Occupational Exposure to Endocrine-Disrupting Chemicals and Birth Weight and Length of Gestation: A European Meta-Analysis

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Background: Women of reproductive age can be exposed to endocrine-disrupting chemicals (EDCs) at work, and exposure to EDCs in pregnancy may affect fetal growth. Objectives: We assessed whether occupational exposure to EDCs during pregnancy as classified by application of a job exposure matrix was associated with birth weight, term low birth weight (LBW), length of gestation, and preterm delivery. Methods: Using individual participant data from 133,957 mother–child pairs in 13 European cohorts spanning births from 1994 through 2011, we linked maternal job titles with exposure to 10 EDC groups as assessed through a job exposure matrix. For each group, we combined the two levels of exposure categories (possible and probable) and compared birth outcomes with the unexposed group (exposure unlikely). We performed meta-analyses of cohort-specific estimates. Results: Eleven percent of pregnant women were classified as exposed to EDCs at work during pregnancy, based on job title. Classification of exposure to one or more EDC group was associated with an increased risk of term LBW [odds ratio (OR) = 1.25; 95% CI: 1.04, 1.49], as were most specific EDC groups; this association was consistent across cohorts. Further, the risk increased with increasing number of EDC groups (OR = 2.11; 95% CI: 1.10, 4.06 for exposure to four or more EDC groups). There were few associations (p < 0.05) with the other outcomes; women holding job titles classified as exposed to bisphenol A or brominated flame retardants were at higher risk for longer length of gestation. Conclusion: Results from our large population-based birth cohort design indicate that employment during pregnancy in occupations classified as possibly or probably exposed to EDCs was associated with an increased risk of term LBW. Acknowledgments: The authors thank the European Community’s Seventh Framework Programme (grant FP7/2007-2013, 226285, 241604) and part of the Environmental Health Risks in European Birth Cohorts project (http://www.enbeoco.org/) and the Developing a Child Cohort: Research Strategies project (European project: http://www.chioscoproject.eu); and by the Instituto de Salud Carlos III (grant CD12/00563). Funding per cohort: All of this work was supported by the Netherlands Organization for Health Research and Development (grant 2180.0076). RAME: This work was supported by the Swedish Heart-Lung Foundation; Stockholm County Council, Swedish Research Council for Health, Working Life and Welfare; and the European Commission’s Seventh Framework 29 Program: the Mechanisms of the Development of Allergy (grant 261357). DNBC: This work was supported by the Danish Epidemiology of Science Centre; Pharmacy Foundation; Egmont Foundation; March of Dimes Birth Defect Foundation; Agustinus Foundation; and the Health Foundation. Generation R: This work was supported by the Erasmus Medical Center Rotterdam; Netherlands Organization for Health Research and Development; European Commission Seventh Framework Programme; and the Contaminant Mixture and Human Reproductive Health Project (grant 212582). V.J. received an additional grant from the Netherlands Organization for Health Research and Development (grant VIDI 016.136.361) and Consolidator Grant from the European Research Council (grant ERC-2014-CoG-648916). Generation XXI: This work was supported by the Programa Operacional de Saúde – Saúde XXI, Quadro Comunitário de Apoio III, Administração Regional de Saúde Norte (Regional Department of Health of Portugal); Portuguese Foundation for Science and Technology; Fundo Europeu de Desenvolvimento Regional, and the Calouse Foundation. INMA New: This work was supported by the Instituto de Salud Carlos III (grants G03/176, CB06/020041). Address correspondence to L. Birks, ISGlobal, Center for Research in Environmental Epidemiology, Doctor Aigües, 88, 08003 Barcelona, Spain. Telephone: 34 932 147 519. E-mail: laura.birks@isglobal.org.

