 Placebo versus chelation therapy
5 NAG- N-acetyl-β-D-glucosaminidase
6 EGF- epidermal growth factor
7 RBP- retinol binding protein, AAP- alanine aminopeptidase, A1M- alpha-1-microglobulin

# Detection of Kidney Toxicity

- Proteinuria
  - Tubular (ie, NAG, KIM, RBP, β-2 microglobulin)
  - Glomerular (ie, albumin)
- Decrease in kidney function (glomerular filtration rate [GFR])
  - Estimated GFR (eGFR)

# Markers of Kidney Function

GFR (mL/min/1.73 $m^2$) = **175** x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) (conventional units)

**MDRD**

GFR (mL/min/1.73 $m^2$) = k (Height) / Serum creatinine

- k = Constant
  - k = 0.33 in preemie infants
  - k = 0.45 in term infants to 1 year of age
  - k = 0.55 in children to 13 years of age
  - k = 0.70 in adolescent males (not females because of the presumed increase in male muscle mass, the constant remains .55 for females)
- Height in cm
- Serum creatinine in mg/dL

**Schwartz**

# Percentile Distribution of Creatinine, Cystatin C, and eGFR in Adolescents Aged 12-17 years, NHANES 99-02

| | 1st | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 99th |
|---|---|---|---|---|---|---|---|---|---|
| Serum Creatinine, mg/dL | 0.5 | 0.5 | 0.6 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 | 1.1 |
| Serum Cystatin C, mg/L | 0.57 | 0.65 | 0.68 | 0.75 | 0.83 | 0.91 | 1.01 | 1.06 | 1.21 |
| Bedside CKiD | 62.9 | 71.1 | 75.6 | 84.4 | 96.6 | 108.8 | 122.1 | 131.6 | 149.1 |
| Counahan et al. | 65.5 | 74.0 | 78.7 | 87.8 | 100.5 | 113.3 | 127.2 | 137.0 | 155.2 |
| Leger et al. | 77.6 | 87.7 | 94.4 | 105.8 | 122.2 | 139.2 | 156.9 | 170.7 | 195.7 |
| Schwartz et al. | 96.0 | 106.8 | 113.4 | 125.4 | 140.0 | 159.1 | 180.6 | 193.2 | 229.0 |
| Filler et al. | 74.0 | 85.8 | 90.6 | 101.9 | 112.9 | 126.6 | 141.3 | 148.6 | 172.2 |
| Grubb et al. | 62.3 | 80.6 | 90.7 | 106.3 | 130.1 | 157.1 | 189.1 | 208.4 | 261.7 |
| Bouvet et al. | 72.3 | 79.6 | 83.6 | 92.4 | 104.6 | 116.6 | 128.5 | 134.3 | 150.6 |
| CKiD | 72.9 | 79.5 | 84.1 | 89.5 | 96.6 | 105.6 | 115.1 | 121.3 | 131.6 |
| Zappitelli et al. | 69.0 | 74.8 | 78.5 | 87.2 | 97.6 | 110.0 | 119.1 | 126.8 | 140.2 |

