Environmental Components of Racial Disparities in CKD

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Potential Conflicts of Interest*

*Activities within the last year

Grants: 1
Honoraria: 2
Consulting: 3
Advisory Boards: 4
Speaker Bureau: 5
Financial Ownership: 6
Integrative framework of psychosocial and environmental concepts

Traditional Cardio-Renal Risk Factors

Environmental Exposures

Psychological Stresses

Increased Oxidative Stress & Inflammation

Accelerated CKD & CVD
Premature Morbidity & Mortality
Glutathione (GSH) is known as the “master” antioxidant and is composed of L-cysteine, L-glutamic acid and glycine

**Increased** oxidative stress accelerates cellular apoptosis (cell death) & other maladaptive downstream cellular activities

GSH/GSSG redox and Cys/CySS redox states can be used as quantitative measures of oxidative stress and used as predictive markers of health

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Jones DP. Rejuvenation Research 9;2:169-181, 2006
Jones DP, Go YM, Anderson CL, Ziegler TR, Kinkade 1M Jr, Kirlin WG. Cysteine/ cystine couple is a newly recognized node in the circuitry for biologic redox signaling and control. FASEB J 2004;18:1246-1248
Community and Individual Stresses
What is

Grounded in the present moment

What was or what we want to be

Thoughts of past and projection to future

(What is) – (What was or what we want to be) = level of Stress/Distress or Lack of Ease/Dis-Ease

Neurohormoal activation/Allostatic load/Maladapative behaviors

Premature Morbidity and Mortality (Dis-Ease)
Impact of Psychological Stress on Oxidative Stress – Telomerase Activity, and Telomere Length (determinants of cell senescence and longevity)

Telomere: a region of repetitive DNA that protects the end of the chromosome from deterioration.

Environmental Exposures
EPA finds toxic agent in air at 15 schools - USA TODAY, Oct 1, 2009

Outside 15 schools in eight states, the Environmental Protection Agency has found elevated levels of acrolein, a substance that — in a more potent form — was also used as a chemical weapon during World War I.
## Varying exposures related to CKD

<table>
<thead>
<tr>
<th>Generally Non-specific</th>
<th>Generally Geographically-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cigarette Smoking</strong></td>
<td><strong>Occupational/Environmental Exposures</strong></td>
</tr>
<tr>
<td><strong>Substance Abuse</strong></td>
<td>• Metals:</td>
</tr>
<tr>
<td></td>
<td>• lead, cadmium, mercury, boron</td>
</tr>
<tr>
<td>• cocaine</td>
<td>• Organic Compounds</td>
</tr>
<tr>
<td>• heroin</td>
<td>• silica</td>
</tr>
<tr>
<td>• methamphetamine</td>
<td>• industrial and organic solvents</td>
</tr>
<tr>
<td>• ecstasy</td>
<td><strong>Pollutants</strong></td>
</tr>
<tr>
<td></td>
<td>• toxic waste/trash dumps</td>
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<td></td>
<td>• heavy industrial transportation routes/diesel particles</td>
</tr>
<tr>
<td></td>
<td>• fine particulate matter</td>
</tr>
<tr>
<td></td>
<td>• persistent organic pollutants</td>
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<tr>
<td></td>
<td>e.g. polycyclic aromatic hydrocarbons (PAH)</td>
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<td></td>
<td>dioxins, and nitrogen oxides</td>
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</tbody>
</table>

Adjusted Risks for Mild Kidney Function Decline in Drug Users Compared with Non–Drug Users Among 647 Hypertensive Men

<table>
<thead>
<tr>
<th>Substance-abusing substance</th>
<th>Age- and Race-Adjusted RR (95% CI)*</th>
<th>Multivariate-Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>2.12 (1.07-4.22)†</td>
<td>2.29 (1.04-5.06)†</td>
</tr>
<tr>
<td>Marijuana</td>
<td>1.89 (0.93-3.82)</td>
<td>1.96 (0.87-4.40)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>1.54 (0.36-6.54)</td>
<td>1.89 (0.41-8.68)</td>
</tr>
<tr>
<td>Cocaine or crack</td>
<td>2.68 (1.10-6.49)†</td>
<td>2.99 (1.12-8.04)†</td>
</tr>
<tr>
<td>Heroin</td>
<td>3.11 (0.93-10.33)</td>
<td>3.04 (0.83-11.07)</td>
</tr>
<tr>
<td>Psychedelics</td>
<td>3.41 (1.21-9.63)†</td>
<td>3.92 (1.06-14.42)†</td>
</tr>
<tr>
<td>Other</td>
<td>4.08 (0.55-30.33)</td>
<td>4.59 (0.54-39.09)</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; CI, confidence interval.
*Adjusted for age, race, education, annual income, smoking, alcohol consumption, systolic blood pressure, BMI, history of diabetes and dyslipidemia, antihypertensive medication use, and ACE-inhibitor use.  †P < 0.05.