Introduction

Background

Potential endocrine-disrupting chemicals (EDCs) have been described as human-made substances that alter hormone regulation in humans or wildlife (WHO/UNEP 2012). The endocrine system regulates many essential body functions such as growth, behavior, and reproduction through the controlled release of hormones. EDCs include many synthetic and natural chemicals such as polycyclic aromatic hydrocarbons (PAHs), phthalates, organic solvents, phenols such as bisphenol A (BPA), alkylphenolic compounds (APCs), brominated flame retardants (BFRs), some metals, and parabens. Human exposure to EDCs has been associated with a wide range of health outcomes such as breast, prostate, and testis cancer, diabetes, obesity, and decreased fertility (De Coster and van Leebeke 2012; McLachlan et al. 2006). Although policy regarding the use of EDCs has evolved over the years, EDCs remain present in some foods and consumer products and in the workplace (De Coster and van Leebeke 2012; WHO/UNEP 2012). Individuals in the general population are exposed to small concentrations of EDCs through diet and consumer products, but some can be exposed to substantially higher concentrations of EDCs at work (WHO/UNEP 2012).

Women make up half of the workforce, and many of them are of reproductive age (European Agency for Safety and Health at Work 2012).
In this study we aimed to assess whether maternal occupational exposure to EDCs as classified by a job exposure matrix was associated with birth weight, term low birth weight (LBW), length of gestation, and preterm delivery in a population of 133,957 mother–child pairs from 13 population-based birth cohorts in 11 European countries.

Methods

Study Population

As part of the Environmental Health Risks in European Birth Cohorts (ENRICO) and Developing a Child Cohort Research Strategy for Europe (CHICOS) projects, data held by existing European birth cohorts were inventoried, including data on birth and child health outcomes and maternal occupation (Larsen et al. 2013; Vrijheid et al. 2012). Among these birth cohorts, 13 participated in a previous study regarding maternal occupations and birth outcomes (Casas et al. 2015) and were invited to participate in this new study. All 13 birth cohorts agreed to participate, including a total of 221,837 mother–child pairs followed at birth in the cohorts from 11 different countries spanning all regions of Europe (Table 1). Informed consent was obtained from all study participants as part of the original studies and in accordance with each study’s institutional review board.

The population sample for the present analysis was limited to live-born infants (defined as a birth of an infant showing signs of life at a gestational age of at least 22 completed weeks or weighing ≥ 500 g), singleton pregnancies, women being employed during the period starting 1 month before conception until birth, and women with occupations coded according to the International Standard Classification of Occupations of 1988 (ISCO88; http://www.ilo.org/public/english/bureau/statISCO88/), and with information on birth weight or length of gestation. From the 221,837 mother–child pairs followed at birth, 133,957 pregnant women fulfilled these criteria (Table 1). Research has shown that the active working population, particularly among women, is healthier than the nonworking population (Shah 2009) and that this is likely to result in differences in birth outcomes such as birth weight (Casas et al. 2015). Therefore, we have excluded nonworking women from our analysis.

Occupational Exposure to EDCs

Information about whether the mother worked during the period starting 1 month before conception until birth and the corresponding job title was collected through self-reports or from questionnaires conducted by trained interviewers during pregnancy or after birth in each participating cohort (Table 1). To estimate maternal occupational exposure to EDCs during pregnancy, we linked the occupational ISCO88 codes of our population to a job exposure matrix (JEM) for EDCs (Brouwers et al. 2009). To develop this JEM, three experts expanded on the United Kingdom EDC JEM created by van Tongeren et al. (2002) and assigned exposure probability scores for all chemical groups to 353 different job titles, made for workers in the Netherlands between 2005 and 2007 (Brouwers et al. 2009). This JEM classified EDCs into 10 general chemical groups and 33 subgroups (Table 2) of those substances in which occupational exposure was expected to contribute significantly to an individual’s body burden compared to other sources such as diet. The 10 chemical groups are the following: PAHs, PCBs, pesticides, phthalates, organic solvents, BPA, APCs, BFRs, metals, and miscellaneous (benzophenones, parabens, and siloxanes); as well as a category dichotomously indicating exposure to one or more EDC groups. This JEM estimated exposure to these chemical groups for these 353 job titles with three levels of exposure probability: “unlikely,” “possible,” and “probable.” The exposure estimates refer to the occupational exposure level that would exceed the background level of exposure in the general population. This JEM makes no distinction between routes of exposure (inhalation, ingestion, or dermal). The JEM includes a fourth exposure category, “unclassifiable,” which indicates that exposure cannot be determined.

