



OPEN ACCESS

Population attributable risks and costs of diabetogenic chemical exposures in the elderly

Leonardo Trasande,^{1,2,3,4} Erik Lampa,⁵ Lars Lind,⁶ P Monica Lind⁷

¹New York University (NYU) School of Medicine, New York, New York, USA

²NYU Wagner School of Public Service, New York, New York, USA

³Department of Nutrition, NYU Steinhardt School of Culture, Education and Human Development, Food & Public Health, New York, New York, USA

⁴NYU College of Global Public Health, New York University, New York, New York, USA

⁵Uppsala Clinical Research Center, Uppsala, Sweden

⁶Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden

⁷Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden

Correspondence to

Dr Leonardo Trasande, Department of Pediatrics, New York University School of Medicine, 403 East 34th Street, New York, NY 10016, USA; leonardo.trasande@nyumc.org

Received 27 June 2016

Revised 22 August 2016

Accepted 23 August 2016

Published Online First

26 October 2016

ABSTRACT

Background A previous analysis examined the contribution of endocrine disruptor exposures (endocrine-disrupting chemicals, EDCs) to adult diabetes, but was limited to effects of phthalates in middle-aged women and did not simultaneously examine multiple EDCs which are known to coexist in the environment. We therefore endeavoured to quantify potential reductions in diabetes and disease costs that could result from reducing synthetic chemical diabetogenic exposures in the elderly in Europe.

Methods We leveraged the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (~1000 participants), which has measured exposure to phthalates; dichlorodiphenyltrichloroethylene; polychlorinated biphenyls (PCBs) and perfluoroalkyl substances to examine their independent contribution to diabetes. We estimated risk reductions assuming identical 25% reductions across levels of 4 selected compounds (PCB 153, monoethylphthalate, dichlorodiphenyldichloroethylene and perfluorononanoic acid), and diabetes costs saved in European men and women if diabetogenic exposures are limited.

Results Reduction of chemical exposures was associated with a 13% (95% CI 2% to 22%) reduction in prevalent diabetes, compared with 40% resulting from an identical (25%) reduction in body mass index (BMI) in cross-sectional analyses. Extrapolating to Europe, 152 481 cases of diabetes in Europe and €4.51 billion/year in associated costs could be prevented, compared with 469 172 cases prevented by reducing BMI.

Conclusions These findings support regulatory and individual efforts to reduce chemical exposures to reduce the burden and costs of diabetes.

INTRODUCTION

Increasing evidence suggests that synthetic chemicals commonly found in the environment contribute to metabolic disorders, especially obesity and diabetes.^{1 2} Though diet and physical activity are the major contributors, chemical exposures can be regulated. The costs of safer alternatives to the diabetogenic and other metabolic disruptors can be compared with the health benefits of prevention.³

A recent report suggests that €15 billion in costs of new-onset, type 2 diabetes in older women are attributable to endocrine-disrupting chemicals (EDCs).⁴ This study leveraged the Nurses' Health Study which associated urinary phthalates with longitudinal increases in diabetes, controlling many relevant confounders. Though this study did control for another plausible diabetogen, bisphenol A, the study was unable to control for persistent

organic pollutants that coexist and may have supra-additive effects.⁵

We therefore examined data from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, which measured persistent and non-persistent chemical exposure to examine their independent contribution to diabetes. Previous publications have associated prevalent diabetes with polychlorinated biphenyls (PCBs), persistent chlorinated pesticides, phthalates and perfluoroalkyl substances (PFASs).^{6–9} Use of PIVUS also permits quantification of attributable burden in men as well as women, in whom exposures are likely to induce diabetes independent of sex steroid disruption, since the age is 70 years in all participants.

To compare risks with other common risks, we modelled identical 25% percentage reductions in contaminant levels, as well as in body mass index (BMI). We also examined the aggregate reduction in risk produced by simultaneously reducing all four contaminants to assess an aggregate burden of diabetes that can be attributed to environmental contaminants. Finally, we leveraged cost-of-illness data to estimate the preventable cost of adult diabetes in Europeans.

