

Transgenerational inheritance of environmental obesogens

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Nowadays, dichlorodiphenyl-dichloroethylene (DDE), the main degradation product of the pesticide dichlorodiphenyl trichloroethane (DDT), is detected in all adults and in nearly all newborns in most countries worldwide.¹⁻⁴ Thus, even a small increase in the risk of obesity that DDE might confer on offspring would have important implications.^{5,6} This is the main finding that Karmaus *et al* (see page 143) report in this issue: the weight and BMI of offspring in adulthood were significantly related to the extrapolated prenatal DDE levels of their mothers.⁷ Specifically, compared to maternal DDE levels below 1.5 µg/l, the authors observed an increase in offspring BMI of 1.65 when prenatal DDE was 1.5–2.9 µg/l, and an increase of 2.88 if DDE was greater than 2.9 µg/l. These concentrations of DDE are common worldwide; in cord blood, amniotic fluid and serum of pregnant women, DDE is often in the range 0.6–1.9 µg/l or 15–500 ng/g.^{1,4,8,9}

It is often overlooked that human concentrations of DDE can vary more than a 1000-fold within the same population¹; in the United States, for example, concentrations range from less than 5 ng/g to over 15 000 ng/g.¹⁰ Traditional thinking suggests that only the descendants of the minority of individuals with higher concentrations of DDE or other organochlorine compounds have a higher risk of overweight and obesity. However, increased risks of obesity have also been seen at very low and usual doses of some organochlorine compounds.¹¹

The association that Karmaus *et al* observed between BMI and DDE was not seen with PCBs; the coefficient of 2.29 for PCBs was not statistically significant (see their table 4).⁷ Because the authors “used the Aroclor 1260 standard

to determine PCBs”, the relative role of specific PCB congeners could not be assessed. Although methods for chemical analyses were fine at the time of the study, the limits of detection are rather far from today’s standards. Specifically, the limit of detection was 3 µg/l for Aroclor 1260 and 1 µg/l for DDE, while today a good laboratory will have limits of detection of 0.015–0.003 µg/l or lower.

The Michigan study is relevant for several additional reasons:

- ▶ first, experimental studies are raising concern about “environmental obesogens”,^{12,13}
- ▶ second, heritable environmentally induced epigenetic modifications are a plausible link between non-mutagenic environmental exposures early in development and reversible transgenerational alterations in gene expression that lead to adult disease phenotypes,^{14,15}
- ▶ third, the vast majority of humans acquire persistent organic pollutants (POPs) from their mothers during pregnancy and lactation, and subsequently from fatty foods, following culturally-inherited familial dietary patterns,¹⁵
- ▶ fourth, in many populations there is a positive association between POP levels and BMI,^{1,16} and
- ▶ fifth, strong associations—although mostly cross-sectional—have been reported between POP level and diabetes.^{6,16}

Therefore, when assessing the biological, clinical and social mechanisms linking diet, fat intake, obesity and diabetes, POPs should also be considered.⁶ A better understanding of how these factors interact will be important for the primary prevention of obesity and to improve knowledge of obesogenic mechanisms.

As a possible mechanism, Karmaus *et al* mainly discuss the oestrogenic and anti-androgenic effects of DDE. However, other nuclear receptors may be involved (eg, peroxisome proliferator activated receptor, PPAR). PPAR-γ is a key regulatory element of adipocyte differentiation, and PPAR is a possible player in the association between POPs and diabetes.

Low birth weight may be a risk marker of future obesity, metabolic syndrome and diabetes. Even though low birth weight is generally considered to indicate undernutrition of the fetus, intrauterine exposure to some POPs might also increase the risk of low birth weight.¹⁷ Thus, perinatal exposure to POPs also needs to be considered when assessing the relationships among birth weight, adult obesity, diabetes and other outcomes.