*Arch Intern Med.* 2010;170(1):75-82

**Table 1. Blood Lead Levels and Estimated GFR by Participant Characteristics[a]**

| Characteristic | No. (%) of Participants[b] | Blood Lead Level, µg/dL | *P* Value[c] | Cystatin C–Estimated GFR, mL/min/1.73 m²[d] | *P* Value[c] | Creatinine-Estimated GFR, mL/min/1.73 m²[e] | *P* Value[c] |
|---|---|---|---|---|---|---|---|
| Total | 769 (100) | 1.5 (0.7-2.9) | . . . | 112.9 (99.4-126.6) | . . . | 108.8 (99.1-118.3) | . . . |
| Sex | | | | | | | |
| Male | 363 (50.4) | 2.2 (1.1-3.4) | <.001 | 105.8 (93.7-114.5) | <.001 | 114.2 (107.3-127.8) | <.001 |
| Female | 406 (49.6) | 1.1 (0.7-2.2) | | 119.4 (108.5-134.6) | | 102.4 (93.1-110.7) | |
| Age, y | | | | | | | |
| 12-15 | 354 (46.0) | 1.7 (0.7-3.0) | .71 | 108.5 (98.2-119.4) | .001 | 112.3 (102.3-123.3) | .03 |
| 16-20 | 415 (54.0) | 1.4 (0.7-2.0) | | 117.7 (104.4-132.5) | | 106.4 (96.5-114.0) | |
| Race/ethnicity | | | | | | | |
| Black | 262 (14.7) | 2.2 (1.3-3.2) | .003 | 121.1 (105.8-136.8) | <.001 | 103.3 (93.8-111.6) | <.001 |
| Mexican | 269 (8.6) | 2.2 (1.2-3.6) | | 117.7 (105.8-130.5) | | 112.8 (103.4-122.9) | |
| White | 199 (69.5) | 1.2 (0.7-2.8) | | 110.0 (98.2-121.1) | | 110.3 (100.8-119.6) | |
| Other | 39 (7.2) | 2.2 (1.1-3.0) | | 119.4 (108.5-126.6) | | 102.7 (86.8-117.5) | |
| Residence | | | | | | | |
| Urban | 341 (44.8) | 2.0 (0.7-3.1) | .19 | 111.4 (98.2-126.6) | .51 | 110.7 (99.6-122.0) | .90 |
| Rural | 428 (55.2) | 1.3 (0.7-2.7) | | 112.9 (101.9-128.5) | | 108.2 (98.8-115.8) | |
| Tobacco smoke exposure | | | | | | | |
| Undetectable | 77 (11.5) | 1.1 (0.7-2.5) | .01 | 112.9 (99.4-124.7) | .002 | 107.3 (99.1-117.0) | .33 |
| Involuntary | 591 (74.3) | 1.4 (0.7-2.9) | | 112.9 (100.6-128.5) | | 109.4 (99.3-119.6) | |
| Active | 101 (14.2) | 2.2 (1.2-3.8) | | 107.1 (91.6-119.4) | | 106.8 (96.8-119.6) | |
| Obese[f] | | | | | | | |
| No | 665 (90.6) | 1.5 (0.7-3.0) | .72 | 112.9 (99.4-126.6) | .07 | 110.7 (101.1-121.7) | .72 |
| Yes | 104 (9.4) | 1.6 (0.7-2.7) | | 107.1 (97.1-121.1) | | 111.4 (97.9-122.0) | |
| Annual household income, $ | | | | | | | |
| <20 000 | 395 (37.7) | 2.3 (1.1-4.1) | <.001 | 114.5 (100.6-128.5) | .08 | 109.7 (100.4-120.4) | .08 |
| ≥20 000 | 374 (62.3) | 1.2 (0.7-2.3) | | 111.4 (99.4-124.7) | | 108.4 (98.7-117.5) | |
| Educational level of family reference person | | | | | | | |
| <12th Grade | 323 (24.7) | 2.2 (1.1-4.0) | .008 | 114.5 (101.9-130.5) | .04 | 109.7 (102.0-123.0) | .15 |
| 12th Grade | 235 (32.6) | 1.4 (0.7-2.5) | | 112.9 (99.4-128.5) | | 110.0 (99.2-119.8) | |
| >12th Grade | 211 (42.6) | 1.5 (0.7-2.7) | | 111.4 (98.2-121.1) | | 107.3 (98.5-115.1) | |

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Jeffrey J. Fadrowski, MD, MHS; Ana Navas-Acien, MD, PhD; Maria Tellez-Plaza, MD, MPH; Eliseo Guallar, MD, DrPH; Virginia M. Weaver, MD, MPH; Susan L. Furth, MD, PhD