METHODS

Sample

PIVUS is a population-based cohort derived from the individuals aged 70 living in the city of Uppsala, Sweden (n=1016; 50% women). For full details, please see Lind *et al.*¹⁰ Prevalent diabetes was defined as antidiabetic therapy or fasting plasma glucose ≥ 7.0 mmol/L (n=119). Fasting blood was drawn in the morning for the determination of 33 environmental contaminants. The following calculations were based on data previously presented regarding the risk of prevalent diabetes of different environmental contaminants.^{6–9} The present analyses use a cross-sectional design. Owing to randomly missing data for some of the contaminants, data from 953 of the participants were used in the calculations.

Statistical methods

Biomarkers were selected based on significance in multivariable, single-exposure models: plasma monoethylphthalate (MEP); serum dichlorodiphenyldichloroethylene (*p,p'*-DDE); serum 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153); and perfluorononanoic acid (PFNA). The analytical procedures have previously been given in detail (6–9). Poisson regression models were used as the bases for the calculations. Included as independent variables in the models were the four contaminants as well as sex, BMI, physical activity, daily energy



CrossMark

To cite: Trasande L, Lampa E, Lind L, *et al.* *J Epidemiol Community Health* 2017;**71**:111–114.

Diabetes

intake and daily alcohol intake. Population attributable fractions (PAFs) were calculated based on the *attribrisk* function in the R-package with the same name with two exceptions. *Attribrisk* uses logistic regression whereas we sought relative risk/prevalence ratio as the outcome could be considered common and an OR would not be a good approximation for the relative risk. Hence, Poisson regression was used instead, following published methods.¹¹ To estimate PAFs, we first note that the estimated probability from the Poisson regression of being a case for any individual in the sample is

$$\hat{P}(case) = e^{X\beta}$$

where $X\beta$ is the linear predictor resulting from the regression model. X denotes the design matrix and β is the vector of regression coefficient. Focusing on cases only, we can estimate the probability of being a case under a hypothetical scenario in which the exposure(s) are reduced by a certain amount given as

$$\hat{P}(case_{hypothetical}|case_{observed}) = e^{X_c\beta}$$

where X_c is the contrast matrix obtained by subtracting the observed exposure(s) from the hypothetical. The sum of all predicted probabilities for the cases in the sample corresponds to the expected number of cases expected under the hypothetical scenario. The PAF is then calculated as

$$PAF = 1 - \frac{1}{N_{cases}} \sum_{cases} e^{\gamma X_c\beta}$$

where γ is a shrinkage factor defined as

$$\gamma = \frac{\text{model } \chi^2 - p}{\text{model } \chi^2}$$

where p is the total degrees of freedom and model χ^2 is the likelihood ratio statistic for testing the joint influence of all variables in the model.¹² As there were few cases of diabetes relative to the model degrees of freedom, the models may overfit. The shrinkage factor shrinks the PAF towards zero and was used to compensate for the overfitting when generalising the results to the European population.

Five models were developed with the difference between the models being the hypothetical scenarios. The first scenario assumed a simultaneous 25% decrease in all four contaminants while the remaining scenarios assumed a 25% decrease in a single contaminant while keeping the other contaminants constant. The bootstrap was used to construct 95% bias corrected and accelerated CIs for PAF using 10 000 replicates.¹³ All analyses were made using R V.3.2.4 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://http://www.R-project.org/> 2016).

Burden of disease and economic estimation

The number of diabetes cases among 70–75 years old was estimated by multiplying age-standardised prevalence of diabetes in Europe (6.5%)¹⁴ against the population estimate of 70–75 years old.¹⁵ Annual cost estimates for diabetes per adult in 2010 were obtained from the analyses by Zhang *et al*,¹⁶ in US dollars. Given that prevalent diabetes results in costs over multiple years

Table 1 Biomarkers of exposure in the Prospective Investigation of the Vasculature in Uppsala Seniors

Biomarker	N	Median	25th centile	75th centile
MEP (ng/mL)	963	11.70	7.22	17.50
<i>p,p'</i> -DDE (ng/g lipid)	953	1858	1024	3415
PCB 153 (ng/g lipid)	953	1427	1111	1843
PFNA (ng/mL)	965	0.71	0.53	0.97

MEP, urinary monoethylphthalate; PCB 153, serum 2,2',4,4',5,5'-hexachlorobiphenyl; PFNA, perfluorononanoic acid; *p,p'*-DDE, serum dichlorodiphenyldichloroethylene.

of each subsequent lifetime, annual costs were aggregated over a 10-year period, using 3% discounting.