The Karmaus study⁷ is an interesting attempt to integrate life course and environmental and molecular epidemiology.¹⁵ Nonetheless, the causal significance of the results rests on several assumptions. One important conjecture is that both lifelong calorie intake and physical activity were similar in offspring of mothers with different DDE values during pregnancy. However, mothers with low concentrations of DDE and PCBs are likely to have had different dietary habits than mothers with high concentrations of these POPs, and the dietary habits of the daughters probably resembled those of their mothers. According to table 2, mothers in the lowest DDE category had lower BMIs. If their daughters followed similar dietary and exercise patterns as their mothers, the positive association observed in the study could partly or totally be due to diet and exercise and not to the mothers’ DDE levels.

Another area in which methodological improvements could be made is the estimation of serum concentrations of POPs during pregnancy on the basis of measurements performed years later. Future studies should also assess the potential confounding and mediating effects of educational level, social position and socioeconomic achievement. Given the different “waves” of environmental pollutants that have differentially contaminated human populations worldwide over the last decades, both classic and multilevel quantitative analyses of age, period and cohort effects of POP levels on BMI are also necessary.^{1,5,6}

Linking perinatal and childhood exposure to POPs and other environmental obesogens to childhood and adult obesity, obesity-related diseases and other POP-related health and social outcomes has significant potential to advance mechanistic knowledge and public health policies.

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REFERENCES

1. **Porta M**, Puigdomènech E, Ballester F, *et al*. Monitoring concentrations of persistent organic pollutants in the general population: the international experience. *Environ Int* 2008;**34**:546–61.
2. **Sagiv SK**, Nugent JK, Brazelton TB, *et al*. Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS). *Environ Health Perspect* 2008;**116**:666–73.
3. **Barr DB**, Weihe P, Davis MD, *et al*. Serum polychlorinated biphenyl and organochlorine insecticide concentrations in a Faroese birth cohort. *Chemosphere* 2006;**62**:1167–82.
4. **Ribas-Fitó N**, Torrent M, Carrizo D, *et al*. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. *Am J Epidemiol* 2006;**164**:955–62.
5. **Porta M**. Persistent toxic substances: exposed individuals and exposed populations. *J Epidemiol Community Health* 2004;**58**:534–5.
6. **Porta M**. Persistent organic pollutants and the burden of diabetes. *Lancet* 2006;**368**:558–9.
7. **Karmaus W**, Osuch JR, Eneli I, *et al*. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. *Occup Environ Med* 2009;**66**:143–49.
8. **Glynn AW**, Granath F, Aune M, *et al*. Organochlorine in Swedish women: determinants of serum concentrations. *Environ Health Perspect* 2003;**111**:349–55.
9. **Foster W**, Chan S, Platt L, *et al*. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. *J Clin Endocrinol Metabol* 2000;**85**:2954–7.
10. **Department of Health and Human Services**. Centers for Disease Control and Prevention, National Center for Environmental Health. *Third national report on human exposure to environmental chemicals*. NECH Pub. No. 05–0570. Atlanta: Centers for Disease Control and Prevention, 2005. Available from <http://www.cdc.gov/exposurereport/report.htm> (accessed 30 December 2008).
11. **Smink A**, Ribas-Fitó N, Garcia R, *et al*. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. *Acta Paediatr* 2008;**97**:1465–9.
12. **Grün F**, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology* 2006;**147**(6 Suppl):S50–S55.
13. **Newbold RR**, Padilla-Banks E, Jefferson WN, *et al*. Effects of endocrine disruptors on obesity. *Int J Androl* 2008;**31**:201–8.
14. **Jirtle RL**, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 2007;**8**:253–62.
15. **Porta M**, ed. *A dictionary of epidemiology*. 5th edn. New York: Oxford University Press, 2008:65–6, 82–3, 128–30.
16. **Lee DH**, Lee IK, Song K, *et al*. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care* 2006;**29**:1638–44.
17. **Rylander L**, Strömberg U, Hagmar L. Lowered birth weight among infants born to women with a high intake of fish contaminated with persistent organochlorine compounds. *Chemosphere* 2000;**40**:1255–62.

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