24. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006;6:40–57.
25. Coresh J, Selvin E, Stevens LA *et al*. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038–47.
26. Schwartz GG, Il'yasova D, Ivanova A. Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. *Diabetes Care* 2003;26:468–70.
27. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA* 2008;300:814–22.
28. Minoia C, Sabbioni E, Apostoli P *et al*. Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ* 1990;95:89–105.
29. Kristiansen J, Christensen JM, Iversen BS, Sabbioni E. Toxic trace element reference levels in blood and urine: influence of gender and lifestyle factors. *Sci Total Environ* 1997;204: 147–60.
30. Merzenich H, Hartwig A, Ahrens W *et al*. Biomonitoring on carcinogenic metals and oxidative DNA damage in a cross-sectional study. *Cancer Epidemiol Biomarkers Prev* 2001;10:515–22.
31. Smith-Sivertsen T, Tchachtchine V, Lund E, Bykov V, Thomassen Y, Norseth T. Urinary nickel excretion in populations living in the proximity of two Russian nickel refineries: a Norwegian-Russian population-based study. *Environ Health Perspect* 1998;106:503–11.
32. Ohashi F, Fukui Y, Takada S, Moriguchi J, Ezaki T, Ikeda M. Reference values for cobalt, copper, manganese, and nickel in urine among women of the general population in Japan. *Int Arch Occup Environ Health* 2006;80:117–26.
33. Komaromy-Hiller G, Ash KO, Costa R, Howerton K. Comparison of representative ranges based on U.S. patient population and literature reference intervals for urinary trace elements. *Clin Chim Acta* 2000;296:71–90.
34. Kiilunen M, Jarvisalo J, Makitie O, Aitio A. Analysis, storage stability and reference values for urinary chromium and nickel. *Int Arch Occup Environ Health* 1987;59:43–50.
35. Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Toxicological Profile for Nickel. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
36. Clayton GD, Clayton FE, Patty FA. *Patty's Industrial Hygiene and Toxicology*. Vol. 2, pt.D. Toxicology. 4th edn. New York: Wiley, 1994.
37. Mertz W (ed). *Trace Elements in Human and Animal Nutrition*. 5th edn. Orlando, FL: Academic Press, 1986.
38. Kazi TG, Afridi HI, Kazi N *et al*. Copper, chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients. *Biol Trace Elem Res* 2008;122:1–18.
39. Forte G, Bocca B, Peruzzu A *et al*. Blood metals concentration in type 1 and type 2 diabetics. *Biol Trace Elem Res* 2013;156:79–90.
40. Gil F, Hernandez AF, Marquez C *et al*. Biomonitorization of cadmium, chromium, manganese, nickel and lead in whole blood, urine, axillary hair and saliva in an occupationally exposed population. *Sci Total Environ* 2011;409:1172–80.
41. Sunderman FW Jr. Biological monitoring of nickel in humans. *Scand J Work Environ Health* 1993;19(Suppl 1):34–38.
42. Horak E, Sunderman FW Jr. Effects of Ni(II) upon plasma glucagon and glucose in rats. *Toxicol Appl Pharmacol* 1975;33:388–91.
43. Das KK, Das SN, DasGupta S. The influence of ascorbic acid on nickel-induced hepatic lipid peroxidation in rats. *J Basic Clin Physiol Pharmacol* 2001;12:187–95.
44. Gupta S, Ahmad N, Husain MM, Srivastava RC. Involvement of nitric oxide in nickel-induced hyperglycemia in rats. *Nitric Oxide* 2000;4:129–38.
45. Calderon RL, Hudgens E, Le XC, Schreinemachers D, Thomas DJ. Excretion of arsenic in urine as a function of exposure to arsenic in drinking water. *Environ Health Perspect* 1999;107 663–67.
46. Rivera-Nunez Z, Meliker JR, Linder AM, Nriagu JO. Reliability of spot urine samples in assessing arsenic exposure. *Int J Hyg Environ Health* 2010;213:259–64.

International Journal of Epidemiology, 2015, 248–250
doi: 10.1093/ije/dyv004

Commentary: Environmental chemicals and diabetes: which ones are we missing?