Human participants

PIVUS was approved by the Ethics Committee of the University of Uppsala and the participants gave informed consent. LT signed a New York University School of Medicine Institutional Review Board attestation form documenting the nature of his involvement as non-human participants research.

RESULTS

Table 1 presents descriptive biomarker data analysed in relation to diabetes, documenting exposures similar to those identified in other European populations. All four exposures taken singly had near-significant prevalence ratios (table 2), though reduction of all four exposures by 25% was associated with a 13% (95% CI 2% to 22%) lower prevalence of diabetes, compared with a 40% reduction in diabetes prevalence in association with an identical (25%) reduction in BMI. Extrapolation to Europe suggests that 152 481 cases of diabetes could be prevented by reducing EDC exposure, compared with 469 172 produced by a population-wide 25% reduction in BMI (table 3). Economic benefits of reducing EDC-attributable diabetes were estimated to be €4.51 billion/year compared with the €13.9 billion benefits of reducing BMI.

DISCUSSION

The present study confirms substantial contribution, especially of mixtures of EDCs, to adult type 2 diabetes, and large annual costs of medical care.⁴ While some will question extrapolation on limited data, our findings regarding chemical diabetogens are not unique and have also been found by several other research groups.^{5 17–22} These epidemiological findings are likely to be causal, since they are in line with experimental mechanistic data.^{23–32}

All the same, we acknowledge that residual confounding may have resulted in effect overestimation for the chemical exposures studied. The calculated PAFs may not apply to older age ranges

Table 2 Population attributable risk in multiexposure models

Biomarker	PAF (95% CI)
All four chemical exposures	0.13 (0.02 to 0.22)
MEP	0.01 (–0.02 to 0.05)
PCB 153	0.02 (–0.02 to 0.06)
<i>p,p'</i> -DDE	0.06 (–0.05 to 0.15)
PFNA	0.06 (–0.02 to 0.13)
BMI	0.40 (0.16 to 0.53)

PAFs assume 25% reduction in each risk factor.

BMI, body mass index; MEP, urinary monoethylphthalate; PAF, population attributable fraction; PCB 153, serum 2,2',4,4',5,5'-hexachlorobiphenyl; PFNA, perfluorononanoic acid; *p,p'*-DDE, serum dichlorodiphenyldichloroethylene.

Table 3 Attributable disease and cost estimates

Risk factor	Body mass index	Endocrine-disrupting chemical exposures
European population, 70–75 years old	18 045 093	
Diabetes prevalence	6.5%	
Prevalent diabetes, Europe	1 172 931	
Preventable cases	469 172	152 481
Cost/case	€29 585	
Preventable costs	€13.9 billion	€4.51 billion

insofar as biomarker levels have decreased ecologically. Exposures much earlier than study entry may have contributed to those measured in biomarkers at study entry.

It should be emphasised that PCBs have already been banned, under the Stockholm Convention.^{33 34} The pesticide dichlorodiphenyltrichloroethylene, for which the measured levels of *p*, *p'*-DDE are proxy, has also been banned, except for the eradication of malaria in some parts of southern Africa. Long-chain perfluoroalkyl compounds, including PFNA, have completed a voluntary phase-out in the USA, though the expected reductions in serum PFNA have not been identified.^{35 36}

Yet, healthcare providers can advise patients to reduce their exposure to diabetogenic contaminants identified in this study. Choosing personal care products labelled as 'phthalate free' has reduced urinary levels of MEP by 27% in young girls in one study.³⁷ Other phthalates known to be metabolic disruptors are known food contaminants, and a fresh food intervention has produced even larger reductions in exposure.³⁸ Short-chain PFASs contaminate food through packaging and contact surfaces, and are increasingly found in food.³⁹ Consumption of a diet according to WHO recommendations has been associated with lower levels of PFASs and PCBs.^{40 41}

Our findings also speak the need for a strong regulatory framework that proactively identifies chemical hazards before they are widely used, and the use of safer alternatives. The European Union is actively considering regulations to limit such exposures,⁴ and the USA recently revised the Toxic Substances Control Act,⁴² but does not consider endocrine disruption. In the absence of such a framework, newly developed synthetic chemicals may emerge as diabetogenic exposures, replacing banned or substituted hazards as contributors.

CONCLUSIONS

Environmental contaminants contribute substantially to diabetes in the elderly, with costs in Europe likely to be in billions of Euros.