Because the JEM coded occupations using the Standard Occupational Classification 2000 (SOC2000; http://www.bls.gov/soc2000/socguide.htm) system, the JEM was first translated from SOC2000 to ISCO88 codes using the CAMSIS tool (CAMSIS 2005). Of the 133,957 women who had occupational history available and had an ISCO88 job code, the JEM provided exposure estimates for 95,280 women and labeled 2,585 women as exposure unclassifiable (Table 3). For the remaining 36,092 women in our population, three occupational experts (S.C., A.M.G., and M.N.) evaluated their corresponding ISCO88 codes and assigned a similar ISCO88 code for which a JEM score was available. For example, our translated JEM did not provide a score for the occupation “chemical engineering technicians” (ISCO88 code 3116); therefore our occupational experts assigned a proxy ISCO88 code that was in our JEM, “chemical and physical science technicians” (ISCO88 code 3111), keeping in mind similar EDC exposure in the workplace (see Excel File Table S2). This yielded exposure estimates for 35,999 more women. Experts categorized 93 women as “exposure unclassifiable.” With the CAMSIS tool and experts’ input together, this yielded EDC exposure scores for 131,279 women (95,280 + 35,999) and labeled 2,678 women...
(2,585 + 93) as “exposure unclassifiable.” The 131,279 women for whom we could estimate exposure were used in our subsequent analysis (Table 3).

**Birth Weight and Length of Gestation**

Birth weight and length of gestation were collected through medical records. The last menstrual period (LMP)–based length of gestation estimate was used if it was consistent by ≤ 7 days with the ultrasound-based estimate. When these estimates were not consistent, or the LMP measurement was unavailable, the ultrasound-based estimate was preferred. If both measurements (LMP and ultrasound) were unavailable, the maternal reported length of gestation measurement was used.

The study focused on the following birth outcomes: birth weight (grams), term LBW (< 2,500 g vs. ≥ 2,500 g for births ≥ 37 weeks of gestation), length of gestation (days), and preterm delivery (< 37 weeks vs. ≥ 37 weeks).

**Covariate Data**

Information on covariates used in this study was collected similarly in each cohort and included sex of the newborn (male, female), parity (0, 1, or ≥ 2), maternal age (continuous in years), maternal country of birth (European, non-European in cohorts where this was available and heterogeneous), marital status (living with the child’s father, or not), maternal education (low, medium, high, defined within cohorts; see Table S3), maternal

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**Table 1.** Description of birth cohorts.

| Cohort      | Location        | Time period of enrollment | Maternal occupational history information | n available for analysis | n with history of work and ISCO88 code | n with unclassifiable exposure | n included in analysis |
|-------------|-----------------|---------------------------|------------------------------------------|-------------------------|----------------------------------------|-------------------------------|------------------------|
| ABCD        | The Netherlands | 2003–2004                 | Time of collection                        | 7,792                   | 3,585                                  | 149                           | 5,216                  |
| BAMBSE      | Sweden          | 1994–1996                 | 1st trimester of pregnancy               | 3,983                   | 3,526                                  | 11                            | 3,525                  |
| DNBC        | Denmark         | 1996–2002                 | Birth                                    | 86,736                  | 70,015                                 | 858                           | 69,157                 |
| Generation R| The Netherlands | 2001–2006                 | 12th week                                | 6,444                   | 3,520                                  | 57                            | 3,500                  |
| Generation XXI | Portugal      | 2005–2006               | 30th pregnancy week                      | 7,859                   | 5,994                                  | 338                           | 5,656                  |
| INMA Granada| Spain          | 2000–2002                 | Birth                                    | 497                     | 220                                    | 34                            | 186                    |
| INMA New    | Spain          | 2004–2008                 | 12th and 32nd weeks                      | 2,008                   | 1,767                                  | 217                           | 1,550                  |
| KANC        | Lithuania       | 2007–2009                 | 3rd trimester of pregnancy               | 4,253                   | 3,538                                  | 61                            | 3,477                  |
| MoBa        | Norway          | 1999–2008                 | 17th pregnancy week                      | 93,891                  | 31,019                                 | 827                           | 30,192                 |
| NINFEA      | Italy           | 2005–2011                 | Before maternity leave began             | 2,865                   | 2,504                                  | 49                            | 2,455                  |
| Pelagie     | France          | 2002–2006                 | 1st trimester of pregnancy               | 3,322                   | 2,918                                  | 43                            | 2,875                  |
| REPRO PL    | Poland          | 2007–2011                 | 8–12th, 20–24th, and 30–34th weeks       | 1,176                   | 996                                    | 26                            | 970                    |
| Rhea        | Greece          | 2007–2008                 | 1st and 3rd trimesters of pregnancy      | 1,111                   | 878                                    | 8                             | 870                    |
| Total       |                 |                           |                                          | 221,837                 | 133,957                                 | 2,678                         | 131,279                |
active smoking during pregnancy (none, < 10 cigarettes/day, or ≥ 10 cigarettes/day), and maternal prepregnancy body mass index (BMI) (< 18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m²).