**Table 2. Mean Difference in Estimated GFR Associated With Blood Lead Levels[a]**

| Characteristic | Unadjusted | Model 1[b] | Model 2[c] | Model 3[d] |
|---|---|---|---|---|
| **Cystatin C Based[e]** | | | | |
| Lead level quartile, μg/dL | | | | |
| 1 (<1.0) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 2 (1.0-1.5) | −0.5 (−6.8 to 5.8) | −1.1 (−7.4 to 5.1) | −1.1 (−7.1 to 4.8) | −1.4 (−7.4 to 4.5) |
| 3 (1.6-2.9) | −5.8 (−11.6 to −0.1) | −4.1 (−9.5 to 1.2) | −2.7 (−7.7 to 2.4) | −2.6 (−7.3 to 2.2) |
| 4 (>2.9) | −8.8 (−15.7 to −2.0) | −6.6 (−12.7 to −0.5) | −5.2 (−11.3 to 0.9) | −6.6 (−12.6 to −0.7) |
| *P* value for trend | .003 | .01 | .03 | .009 |
| Per doubling of blood lead level, μg/dL[f] | −3.8 (−6.3 to −1.3) | −3.0 (−5.2 to −0.7) | −2.4 (−4.6 to −0.2) | −2.9 (−5.0 to −0.7) |
| **Creatinine Based[e]** | | | | |
| Lead level quartile, μg/dL | | | | |
| 1 (<1.0) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 2 (1.0-1.5) | −0.1 (−6.7 to 6.4) | −0.3 (−5.7 to 5.0) | −0.6 (−6.3 to 5.0) | −0.5 (−6.1 to 5.1) |
| 3 (1.6-2.9) | 2.4 (−2.2 to 7.1) | −1.4 (−6.7 to 3.9) | −1.7 (−6.5 to 3.1) | −1.7 (−6.9 to 3.5) |
| 4 (>2.9) | 3.8 (−2.4 to 9.9) | −0.4 (−6.0 to 5.2) | −0.8 (−6.2 to 4.7) | −1.9 (−7.4 to 3.5) |
| *P* value for trend | .16 | .70 | .59 | .31 |
| Per doubling of blood lead level, μg/dL[f] | 1.4 (−0.6 to 3.3) | −0.4 (−2.3 to 1.6) | −0.5 (−2.4 to 1.4) | −1.0 (−2.8 to 0.9) |

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.

SI conversion factor: To convert blood lead level to micromoles per liter, multiply by 0.0483.

[a] N=769 for all models. Data are given as the difference in estimated GFR (in milliliters per minute per 1.73 $m^2$) compared with the reference category (95% CI) unless otherwise indicated.

[b] Model 1 is adjusted for age, sex, and race/ethnicity.

[c] Model 2 is adjusted for age, sex, race/ethnicity, urban vs rural residence, and tobacco smoke exposure.

[d] Model 3 is adjusted for age, sex, race/ethnicity, urban vs rural residence, tobacco smoke exposure, obesity, annual household income, and educational level of the family reference person.

[e] Cystatin C–estimated GFR was calculated using the Filler and Lepage equation[27] and creatinine-estimated GFR using the Schwartz et al equation.[41,42]

[f] Mean difference in estimated GFR associated with a doubling of the blood lead level (ie, 1-2 or 2-4 μg/dL).