What is already known on this subject

Increasing evidence suggests that synthetic chemicals commonly found in the environment contribute to metabolic disorders, especially obesity and diabetes. Yet, only one study has quantified attributable disease and costs, did not examine mixtures of chemicals which may have synergistic effects and was limited to effects in middle-aged women.

What this study adds

Reduction of chemical exposures was associated with a 13% (95% CI 2% to 22%) reduction in diabetes in the elderly, preventing 152 481 cases of diabetes in Europe and €4.51 billion/year in associated costs. These findings support regulatory and individual efforts to reduce chemical exposures.

Twitter Follow Leonardo Trasande at @leotrasande

Contributors LT wrote the manuscript, and performed economic analyses. PML and LL provided primary study access and reviewed/edited the manuscript. EL performed statistical analyses. LT and PML are the joint guarantors of this work, including the study design, access to data, and the decision to submit and publish the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- Hauser R, Skakkebaek NE, Hass U, *et al.* Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab* 2015;100:1267–77.
- Lind L, Lind PM, Lejonklou MH, *et al.* Uppsala consensus statement on environmental contaminants and the global obesity epidemic. *Environ Health Perspect* 2016;124:A81–3.
- Trasande L, Massey RI, DiGangi J, *et al.* How developing nations can protect children from hazardous chemical exposures while sustaining economic growth. *Health Aff (Millwood)* 2011;30:2400–9.
- Trasande L, Zoeller RT, Hass U, *et al.* Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab* 2015;100:1245–55.
- Sun Q, Cornelis MC, Townsend MK, *et al.* Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. *Environ Health Perspect* 2014;122:616–23.
- Lind L, Lind PM. Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease? *J Intern Med* 2012;271:537–53.
- Lind L, Zethelius B, Salihovic S, *et al.* Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly. *Diabetologia* 2014;57:473–9.
- Lind PM, Zethelius B, Lind L. Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly. *Diabetes Care* 2012;35:1519–24.
- Lee DH, Lind PM, Jacobs DR Jr, *et al.* Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* 2011;34:1778–84.
- Lind L, Fors N, Hall J, *et al.* A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Arterioscler Thromb Vasc Biol* 2005;25:2368–75.
- Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–6.
- Harrell JF. Regression modeling strategies. With applications to linear models, logistic and ordinal regression, and survival analysis. Springer Series in Statistics, 2015. ISBN: 978-3319194240.
- Efron B, Tibshirani RJ. *An introduction to the bootstrap*. Chapman & Hall/CRC, 1993. ISBN: 0-412-04231-2.
- European Commission. Prevalence estimates of diabetes, adults aged 20–79 years, 2010. Chapter 1.14.1 in Health at a Glance: Europe 2010. http://ec.europa.eu/health/reports/docs/health_glance_en.pdf (accessed 31 May 2016).
- United Nations Economic Commission for Europe. Population, 5-year age groups, by sex. 2014. http://w3.unece.org/pxweb/Dialog/varval.asp?ma=001_GEPOAGESEX_REG_&ti=Population%2C+5-year+age+groups%2C+by+Age%2C+Sex%2C+Country+and+Year&path=../DATABASE/Stat/30-GE/01-Pop/&lang=1 (accessed 26 Aug 2014).