**Statistical Analysis**

During the previous study all data were cleaned, variables were labeled, and categories were harmonized among all data sets in the 13 cohorts (Casas et al. 2015). All analyses were performed using Stata 12 statistical software (StataCorp, College Station, TX). For all associations, a p-value of ≤ 0.05 was used to define statistical significance.

Classification of maternal occupational exposure to EDCs overall was first evaluated by comparing exposure to one or more of the 10 EDC groups ("possible" and "probable" categories combined) with the unexposed group ("unlikely" exposure in all EDC groups), and second by comparing classified exposure to 1–3 EDC groups and ≥ 4 EDC groups with the unexposed group. Models for birth weight and term LBW were additionally adjusted for gestational length in weeks. The associations between classified maternal occupational exposure to EDCs and birth outcomes were first estimated for each individual cohort, using the above-described covariate models, which differed between cohorts only with regard to the maternal country of birth variable. Then, the estimated effects were meta-analyzed, combining separate estimations from each cohort (Cochran 1994; Harris et al. 2008). Results of meta-analyses for term LBW and preterm birth are reported only for exposures with a total of at least five exposed cases among all of the cohorts (combined). To test heterogeneity among cohorts, we used Cochran’s Q-test and the $I^2$ statistic (Higgins et al. 2003; Thompson and Sharp 1999). If the Q-test was significant (p < 0.05) and $I^2$ ≥ 25%, random-effects analysis was used. We then used meta-regressions (Baker et al. 2009) to assess whether heterogeneity across cohorts was attributable to the timing during pregnancy when occupational history was collected (whole pregnancy period: 1st, 2nd, and 3rd trimesters; birth), the geographical region (southern cohorts: Generation XXI, INMA Granada, INMA New, NINFEA, Pélagie, and Rhea versus northern cohorts: ABCD, BAMSE, DNBC, Generation R, KANC, MoBa, and REPRO_PL), or the period of enrollment (before or after 2003). Further sensitivity analysis was performed to assess the robustness of our results by excluding DNBC and MoBa, the largest cohorts, from meta-analyses. Robustness was also explored by excluding selected cesareans and by stratifying associations by sex of the newborn, maternal education (primary or secondary versus university or more), and maternal active smoking during pregnancy (any or none) to evaluate the results in different strata of these variables.

**Role of the Funding Source**

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Among the 131,279 women in our analysis, the mean (± SD) birth weight for newborns was 3,541 ± 561 g. Babies in the Rhea cohort were the smallest with a mean birth weight of 3,156 ± 488 g, and babies in the MoBa cohort were the largest (3,604 ± 553 g) (Table 4). The mean gestational length for all newborns in analysis was 39.8 ± 1.8 weeks. Newborns in the Rhea cohort had also the shortest gestational period with a mean gestational length of 38.5 ± 1.6 weeks, and newborns in the DNBC cohort had the largest gestational length of 40.0 ± 1.7 weeks (Table 4). In 8 of the 13 cohorts, < 2% of newborns were term LBW, compared with 2.2–5.6% in the remaining cohorts (Generation XXI, INMA Granada, INMA New, NINFEA, and Rhea). The prevalence of preterm delivery was < 6%, except in Generation XXI, NINFEA, and Rhea (7.2, 6.8, and 12.9%, preterm, respectively) (Table 4). The distribution of covariates across cohorts is shown in Table S4. Reported results are from complete case analysis.

