suggested by Stobaugh and colleagues, is even more contentious in view of the lack of evidence of effective bone-protective treatments in this age group. Strategies to reduce the risk of osteoporotic fracture in patients with IBS should broadly follow those advised for the general population of postmenopausal women and older men, which are based on the presence of previous fracture, low BMD and/or 10-year fracture probability.[10] Similarly, advice should be given on lifestyle measures, including physical activity and diet. Particular emphasis should be put on maintenance of an adequate calcium intake, with the use of supplements recommended in those who avoid dairy produce. Finally, exploration of the potential mechanisms that predispose patients with IBS to osteoporosis and osteoporotic fractures might throw further light on whether more specific preventive measures are required.

University of Cambridge School of Clinical Medicine, Department of Medicine, Box 157, Addenbrooke's Hospital, Cambridge, Cambridgeshire CB2 2QQ, UK.
jec1001@cam.ac.uk

Competing interests
The author declares no competing interests.

1. Stobaugh, D. J., Deepak, P. & Ehrenpreis, E. D. Increased risk of osteoporosis-related fractures in patients with irritable bowel syndrome. *Osteoporos. Int.* http://dx.doi.org/10.1007/s00198-012-2141-4.
2. Suares, N. C. & Ford, A. C. Diagnosis and treatment of irritable bowel syndrome. *Discov. Med.* **11**, 425–433 (2011).
3. Barbara, G. *et al.* The immune system in irritable bowel syndrome. *J. Neurogastroenterol. Motil.* **17**, 349–359 (2011).
4. Cremon, C. *et al.* Intestinal serotonin release, sensory neuron activation, and abdominal pain in irritable bowel syndrome. *Am. J. Gastroenterol.* **106**, 1290–1298 (2011).
5. Vesa, T. H., Seppo, L. M., Marteau, P. R., Sahi, T. & Korpela, R. Role of irritable bowel syndrome in subjective lactose intolerance. *Am. J. Clin. Nutr.* **67**, 710–715 (1998).
6. Ladabaum, U. *et al.* Diagnosis, comorbidities, and management of irritable bowel syndrome in patients in a large health maintenance organization. *Clin. Gastroenterol. Hepatol.* **10**, 37–45 (2012).
7. Rizzoli, R. *et al.* Antidepressant medications and osteoporosis. *Bone* **51**, 606–613 (2012).
8. Choung, R. S. & Locke, G. R. 3rd. Epidemiology of IBS. *Gastroenterol. Clin. North Am.* **40**, 1–10 (2011).
9. Whitehead, W. E. *et al.* Comorbidity in irritable bowel syndrome. *Am. J. Gastroenterol.* **102**, 2767–2776 (2007).
10. National Osteoporosis Foundation. *NOF clinician's guide to prevention and treatment of osteoporosis* [online], http://www.nof.org/professionals/clinical-guidelines (2010).

OBESITY

Fat from plastics? Linking bisphenol A exposure and obesity

Angel Nadal

The weight of evidence indicates that bisphenol A (BPA), a widespread endocrine disruptor, might be an important risk factor for obesity and metabolic disorders. An epidemiological study shows an association between urinary BPA levels and increased body mass in children and adolescents.

Nadal, A. *Nat. Rev. Endocrinol.* **9**, 9–10 (2013); published online 13 November 2012; doi:10.1038/nrendo.2012.205

The general agreement is that obesity occurs because energy intake exceeds energy expenditure.[1] Obesity is a multifactorial and complex disease, and its aetiology involves the interaction between genes and the environment.[1,2] During the past two decades, our knowledge about genetic factors influencing obesity has grown exponentially. By contrast, our knowledge about environmental factors, including endocrine disruptors such as bisphenol A (BPA, the main component of polycarbonate plastic), which are able to influence transcriptional regulation of genes involved in obesity, is only now beginning to emerge. In an epidemiological study, Trasande and colleagues[3] found an association between urinary concentrations of the ubiquitous endocrine disruptor BPA and body mass outcomes in children and adolescents aged 6–19 years.

According to the WHO, over 700 million people with obesity exist worldwide and about 2 billion people are overweight. The WHO estimated that the number of children aged >5 years who are overweight was over 42 million in 2010. Childhood obesity and overweight are strong risk factors for becoming a young adult with obesity, and for developing cardiovascular diseases and type 2 diabetes mellitus at a young age. For these reasons, obesity is an issue of high concern and the prevention of childhood obesity is a public health priority.