Chin-Chi Kuo[1,2,3,4] and Ana Navas-Acien[1,2,3]*

[1]Department of Epidemiology, and [2]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [3]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD, USA and [4]Kidney Institute and Division of Nephrology, Department of Internal Medicine, China Medical University Hospital and College of Medicine, Taichung, Taiwan

*Corresponding author: 615 N Wolfe Street, Room W7513D, Baltimore, MD 21205. E-mail: anavas@jhu.edu

The ever-increasing global epidemic of type 2 diabetes has overwhelmed the capacity of healthcare systems and economies in both developing and developed countries.[1] Economic development, rapid industrialization and social re-organization may play a critical role in driving the diabetes epidemic, possibly due to discordant gene-environment interactions.[1,2] The evolution discordance induced by rapid environment modifications is most acknowledged in nutrition transition to ubiquitous refined and processed foods, and in physical activity transition to sedentary lifestyle — especially screen watching and driving.[1,2] Compared with diet and physical activity, the impact of environmental chemicals on diabetes development has been grossly under-researched and their effects possibly underestimated. By the end of the 20th century, however, growing epidemiological and mechanistic evidence had started to link environmental chemicals (both synthetic and naturally occurring) to type 2 diabetes and obesity.[3,4]

In 2011, the U.S. National Toxicological Program at the National Institute of Environmental Health Sciences in the USA organized a workshop to systematically review the epidemiological and experimental evidence on the relationship of environmental chemicals with obesity, diabetes and the metabolic syndrome for a wide variety of chemicals including metals (arsenic), persistent organic pollutants, phthalates, bisphenol A, non-persistent pesticides and air pollution.[4] Although the evidence has been updated in recent reviews, it is far from establishing causality. A major limitation is that most available studies are cross-sectional, except for arsenic, hexachlorobenzene (HCB) and total polychlorinated biphenyls (PCBs) for which increasing prospective evidence is generally consistent with an increased risk of type 2 diabetes.[3]

Among toxic metals associated with the risk of diabetes, arsenic, a metalloid, has received special attention for more than two decades since the publication in 1994 of a cross-sectional study in the historically high-arsenic area of south-western Taiwan.[5] The research focus has since then expanded from high to low-moderate arsenic exposures and from occupational populations to general populations, with increasing evidence supporting the diabetogenic effects of arsenic even at exposure levels below the World Health Organization standard of 10 ppb in drinking water. However, the debate on the causality of the observed associations between arsenic and diabetes remains unresolved, mainly because of limited quality assessment of arsenic and diabetes outcomes and still relatively limited prospective data.[3,4]

For other metals, the evidence is scarce. A handful of studies are available for mercury, with inconsistent evidence, and for cadmium, with evidence generally supporting no association.[3] In this issue of the *International Journal of Epidemiology*, Liu *et al*. report a cross-sectional association between nickel exposure, as measured in urine, with the prevalence of diabetes in a representative sample of adults aged 50 to 70 years from two main cities in China, Beijing and Shanghai.[6] This is the first study formally evaluating the hypothesis of an association between nickel exposure and the risk of diabetes, and the results could represent a novel finding. However, we must exert great caution in interpreting the findings of this single study, especially given important limitations, namely the cross-sectional design. Reverse causation is an inherent limitation in cross-sectional studies, especially when the exposure is based on urine analysis and the disease outcome is potentially associated with kidney injury ranging from glomerular hyperfiltration to impaired glomerular filtration. The possibility of reverse causality in the exposure-outcome relationship poses a serious challenge for researchers investigating the association between diabetes and urinary chemicals. For example, in Liu *et al*.'s study, it would be important to report the association between estimated glomerular filtration rate (eGFR) and urine nickel concentrations and whether the eGFR is comparable between participants with and without diabetes. This information, however, was not reported. In general, for diseases that could affect kidney function, prospective evidence is particularly important when exposure assessment is based on urine biomarkers.