Overall, 11% of women held jobs that were classified as possibly or probably exposed to EDCs (Table 5). INMA New and Rhea were the cohorts with the highest proportion

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**Table 3. Application of a job exposure matrix (JEM) and input of experts’ proxy codes.**

| JEM score | Direct CAMSIS SDC2000 to ISCO88 translation available | Experts assigned proxy ISCO88 code | Total |
|-----------|---------------------------------------------------------|----------------------------------|-------|
| 0, 1, or 2 | 95,280                                                  | 35,999                           | 131,279 |
| 88        | 2,585                                                   | 28,678                           | 31,263 |
| Total     | 97,865                                                  | 63,697                           | 161,562 |

Score key: 0 = exposure is unlikely to occur; 1 = exposure is possible for some workers but probability is low; 2 = exposure is likely to occur; 88 = job title provides too little information to classify exposure.

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**Table 4. Distribution of birth outcomes by cohorts.**

| Outcomes          | ABCD | BAMSE | DNBC | INMA Granada | INMA New | KANC | MoBa | NINFEA | Pélagie | REPRO_PL | Rhea | Total |
|-------------------|------|-------|------|--------------|----------|------|------|--------|---------|----------|------|-------|
| Birth weight (g)  | 3,451| 3,557 | 3,592| 3,464        | 3,194    | 3,298| 3,244| 3,489  | 3,604   | 3,214    | 3,390| 3,156 | 3,541 |
| (mean ± SD)       | ± 562| ± 537 | ± 561| ± 545 ± 480 | ± 443    | ± 486| ± 540| ± 553  | ± 522 ± 486| ± 461    | ± 488| ± 561 |
| Missing (n)       | 0    | 28   | 0    | 0            | 14       | 0    | 14   | 0      | 0       | 14       | 540  |
| Gestational length (weeks) | 39.8 | 39.9 | 40   | 39.9         | 39.8     | 39.3| 39.6 | 39.3   | 39.6    | 39.4     | 39.5| 38.5 | 39.8 |
| (mean ± SD)       | ± 1.8| ± 1.9| ± 1.7| ± 1.7 ± 1.7 | ± 1.5    | ± 1.7| ± 1.7| ± 1.7  | ± 1.8 ± 1.8| ± 1.5 ± 1.8| ± 1.8| |
| Term low birth weight (n [%]) | 84 (1.7) | 27 (0.8) | 624 (9.9) | 89 (1.8) | 194 (3.7) | 4 (2.2) | 42 (2.8) | 47 (1.4) | 201 (0.7) | 77 (3.0) | 32 (1.2) | 18 (1.9) | 44 (5.8) | 1,483 (1.2) |
| Preterm birth (n [%]) | 271 (5.2) | 170 (4.8) | 3,036 (4.4) | 238 (4.5) | 907 (17.2) | 8 (1.4) | 68 (4.4) | 190 (5.6) | 1,390 (4.5) | 196 (6.9) | 90 (3.4) | 43 (4.4) | 87 (12.9) | 6,141 (4.7) |
| Total (n)         | 5,216| 3,525 | 69,157| 5,150        | 5,056    | 186 | 1,550| 3,477  | 30,192  | 2,455    | 2,857| 970  | 870  | 131,279 |

*Frequencies and percentages were calculated for categorical variables whereas mean and SD were calculated for continuous variables. **Number of mothers with exposure and outcome data.
of women with job titles classified as exposed to EDCs at work (27% and 30%, respectively) (Table 5). Many pregnant women held jobs classified as exposed in INMA Granada and Pelagie cohorts, with 25% and 16% of pregnant women exposed, respectively. NINFEA and MoBa had the lowest proportion of maternal occupational exposure to EDCs, with 6% and 9% of women holding jobs classified as exposed, respectively.