Trasande *et al.*[3] used data from the 2003–2008 National Health and Nutrition Examination Survey (NHANES), which was conducted in the noninstitutionalized US population. High urinary BPA concentrations were associated with increased obesity after taking into account a number of risk factors for obesity to correct for potential confounding. Specifically, individuals whose urinary BPA levels were in higher quartiles (1.5–2.7 ng/ml, 2.8–5.5 ng/ml and ≥5.6 mg/ml) were at a higher risk of obesity than those whose urinary levels were in the lowest quartile (<1.5 ng/ml). The prevalence of obesity was 22.3% (95% CI 16.6–27.9%) among children and adolescents with urinary BPA levels in the three higher quartiles (≥1.5 ng/ml) compared with 10.3% (95% CI 7.5–13.1%) in those with urinary BPA concentrations in the lowest quartile. Remarkably, obesity was not associated with exposure to other environmental phenols found in daily products such as soaps or sunscreens, which points to specificity in the association between obesity and BPA levels.

> "The oestrogenic effect of BPA has been shown to alter glucose and lipid metabolism..."

Trasande and co-workers[3] performed an analysis stratified by ethnicity and found that the association between obesity and urinary BPA levels was statistically significant only in white children and adolescents. The prevalence of obesity was 22.8% (95% CI 15.8–29.8%) among white children and adolescents in the highest quartile, compared with 4.7% (95% CI 1.8–7.6%) among those in the lowest quartile of urinary BPA levels. The interpretation of these results is not easy, as the authors acknowledge, but the reason for the lack of an association between urinary BPA levels and obesity specifically in non-white ethnic groups could be the fact that obesity prevalence was, for example, 20.8% and 22.4% in non-Hispanic black and Hispanic children and adolescents, respectively, who had urinary BPA levels in the lowest quartile.

What are the molecular mechanisms involved in such an association between BPA and obesity? Although the molecular

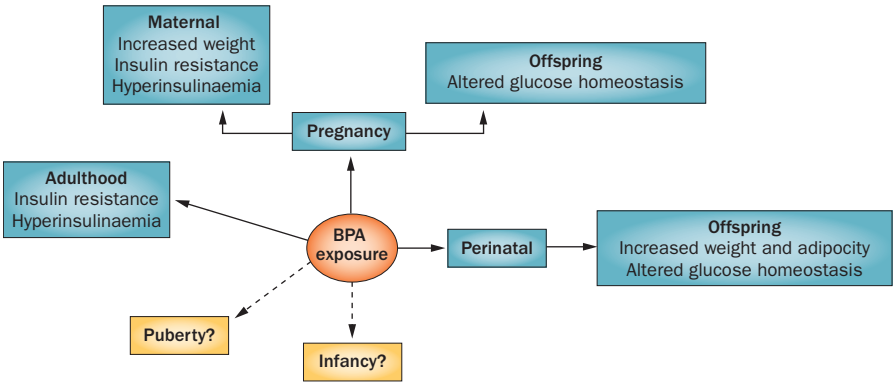

Figure 1 | Potential effects of BPA exposure during different stages of development. During adulthood, BPA exposure modifies insulin sensitivity and insulin release without affecting weight. Exposure during pregnancy has effects on both mother and offspring later in life. During pregnancy and lactation (perinatally) BPA exposure induces metabolic alterations, including weight gain. Effects of BPA exposure during infancy and puberty have not been studied yet and should be the subject of future research. Abbreviation: BPA, bisphenol A.

mechanisms linking BPA exposure and obesity are not yet known, cell-based *in vitro* studies have helped to understand how BPA works at the molecular level. BPA might have an effect at different points in signalling cascades but this compound works mainly by imitating the natural hormone 17β-oestradiol. Traditionally, BPA was considered a weak oestrogen mimetic, but evidence now indicates that, in fact, it is a potent oestrogen mimetic. BPA binds to oestrogen receptors (ERα and ERβ), triggering non-classical oestrogenic effects that are initiated outside the nucleus, in which oestrogen receptors do not act as transcription factors.[4,5] The oestrogenic effect of BPA has been shown to alter glucose and lipid metabolism in animal studies and, in some cases, to cause weight gain.[6] Through these novel oestrogen-receptor-triggered pathways, BPA alters the function of key cell types involved in metabolism, such as pancreatic β cells and adipocytes, in both mice and humans.[5,6]