Another challenge is how to deal with multiple toxic metals, or by extension with multiple environmental chemicals, that are potentially diabetogenic. Liu *et al*. mentioned that urine arsenic and cadmium levels were adjusted for in sensitivity analyses yielding consistent results.[6] However, effect modification by arsenic or cadmium exposure was not approached systematically, including the evaluation of additive or multiplicative effects. It would have been useful to report the association of arsenic and cadmium with prevalent diabetes in this population, since the information was available and given the need to assess multi-exposure. Residual confounding is an inherent threat to the validity of any observational study. For instance, higher nickel exposure may be attributable to higher particulate air pollution, which has also been linked to the development of diabetes, as nickel concentrations and particulate matter exposure can be correlated.[7,8] Other sources of nickel exposure include electronic devices such as laptops and cellphones.[9] Clarifying the main source of nickel exposure in the general population would be critical to control residual confounding and perform bias estimation.

Unlike arsenic, where the evidence at high levels of exposure is generally consistent, no information is available on a link between nickel exposure and type 2 diabetes in

occupational populations or in highly exposed general populations. Targeting prospective research studies in occupationally exposed populations in industries such as mining, alloy manufacturing and production of nickel-based batteries may be a practical and cost-effective approach. Overall, well-designed prospective studies are warranted to evaluate the joint effect between nickel and other nutrients and toxicants and its impact on the risk of diabetes. It is also fundamental to estimate the repeatability of urine nickel measurements collected over time to justify the use of single urine nickel measurements, as the half-life of nickel in urine is relatively short. As multi-element analytical methods have become standard in metal assessment, developing statistical methods to deal with multi-exposures is critical.

With the publication of the study by Liu *et al.*,[6] nickel appears as a potential new chemical that was missing in our list of environmental chemicals that may be related to diabetes. At this point, the limited evidence available is insufficient to evaluate this relationship. In one ecological study, nickel concentration in the air was associated with diabetes mortality.[10] In two case-control studies, on the other hand, serum nickel levels were similar between participants with and without diabetes.[11,12] The study by Liu *et al.*, however, highlights the possibility that a number of diabetes-related environmental chemicals might have been overlooked. With hundreds of new chemicals released every year, and studies that tend to focus on the same chemicals, it is important to acknowledge that new approaches are needed that can identify a larger number of environmental chemicals simultaneously while appropriately preserving quality in exposure assessment and control of bias, in particular confounding. Identifying environmental hazards for chronic disease such as diabetes is an urgent need as modernization contributes to rapid changes in environmental exposures. Environmental chemicals could also challenge the dynamic interplay with genetic, nutritional and physical activity factors and alter public health risk to chronic diseases, especially in countries with rapid socio-economic growth and urbanization, such as China and India.[1]

Funding

A.N-A. is supported by the National Institute of Environmental Health Sciences [R01ES021367].

Conflict of interest: None declared.

References

1. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care* 2011;34:1249–57.
2. Cordain L, Eaton SB, Sebastian A *et al*. Origins and evolution of the Western diet: health implications for the 21st century. *The Am J Clin Nutr* 2005;81:341–54.
3. Kuo CC, Moon K, Thayer KA, Navas-Acien A. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Curr Diab Rep* 2013;13:831–49.
4. Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environ Health Perspect* 2012;120:779–89.
5. Lai MS, Hsueh YM, Chen CJ *et al*. Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am J Epidemiol* 1994;139:484–92.
6. Liu G, Sun L, Pan A *et al*. Nickel exposure is associated with the prevalence of type 2 diabetes in Chinese adults. *International Journal of Epidemiology* 2015;44:238–46.
7. Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. *Diabetes* 2012;61:3037–45.
8. Park SK, Wang W. Ambient Air Pollution and Type 2 Diabetes: A Systematic Review of Epidemiologic Research. *Curr Environ Health Rep* 2014;1:275–86.
9. Aquino M, Mucci T, Chong M, Lorton MD, Fonacier L. Mobile Phones: Potential Sources of Nickel and Cobalt Exposure for Metal Allergic Patients. *Pediatric Allergy, Pediatr Allergy Immunol Pulmonol* 2013;26:181–6.
10. Spangler JG. Diabetes mortality and environmental heavy metals in North Carolina counties: An ecological study. *J Diab Mellit* 2012;2:369–272.
11. Yarat A, Nokay S, Ipbuker A, Emekli N. Serum nickel levels of diabetic patients and healthy controls by AAS with a graphite furnace. *Biol Trace Elem Res* 1992;35:273–80.
12. Kazi TG, Afridi HI, Kazi N *et al*. Copper, chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients. *Biol Trace Elem Res* 2008;122:1–18.