All other cohorts had an average exposure prevalence of around 11% (Table 5). A total of 116,358 mothers (89%) had jobs classified as unexposed to any EDCs at work, and these were used as reference group in all analyses (Table 5).

There was no evidence for any statistically significant association with birth weight for job titles exposed to single EDC groups or for simultaneous exposure to multiple EDC groups (Table 6). The risk of delivering a term LBW baby was significantly increased among women with job titles classified as exposed to most single EDC exposure groups with odds ratios (ORs) ranging from 1.33 [95% confidence interval (CI): 1.02, 1.74] for APCs to 3.88 [95% CI: 1.37, 11.02] for BFRs (though for BFRs, this was based on only five exposed cases) (Table 6). This resulted in a 25% increased risk for delivering a term LBW baby.
for women holding jobs classified as exposed to one or more EDC groups (OR = 1.25; 95% CI: 1.03, 1.52; ≥ 4 EDC groups: OR = 2.11; 95% CI: 1.10, 4.06), though there was heterogeneity among cohorts for those exposed to ≥ 4 EDC groups (Table 6).

Maternal occupations classified as exposed to BPA or BFRs during pregnancy were associated with significantly longer gestational length (3.9 days; 95% CI: 0.7, 7.1 and 2.8 days; 95% CI: 0.7, 3.0, respectively) (Table 6). Among pregnant women who held job titles with exposure to any other EDC group, no significant associations were found with gestational length or preterm delivery (Table 6).

Among significant associations, we observed heterogeneity only between occupational exposure to phthalates and term LBW; and between occupational exposure to ≥ 4 EDC groups and term LBW (Table 6; see also Figures S1 and S2). Meta-regressions revealed that this heterogeneity was not attributable to the timing during pregnancy when occupational history was collected (whole pregnancy period; 1st, 2nd, and 3rd trimesters; birth), the geographical region (southern cohorts: Generation XXI, INMA Granada, INMA New, NINFEA, Pélagie, and Rhea vs. northern cohorts: ABCD, BAMSE, DNBC, Generation R, KANC, MoBa, and REPRO_PL, or the period of enrollment (before or after 2003). Sensitivity analysis revealed that after excluding the two largest cohorts in analysis (DNBC and MoBa), associations for exposure to phthalates and ≥ 4 EDC groups and term LBW were no longer heterogeneous. Further, women with occupations classified as exposed to ≥ 4 EDC groups, PAHs, pesticides, phthalates, or metals were at an increased risk for term LBW. Exposure to BFR and risk for term LBW could not be evaluated because there were only two exposed cases. For exposures to BPA or BFR and extended length of gestation, this association lost significance for exposure to BPA and stayed the same for BFR. All other significant analyses results maintained significance and ORs of similar magnitude (see Table S5). Upon excluding women who elected cesareans (n = 6,889), all associations with term LBW and length of gestation were generally consistent, except for exposure to ≥ 4 EDC groups or phthalates, where ORs remained significant but weakened. Exposure to BFRs and association with term LBW lost significance (see Table S6). Stratified analyses by sex of the newborn did not change associations (Table 7). The association between exposure to one or more EDCs and term LBW was somewhat stronger in those without university education (OR = 1.32; 95% CI: 1.06, 1.64) compared to those with university education (OR = 1.24; 95% CI: 0.87, 1.77), and in smokers (OR = 1.38 95% CI: 1.01, 1.87) compared to nonsmokers (OR = 1.18; 95% CI: 0.93, 1.50) (Table 7).

Discussion

This large meta-analysis suggests that maternal employment during pregnancy in occupations classified as possibly or probably exposed to EDCs during pregnancy is associated with a significant increased risk of term LBW in newborns, and that this association is fairly consistent across European populations and across specific groups of EDCs. We also observed that occupational exposure to BPA and BFRs as classified by the JEM was associated with significantly longer length of gestation, although few mothers were occupationally exposed (n = 59 and n = 149, respectively). Birth weight and preterm delivery were not significantly associated with JEM-classified occupational EDC exposure.