Of note, the age at exposure to BPA seems to be a critical factor for the development of a specific phenotype (Figure 1). For example, in adult male mice, exposure to environmentally relevant doses of BPA (100 μg/kg per day) near the tolerable daily intake—the amount of contaminant which, on the basis of all known facts, can be consumed without resultant harm—of 50 μg/kg induces insulin resistance and hyperinsulinaemia, but does not induce weight gain.[4] Similar results are obtained in 6 month-old offspring of mice exposed to BPA during pregnancy only.[7] However, in all the studies in which offspring were exposed to BPA during pregnancy and lactation, weight gain occured later in life.[6] An increase in weight was found in two studies in which rats were exposed to BPA just before puberty.[6] Although adipocyte differentiation in mice takes place neonatally, differentiation of preadipocytes into adipocytes in humans begins before birth and persists postnatally. In humans, the number of adipocytes greatly increases between birth and 18 months of age.[6] Therefore, pregnancy and early periods of life should be considered crucial periods to avoid BPA exposure.

Similar to any cross-sectional study, the work by Trasande and collaborators[3] does not establish a causal link between BPA exposure and obesity. A possibility exists that children with obesity ingest more BPA through consumption of canned food and bottled beverages and that this factor is the primary cause of high urinary BPA concentrations in this group. Further epidemiological, animal and cell-based studies would add weight to the findings of Trasande *et al.*[3], which suggest that BPA might be involved in the aetiology of obesity. No other articles detailing epidemiological studies of this association in child populations have yet been published. However, several cross-sectional studies in adults have been published in the past 2 years that clearly establish a link between BPA exposure and obesity.[7–9]

The high-scale production and ubiquitous distribution of plastics coincides with the onset of the obesity and type 2 diabetes mellitus epidemics. We must bear in mind, however, that we are all exposed to a cocktail of chemicals besides BPA. These chemicals might act additively, or even synergistically, to alter metabolism. Strikingly, the weight gain epidemic is not only affecting humans, but also other mammals, including primates and rodents in research colonies, domestic dogs and cats, and even feral rodents.[10] These data indicate that some common environmental factors might be involved in the aetiology of obesity, such as low levels of environmental endocrine disruptors, including BPA.

Surprisingly, the medical community still gives insufficient attention to the role that endocrine disruptors might have in the emerging pandemic of obesity and type 2 diabetes mellitus. The work by Trasande and collaborators[3] should act as a wake-up call. I would recommend counselling of patients and their families by paediatricians, obstetricians, endocrinologists and general practitioners to decrease levels of exposure to endocrine disruptors particularly during important periods of development such as pregnancy, infancy and puberty.

Instituto de Bioingeniería and CIBERDEM, Universidad Miguel Hernández de Elche, 03202 Elche, Alicante, Spain.
nadal@umh.es

Competing interests
The author declares no competing interests.

1. Speakman, R. J. & O'Rahilly, S. Fat: an evolving issue. *Dis. Model. Mech.* **5**, 569–573 (2012).
2. Newbold, R. R., Padilla-Banks, E., Jefferson, W. N. & Heindel, J. J. Effects of endocrine disruptors on obesity. *Int. J. Androl.* **31**, 201–208 (2008).
3. Trasande, L., Attina T. M. & Blustein J. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. *JAMA* **308**, 1113–1121 (2012).
4. Alonso-Magdalena, P., Quesada, I. & Nadal, A. Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **7**, 346–353 (2011).
5. Soriano, S. *et al.* Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor β. *PLoS ONE* **7**, e31109 (2012).
6. vom Saal, F. S., Nagel, S. C., Coe, B. L., Angle, B. M. & Taylor J. A. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. *Mol. Cell. Endocrinol.* **354**, 74–84 (2012).
7. Carwile, J. L. & Michels, K. B. Urinary bisphenol A and obesity: NHANES 2003–2006. *Environ. Res.* **111**, 825–830 (2011).
8. Shankar, A., Teppala, S. & Sabanayagam, C. Urinary bisphenol A levels and measures of obesity: results from the national health and nutrition examination survey 2003–2008. *ISRN Endocrinol.* **2012**, 965243 (2012).
9. Wang, T. *et al.* Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J. Clin. Endocrinol. Metab.* **97**, E223–E227 (2012).
10. Klimentidis, Y. C. *et al.* Canaries in the coal mine: a cross-species analysis of plurality of obesity epidemics. *Proc. Biol. Sci.* **278**, 1626–1632 (2011).