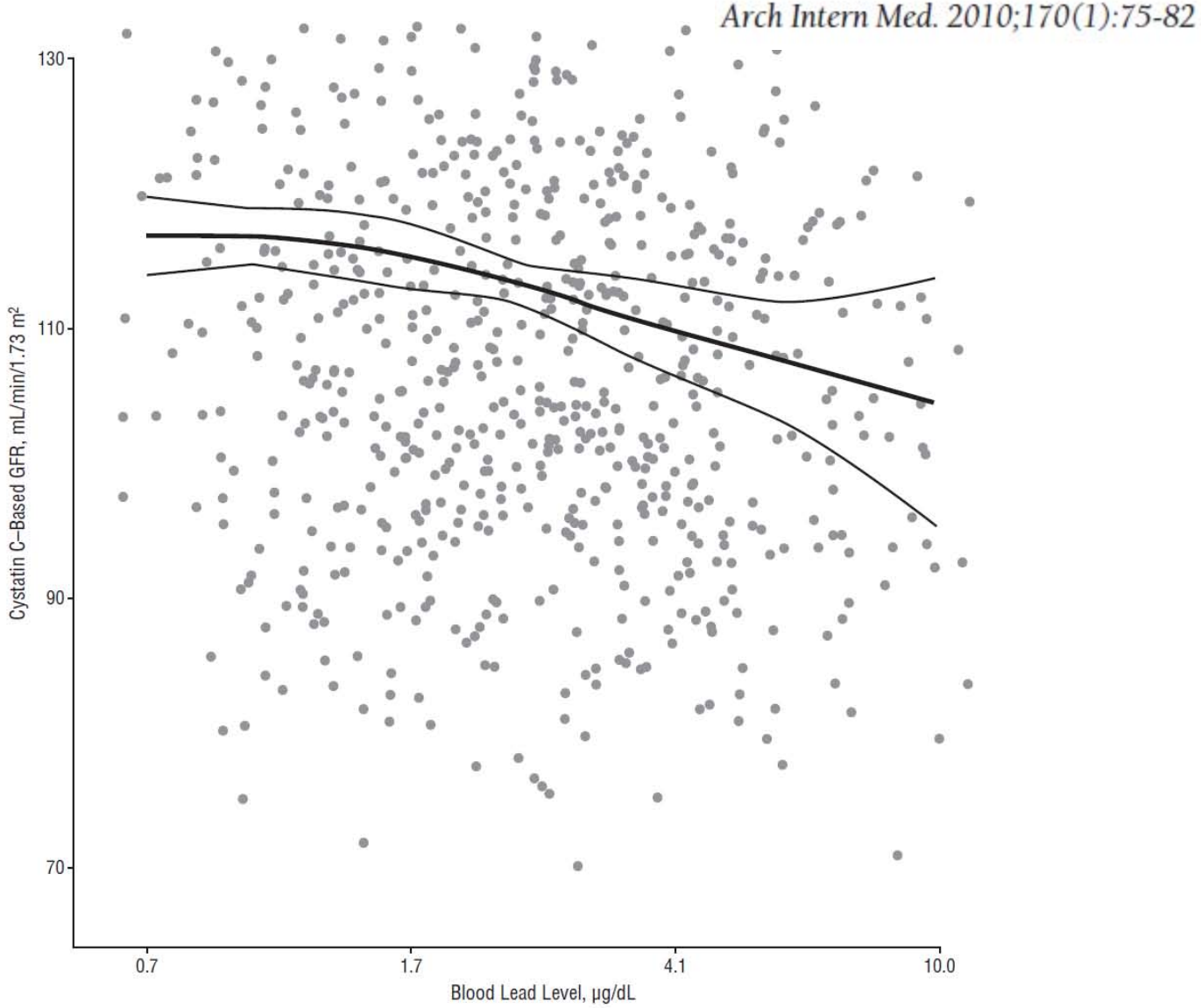



**Figure.** Cystatin C–estimated glomerular filtration rate (GFR) by blood lead levels. The thick line represents estimated GFR based on restricted quadratic splines transformation for log-transformed blood lead levels (restricted to ≤10 µg/dL [to convert to micromoles per liter, multiply by 0.0483]) with knots at the 10th, 50th, and 90th percentiles. Thin lines represent corresponding 95% confidence intervals. Data points for the scatterplot represent adjusted blood lead and estimated GFR values and were calculated as the residuals from the weighted linear regression models of log-lead and estimated GFR on the covariates used in model 3 in Table 2. Mean log-lead and estimated GFR levels were added to the residuals to facilitate interpretation of the scatterplot. The horizontal axis is in log scale.