For term LBW, we found that pregnant women classified as exposed to PAHs,
pesticides, phthalates, APCs, BFRs, or metals in the workplace were at significantly higher risk, and that the term LBW risk increased with increasing number of EDC groups, possibly indicating an exposure–response relationship. We restricted our analyses of LBW to term births as a way to distinguish between babies with LBW because of growth restriction and those with LBW because of early delivery. Indeed, term LBW may be a more sensitive outcome than birth weight, as suggested in relation to other environmental exposures such as air pollution (Dadvand et al. 2013; Pedersen et al. 2013).

In our study population, agricultural workers and hairdressers were classified as simultaneously exposed to at least four of these chemical groups, which made it difficult to determine whether a specific EDC group (or groups) was key for explaining associations with term LBW. It is possible also that the significant increase in risk with increasing number of EDCs is the result of other conditions related to these occupations, such as exposure to heat, unsanitary conditions, or lifting, among others (Poppendorf and Donham 1991). Medical assistants, transport laborers, and waitresses were those job titles classified as exposed solely to PAHs (see Excel File Table S1). Our findings regarding occupational exposure to PAHs and term LBW agree with other studies assessing PAH exposure through air monitoring or biomarkers (Choi et al. 2006; Dejmek et al. 2000; Suzuki et al. 2010). Term LBW risk was significantly associated with pesticide exposure in our study. Agricultural workers were classified as exposed to this chemical group, among several other EDC groups, whereas pesticides was the only EDC group to which veterinarians and life science technicians were classified as exposed. In the past, exposure to pesticides among pregnant women has been widely investigated (Chevrier et al. 2011; Gemmill et al. 2013; Rauch et al. 2012; Wickerham et al. 2012), and our findings fall in line with other studies that have reported associations between reduced birth weight and maternal exposure to pesticides, both ambient and occupational (Burdorf et al. 2011; Chevrier et al. 2011; Wickerham et al. 2012; Wohlfahrt-Veje et al. 2011). However, these studies evaluated continuous birth weight, not term LBW. Agricultural workers and hairdressers were classified as being exposed to phthalates, among other chemicals, and phthalate exposure was significantly associated with term LBW. Other studies report both negative (Huang et al. 2014; Zhang et al. 2009; Zhao et al. 2015) and null (Philippat et al. 2012; Suzuki et al. 2010; Wolff et al. 2008) associations between phthalates and birth weight, but these have generally not focused on occupationally exposed populations. In our study, domestic cleaners and launderers were classified as exposed to APCs, including alkylphenols and alkylphenolic ethoxylates. Other studies regarding maternal APC exposure are rare; only the previously mentioned analysis in the Generation R cohort found a significant association with restricted fetal growth, but it did not evaluate term LBW (Snijder et al. 2012). One study in China analyzed exposure to other phenols (BPA, benzophenone-3, 4-n-octylphenol, and 4-n-nonylnophenol) and found that elevated maternal levels of benzophenone-3 in urine were associated with significant reduction in gestational length only in boys, but were not significantly associated with LBW (Tang et al. 2013). More studies regarding the fetal impacts of APCs and other phenolic compounds in the general population in and the workplace are needed. The small group of mothers classified as exposed to BFRs with term LBW newborns in our study (n = 5) worked in plastics or textile operatives. BFRs were recently classified as EDCs by researchers at an international BFR workshop after they reviewed various publications from 2003 through 2007 (Legler 2008). Literature regarding the impact of BFRs on fetal development in humans is limited (Chen Zee et al. 2013). In our study, metals were the sole occupational EDC exposure for dental professionals, health professionals, and machine workers. Regarding exposure to metals and term LBW, our findings reflect those found in other studies regarding maternal exposure to cadmium, but in these studies, maternal exposures were not exclusively occupational (Al-Saleh et al. 2014; Sun et al. 2014; Tang et al. 2013).