Substance abusers are 2-4 times more likely to have CKD
Overview of Select Potential Mechanisms for Environmental-Induced Renal Damage

*smoking, lead/mercury exposures, persistent organic pollutants such as polycyclic aromatic hydrocarbons [PAH] and dioxins, nitrogen oxides, and small particulate matter

AChR, acetylcholine receptor; CKD, chronic kidney disease; EC, extracellular.

Biomarkers, Inflammation & outdoor air pollutants

Increased pollutants – increased expression of inflammatory biomarkers

Increased pollutants – reduced antioxidants: glutathione peroxidase-1 (GPx-1) and copper-zinc superoxide dismutase

SUMMARY
Summary

• Environmental (psychological and physical) factors can affect the kidney
• Each influences the initiation and/or the progression of CKD (& CKD complications)
• They may act directly or through oxidative and inflammatory pathways
Framework for Environmental Hazards and CKD

**Traditional CKD Risk Factors & Initiation of CKD**
(e.g.: Diabetes, HTN, Vascular Disease)

- Smoking and substance abuse; occupational/environmental exposures, organic compounds, industrial and organic solvents and pollutants, psychological stresses.

**Established CKD**

**Adverse Environmental Exposures* (-)**

**Pharmacologic & Non Pharmacologic Therapy (+)**

**CKD Complications**
(e.g.: End-Stage Renal Disease, Premature Mortality)

* Smoking and substance abuse; occupational/environmental exposures, organic compounds, industrial and organic solvents and pollutants, psychological stresses.

Adapted from Conner R, Norris K. Smoking, substance abuse, and environmental hazards. In Daugirdas JT editor Handbook of Chronic Kidney Disease (stage 1-4) management, in press.
Conclusion
Conclusion

• In an era of increasing rates of critical CKD risk factors such as hypertension, diabetes and other chronic disorders, the coexistence of environmental exposures can play an important role in initiating and/or modifying the progression of CKD (& CKD complications), such as refractoriness to evidence-based therapies and accelerated CVD.
Conclusion cont.

• Low socioeconomic status (and often race) is a risk factor for both environmental exposures and diseases that increase CKD susceptibility.

• Key environmental exposures include:
  – smoking and substance abuse
  – occupational heavy metal exposures such as lead, cadmium, mercury or lead-based paint in houses
  – heavy industrial traffic patterns which produce persistent organic pollutants
Conclusion cont.

• Understanding such exposures is important as part of a history for a patient with CKD, particularly when the etiology is unclear or the disease is progressing despite evidenced-based therapy.

• Such insights can help refine the diagnosis, modify patient management, and inform local public health prevention messages and policy action plans such as advancing social justice.
"The greatest obstacle to discovery is not ignorance – it is the illusion of knowledge.

-Daniel Boorstin
Conceptual Framework: Traditional Cardio-Renal and Emerging Risk Factors are Linked to Adverse Outcomes Via Oxidative Stress


VSMC, vascular smooth muscle cell; MMP, matrix metalloproteinase; ROS, reactive oxygen species.
Theoretical Model of Energies of Consciousness and Impact on Health

Two Main Energies of Consciousness (Spiritual & Ego)

- Spiritual awareness >>> Ego based conditioned thought
- Ego based conditioned thought >>> Spiritual awareness

Grounded in the present moment

- Awareness of life and the relevance/role of thought. Minimal psychological and emotional conflict.
- Minimum stress and optimum physiological functioning. Developing societal systems that are holistic.

What is

- Reduced self-awareness and sense of compassion for others/life. Increased psychological & emotional conflict.
- Exaggerated stress & physiologic stress response. Compensatory lifestyle habits – e.g., eating disorders, substance abuse.

- Increased cardio-metabolic, vascular and renal disease; accelerated aging.

OPTIMUM HEALTH

What was or what we want to be

- Premature morbidity & mortality

Norris KC. The Role of Spirituality in the Continuum of Health and Disease: Implications for improving health outcomes at an individual and community level. Dissertation.
Additional References

Racial Disparities in CKD: Biology & Environment

Extracellular Cys/CySS signals cell proliferation and increased expression of cell adhesion molecules without measurable effects on cellular thiol/disulfide systems. Keap-1 is activated by changes in GSH, not TrxI. TrxI stimulates Nrf-2/ARE reporter expression, and oxidation of TrxI results in activation of ASK-1, without effects on GSH/GSSG redox. Thus, discrete redox circuits exist for redox signaling and control, and disruption of these circuits provides a mechanism for oxidative stress that does not depend on changes in the oxidant/prooxidant balance.
Relationships of biomarkers of inflammation to outdoor air pollutants

Increased Outdoor Air Pollutants & Diminished Antioxidant Response –

Increased pollutants – reduced antioxidants: glutathione peroxidase-1 (GPx-1) and copper-zinc superoxide dismutase

Relationship of Cu,Zn-SOD to outdoor and indoor air pollutants (adjusted coefficient and 95% CI).
(A) Outdoor air pollutants. (B) Indoor air pollutants