# 'Cuida tu corazon' Study
# PI: Eliseo Guallar, JHSPH

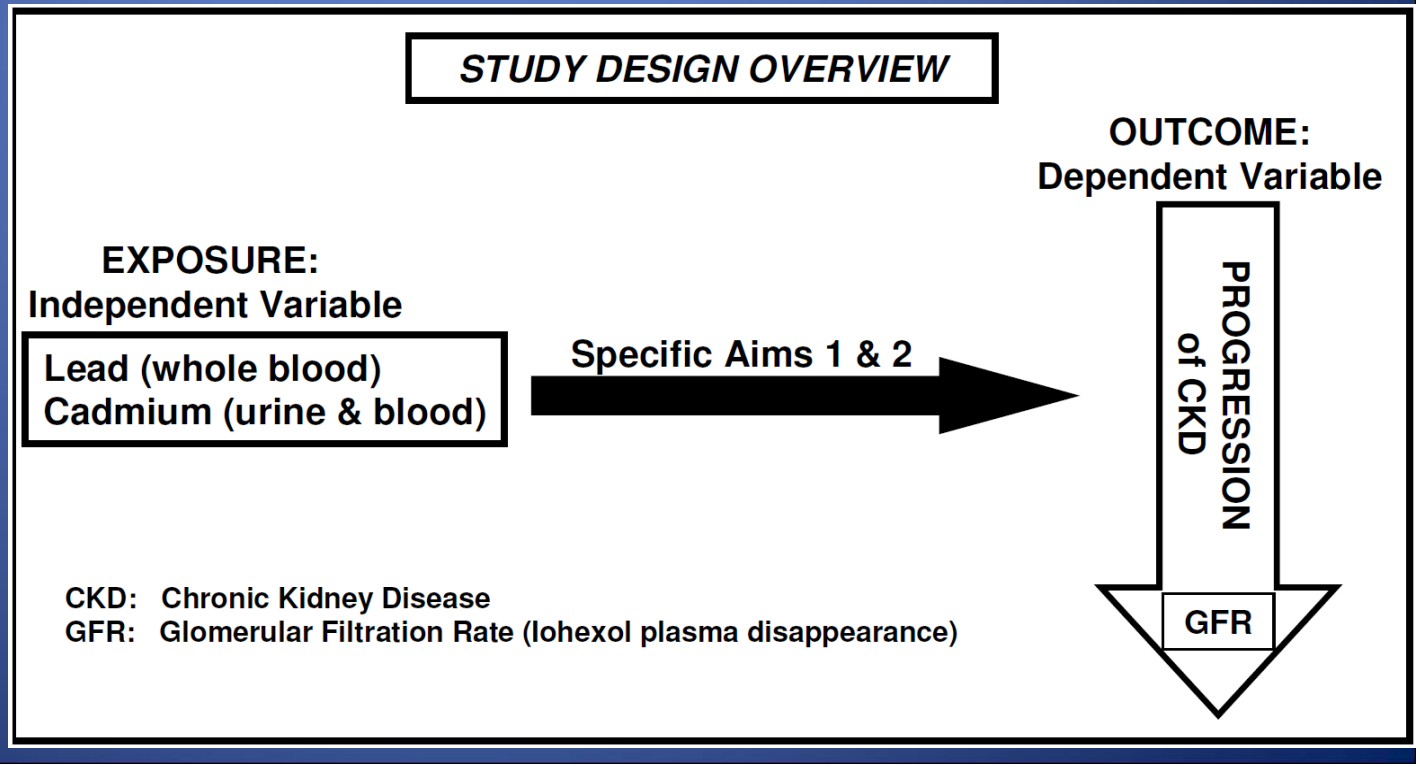
- **DESIGN: Cross-sectional study to evaluate the association between exposure to metals and cardiovascular function tests**
- **STUDY POPULATION: 512 male and female adolescents (14-16 year of age) residents in the city of Torreon, Mexico (home to the largest lead smelter in the Americas)**
- **EXPOSURES:**
  - **Blood lead levels**
  - **Urine levels of arsenic, cadmium, molybdenium, antimony, thallium, tungsten, and uranium**
- **OUTCOMES**
  - **Blood pressure**
  - **Heart rate variability**
  - **Continuous performance test**
  - ***Kidney function and injury markers***
  - **Cytokines and markers of endothelial function**
  - **Glucose metabolism parameters**

# 'Cuida tu corazon' Study – Preliminary findings (N=512)

- **Blood lead (median; 5th – 95th percentiles): 4.0 (1.7 – 9.8) µg/dl**
- **Kidney function and damage markers (median; 5th – 95th percentiles):**
  - **Serum cystatin C: 0.76 (0.61 - 1.0) mg/L**
  - **Serum creatinine: 0.58 (0.45- 0.82) mg/dL**
  - **Urine NAG: 220.5 (101.2 - 647.3) µmol/h/g creatinine**
- **Association between blood lead and kidney function and damage markers, per 2x increase in blood lead levels (95% CI), adjusted for age, sex, and body mass index:**
  - **Serum cystatin C: 0.02 mg/L (0.01 to 0.03)**
  - **Serum creatinine: -0.01 mg/dL (-0.02 to 0.002)**
  - **Urine NAG (log-transformed): 0.03 log(µmol/h/g creat) (0.0002 to 0.06)**