Continuous birth weight was not significantly associated with any category of maternal occupational exposure to EDCs in our analysis. Previous research regarding general population exposure to EDCs and birth weight is not consistent, with varied study designs and decreases and null associations reported (Meeker 2012). Research regarding occupational exposure to EDCs during pregnancy and birth weight is very scarce. A recent study in the Generation R cohort using the same JEM found that occupational exposure to PAHs and phthalates during pregnancy was significantly associated with reduced fetal weight as estimated from ultrasounds (Snijder et al. 2012). Analyses of fetal growth measures could be a more sensitive evaluation of environmental influences during pregnancy instead of birth weight (Slama et al. 2014), but for our analysis, fetal measurements were not available for all cohorts.

Estimated exposure to BPA or BFRs was significantly associated with extended length of gestation. Workers were classified with possible or likely exposure to BPA if they held a job title as any kind of plastics operative, whereas job titles classified as exposed to BFRs were typically textile machine operators, fire service officers, or working as plastic or rubber operatives. In a smaller study (n = 219) embedded in the Generation R cohort, BPA in maternal urine was associated with significantly shorter gestational times or reduced fetal growth (Snijder et al. 2013), contradicting our results. However, a biomarker-based birth cohort study (n = 488) embedded in the INMA cohort found a small but not significant increase in length of gestation for mothers with higher levels of BPA in urine during pregnancy (Casas et al. 2016), supporting our findings. The number of pregnant women with job titles estimated as occupationally exposed to BPA or BFR (n = 59 and n = 149, respectively) among our sample was small, so these results should be interpreted with caution.

Pretterm delivery was not significantly associated with estimated exposure to any EDC group in our study. Previous research regarding EDC exposure and preterm delivery is rare and has yielded conflicting results, with reports of positive, negative, and null associations with length of gestation, not necessarily preterm delivery (Meeker 2012). More research regarding this potential association, specifically among occupationally exposed mothers, is needed.

Our study has some important strengths: the harmonized and detailed information about individual maternal characteristics (e.g., parity, country of origin, marital status, education, smoking during pregnancy, and prepregnancy height and weight), enabling adjustment for potential confounders across the cohorts; the prospective data collection in most cohorts, avoiding recall bias (except BAMSE, Generation XXI, and INMA Granada: Table 1); and the large population spread throughout Europe, including data from the North, East, South and West. Previous studies of maternal occupational exposure to EDCs and associated birth weight and length of gestation have been few and relatively small and are also embedded in the Generation R study (Snijder et al. 2012, 2011). Because many cohorts participated in our study, and estimates from all participating cohorts are reported, our design also reduces the potential for publication bias, at least within the European setting. Finally, in our complete case analyses, we believe missing covariates did not influence associations. In minimally adjusted models, associations were consistent among full and complete case populations (see Table S7).

In assessing robustness of our findings, we stratified models for maternal education and maternal smoking during pregnancy, common confounders in fetal growth (Abel 1980;
Birks et al. validated across countries, this JEM is the best windows of time for which each JEM was cohorts in our study, most occupational data population of workers in The Netherlands (van Tongeren et al. 2002). Brouwers et al. particular JEM by adapting van Tongeren’s time as that for which it was originally measurements, it is a tool meant to be used it cannot be captured via questionnaires or observed associations. ground level is believed to be much lower and consumer products. However, this back - et al. 2014). Finally, we suspect that almost lifting relates to significant risk of preterm newborns in cohorts throughout Europe. This large-scale prospective study suggests that maternal employment during pregnancy in occupations classified as possibly or probably exposed to EDCs was associated with a significant increased risk of term LBW newborns in cohorts throughout Europe. This finding should be followed up by studying health outcomes throughout childhood and by focusing more specifically on occupations classified as exposed to multiple EDCs.

**Conclusions**

This large-scale prospective study suggests that maternal employment during pregnancy in occupations classified as possibly or probably exposed to EDCs was associated with a significant increased risk of term LBW newborns in cohorts throughout Europe. This finding should be followed up by studying health outcomes throughout childhood and by focusing more specifically on occupations classified as exposed to multiple EDCs.

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