Diabetes

- 16 Zhang P, Zhang X, Brown J, *et al*. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:293–301.
- 17 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.
- 18 Rignell-Hydbom A, Lidfeldt J, Kiviranta H, *et al*. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. *PLoS ONE* 2009;4:e7503.
- 19 Longnecker MP, Michalek JE. Serum dioxin level in relation to diabetes mellitus among air force veterans with background levels of exposure. *Epidemiology* 2000;11:44.
- 20 Turyk M, Anderson H, Knobeloch L, *et al*. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. *Environ Health Perspect* 2009;117:1076–82.
- 21 Svensson K, Hernández-Ramírez RU, Burguete-García A, *et al*. Phthalate exposure associated with self-reported diabetes among Mexican women. *Environ Res* 2011;111:792–6.
- 22 Su TC, Kuo CC, Hwang JJ, *et al*. Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults. *Environ Int* 2016;88:15–22.
- 23 Wilson VS, Blystone CR, Hotchkiss AK, *et al*. Diverse mechanisms of anti-androgen action: impact on male rat reproductive tract development. *Int J Androl* 2008;31:178–87.
- 24 Shekhar PV, Werdell J, Basrur VS. Environmental estrogen stimulation of growth and estrogen receptor function in preneoplastic and cancerous human breast cell lines. *J Natl Cancer Inst* 1997;89:1774–82.
- 25 Moreno-Aliaga MJ, Matsumura F. Effects of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)-ethane (p,p'-DDT) on 3T3-L1 and 3T3-F442A adipocyte differentiation. *Biochem Pharmacol* 2002;63:997–1007.
- 26 Desvergne B, Feige JN, Casals-Casas C. PPAR-mediated activity of phthalates: a link to the obesity epidemic? *Mol Cell Endocrinol* 2009;304:43–8.
- 27 Jepsen KF, Abildtrup A, Larsen ST. Monophthalates promote IL-6 and IL-8 production in the human epithelial cell line A549. *Toxicol In Vitro* 2004;18:265–9.
- 28 Gourlay T, Samartzis I, Stefanou D, *et al*. Inflammatory response of rat and human neutrophils exposed to di-(2-ethyl-hexyl)-phthalate-plasticized polyvinyl chloride. *Artif Organs* 2003;27:256–60.
- 29 Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. *Free Radic Biol Med* 2011;51:993–9.
- 30 Herbstman JB, Sjödin A, Apelberg BJ, *et al*. Birth determinants of prenatal exposure to polychlorinated biphenyl (PCBs) and polybrominated diphenyl ethers (PBDE) in an urban population. *Environ Health Perspect* 2007;115:1794–800.
- 31 Herbstman JB, Sjödin A, Apelberg BJ, *et al*. Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. *Environ Health Perspect* 2008;116:1376.
- 32 Korashy HM, El-Kadi AO. The role of aryl hydrocarbon receptor in the pathogenesis of cardiovascular diseases. *Drug Metab Rev* 2006;38:411–50.
- 33 Porta M, Zumeta E. Implementing the Stockholm treaty on persistent organic pollutants. *Occup Environ Med* 2002;59:651–2.
- 34 Valvi D, Mendez MA, Garcia-Esteban R, *et al*. Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy. *Obesity (Silver Spring)* 2014;22:488–96.
- 35 Calafat AM, Wong LY, Kuklenyik Z, *et al*. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ Health Perspect* 2007;115:1596–602.
- 36 Ode A, Rylander L, Lindh CH, *et al*. Determinants of maternal and fetal exposure and temporal trends of perfluorinated compounds. *Environ Sci Pollut Res Int* 2013;20:7970–8.
- 37 Harley KG, Kogut K, Madrigal DS, *et al*. Reducing phthalate, paraben, and phenol exposure from personal care products in adolescent girls: findings from the hermosa intervention study. *Environ Health Perspect* 2016; doi:10.1289/ehp.1510514
- 38 Rudel RA, Gray JM, Engel CL, *et al*. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect* 2011;119:914–20.
- 39 Glynn A, Berger U, Bignert A, *et al*. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996–2010. *Environ Sci Technol* 2012;46:9071–9.
- 40 Ax E, Lampa E, Lind L, *et al*. Circulating levels of environmental contaminants are associated with dietary patterns in older adults. *Environ Int* 2015;75:93–102.
- 41 Sjogren P, Montse R, Lampa E, *et al*. Circulating levels of perfluoroalkyl substances are associated with dietary patterns—a cross sectional study in elderly Swedish men and women. *Environ Res* 2016;150:59–65.
- 42 Trasande L. Updating the toxic substances control act to protect human health. *JAMA* 2016;315:1565–6.



Population attributable risks and costs of diabetogenic chemical exposures in the elderly

Leonardo Trasande, Erik Lampa, Lars Lind and P Monica Lind

J Epidemiol Community Health 2017 71: 111-114 originally published online October 27, 2016
doi: 10.1136/jech-2016-208006

Updated information and services can be found at:
<http://jech.bmj.com/content/71/2/111>

These include:

- Supplementary Material** Supplementary material can be found at:
<http://jech.bmj.com/content/suppl/2016/10/28/jech-2016-208006.DC1>
- References** This article cites 37 articles, 6 of which you can access for free at:
<http://jech.bmj.com/content/71/2/111#BIBL>
- Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>
- Email alerting service** Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

-
- Topic Collections** Articles on similar topics can be found in the following collections
- [Open access](#) (310)
 - [Press releases](#) (82)
-

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>