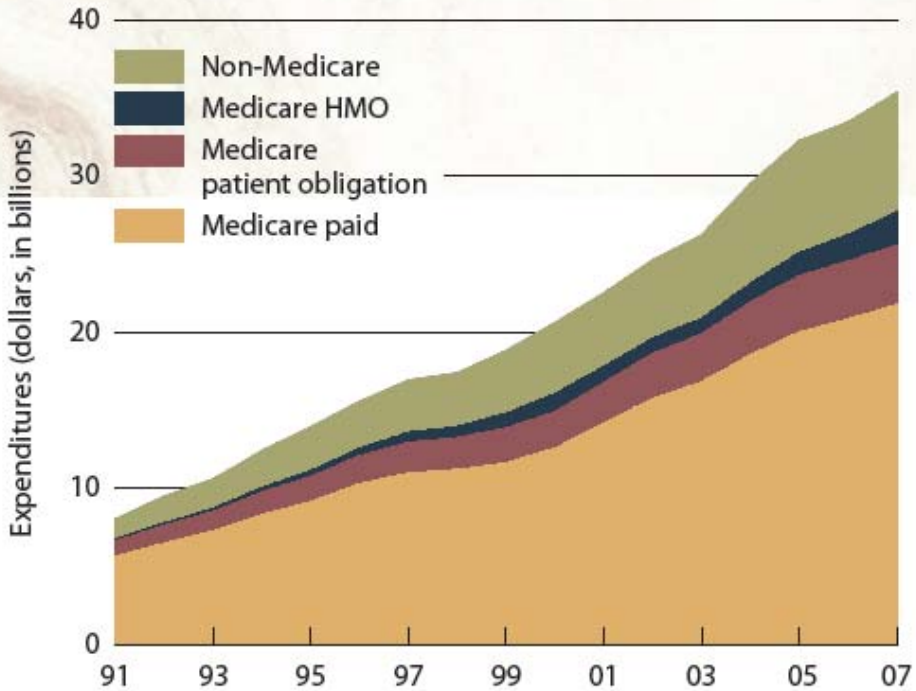
# CKiD

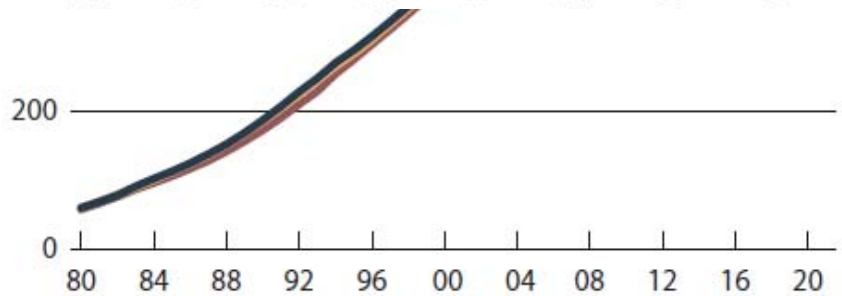
## Chronic Kidney Disease in Children



## [2]1ii Projected counts of incident & prevalent ESRD patients through 2020

## [11]1ii ESRD spending, by payor



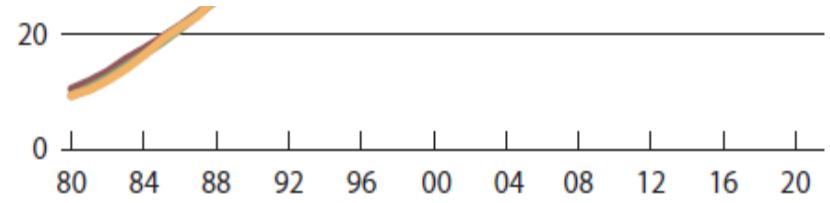

## [2]2ii Projected number of ESRD patient deaths through 2020

s Aged 20 Years or Older Based on NHANES 1988-1994 and

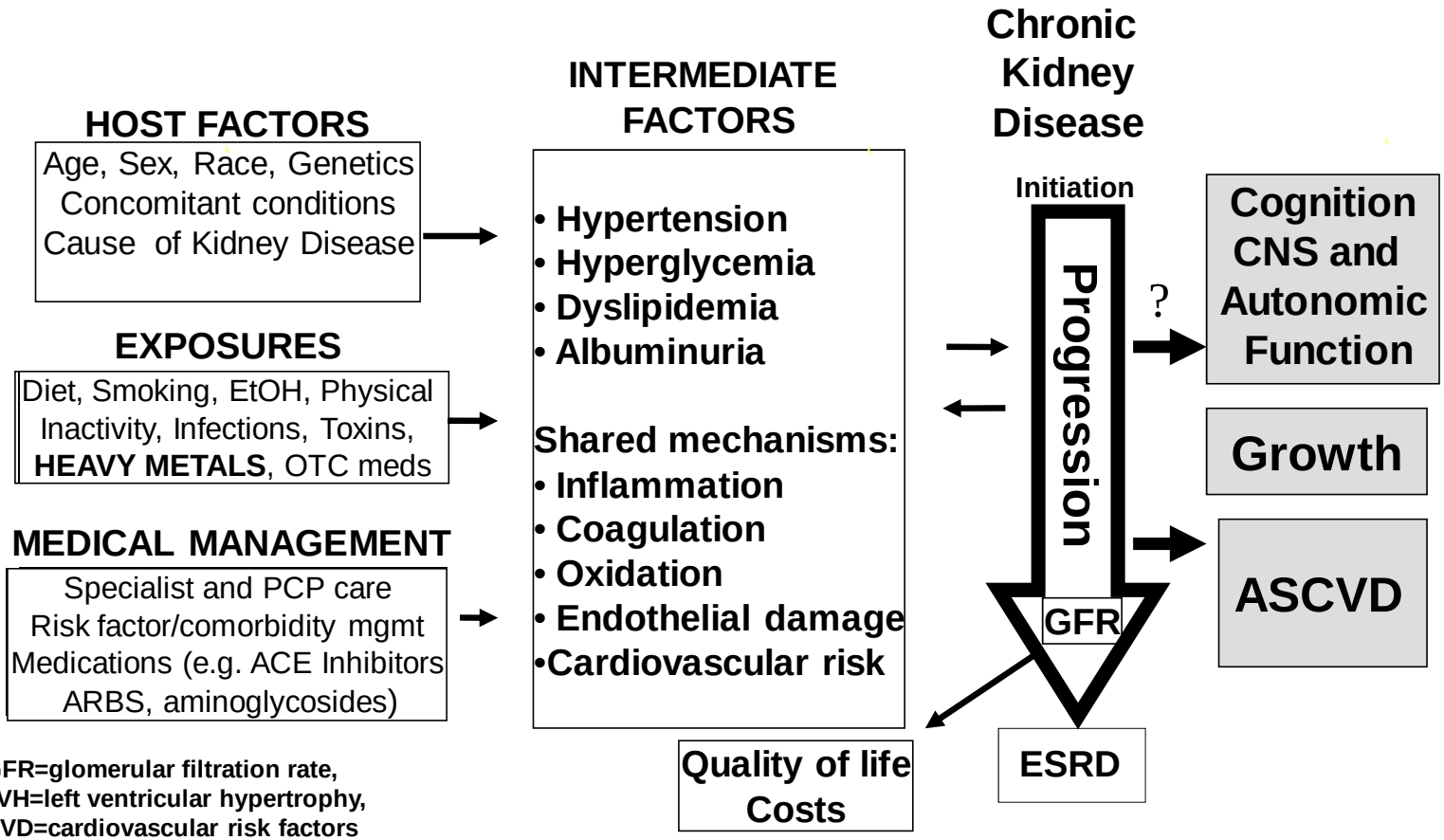
JAMA, November 7, 2007—Vol 298, No. 17

| | Prevalence Ratio for NHANES 1999-2004 to 1988-1994 (95% CI) | Estimated No. of US Adults in 2000, No. in Millions (95% CI) |
|---|---|---|
| | 1.05 (0.85-1.30) | 3.6 (2.7-4.5) |
| | 1.21 (1.03-1.41) | 6.5 (5.2-7.8) |
| | 1.42 (1.25-1.62) | 15.5 (14.1-16.8) |
| | 1.70 (1.11-2.51) | 0.7 (0.5-0.9) |
| | NA | NA |
| | 1.30 (1.19-1.43) | 26.3 (24.2-28.3) |

age 5 were excluded; NHANES, National Health and Nutrition Examination Surveys.
on rate (GFR) higher than 90 mL/min/1.73 m²; stage 2, persistent albuminuria with GFR
5 to 29 mL/min/1.73 m². The age-adjusted prevalence rates for CKD stages 1, 2, 3, and
.6%, and 0.2%, respectively, for a total of 10.3%.



# Progression of CKD




GFR=glomerular filtration rate,
LVH=left ventricular hypertrophy,
CVD=cardiovascular risk factors
ASCVD= atherosclerotic cardiovascular disease
OTC =over the counter meds (e.g. ibuprofen), PCP=primary care provider