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Maternal occupational exposure to endocrine-disrupting chemicals and urogenital anomalies in the offspring

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STUDY QUESTION: Is there an association between maternal occupational exposure to endocrine-disrupting chemicals (EDCs) early in pregnancy and subgroups of congenital anomalies of kidney and urinary tract (CAKUT), and hypospadias?

SUMMARY ANSWER: Exposure to specific EDCs can increase the risk of CAKUT and no association with hypospadias was observed.

WHAT IS KNOWN ALREADY: Previous studies showed an association between maternal occupational exposure to EDCs and hypospadias. However, little is known about the effect of these chemicals on the development of CAKUT, especially subgroups of urinary tract anomalies.

STUDY DESIGN, SIZE, DURATION: For this case–control study, cases with urogenital anomalies from the European Concerted Action on Congenital Anomalies and Twins Northern Netherlands (Eurocat NNL) registry and non-malformed controls from the Lifelines children cohort (living in the same catchment region as Eurocat NNL) born between 1997 and 2013 were selected. This study included 530 cases with CAKUT, 364 cases with hypospadias, 7 cases with both a urinary tract anomaly and hypospadias and 5602 non-malformed controls. Cases with a genetic or chromosomal anomaly were excluded, and to avoid genetic correlation, we also excluded cases in which a sibling with the same defect was included.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Information on maternal occupation held early in pregnancy was collected via self-administered questionnaires. Job titles were translated into occupational exposure to EDCs using a job-exposure matrix (JEM). Adjusted odds ratios (aORs) and 95% CIs were estimated to assess the association between maternal occupational exposure to EDCs (and to specific types of EDCs) and CAKUT and hypospadias.

MAIN RESULTS AND THE ROLE OF CHANCE: For CAKUT and hypospadias, 23.1% and 22.9% of the cases were exposed to EDCs, respectively, whereas 19.8% of the controls were exposed. We found an association between maternal occupational exposure to organic solvents/alkylphenolic compounds and CAKUT (aOR 1.41, 95% CI 1.01–1.97) that became stronger when combinations of urinary tract anomalies co-occurred with other defects (aOR 7.51, 95% CI 2.41–23.43). An association was also observed for exposure to phthalates/benzophenones/parabens/siloxanes and CAKUT (aOR 1.56, 95% CI 1.06–2.29), specifically urinary collecting system anomalies (aOR 1.62, 95% CI 1.03–2.54) and combinations of urinary tract anomalies (aOR 2.90, 95% CI 1.09–7.71). We observed no association between EDC exposure and hypospadias.

LIMITATIONS, REASONS FOR CAUTION: The different study designs of Eurocat NNL and Lifelines could have introduced differential information bias. Also, exposure misclassification could be an issue: it is possible that the actual exposure differed from the exposure estimated by the JEM. In addition, women could also have been exposed to other exposures not included in the analysis, which could have resulted in residual confounding by co-exposures.

WIDER IMPLICATIONS OF THE FINDINGS: Women, their healthcare providers, and their employers need to be aware that occupational exposure to specific EDCs early in pregnancy may be associated with CAKUT in their offspring. An occupational hygienist should be consulted in order to take exposure to those specific EDCs into consideration when risk assessments are carried out at the workplace.

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Key words: congenital anomalies of kidney and urinary tract / hypospadias / periconceptional / occupation / exposure / endocrine-disrupting chemicals

Introduction

Urogenital anomalies are congenital anomalies representing any defect in the organs and tissues responsible for the formation and excretion of urine. The total prevalence of congenital anomalies of kidney and urinary tract (CAKUT) is 31 per 10 000 births in Europe (EUROCAT, 2017). These anomalies comprise a broad range of disorders that result from abnormal embryonic renal development, such as renal parenchymal malformations, abnormalities in renal migration or abnormalities of the urinary collecting system. The severity of urinary anomalies can differ. Total absence of the kidneys will cause neonatal death, whereas milder kidney and urinary collecting system anomalies (e.g. vesico-ureteral-renal reflux—the retrograde passage of urine from the bladder into the upper urinary tract) can lead to chronic renal failure if untreated (Salmasi *et al.*, 2010).

Hypospadias is the most common genital anomaly, with a total prevalence of 14 per 10 000 births in Europe (EUROCAT, 2017). Hypospadias is present only in males and is characterised by an abnormal position of the urethral opening that ranges from the urethral opening being near the tip of the penis to further down the shaft of the penis, scrotum or in the perineum. Most types of hypospadias need surgical correction after birth.

Foetal development occurs under the influence of hormones. It has been proposed that hypospadias develops through disruption of the androgenic stimulation required for the development of the normal male external genitalia. Both genetic and environmental factors can negatively affect androgenic stimulation (Baskin, 2019). For CAKUT, the pathogenesis is largely unknown, but both genetic and environmental factors are thought to be involved (Rosenblum, 2017). Exposure to certain chemicals can influence hormonal activity and adversely affect foetal development of the urogenital tract (Yiee and Baskin, 2010). These potentially endocrine-disrupting chemicals (EDCs) can be man-made or naturally occurring. Sources of EDC exposure in the general population are diet, personal care products, cosmetics, plastics, textiles and construction materials, among others (Brouwers *et al.*, 2009; World Health Organisation and United Nations Environment Program, (UNEP), 2012). However, a relatively high level of exposure may occur in specific occupations as EDCs are present in a large variety of materials and products used in the workplace, such as pesticides, phthalates and organic solvents, or can be by-products formed during manufacturing, for example dioxins (Brouwers *et al.*, 2009; World Health Organisation and United Nations Environment Program, (UNEP), 2012).

Several studies have found an association between maternal occupational exposures to EDCs and hypospadias (Ormond *et al.*, 2009; Haraux *et al.*, 2016), while a few other studies have found associations between specific EDCs, such as pesticides (Rocheleau *et al.*, 2009) and solvents (Kalfa *et al.* 2015; Warembourg *et al.*, 2018), and hypospadias. However, other studies have found no association between maternal occupational exposure to pesticides or metals and increased risk of hypospadias (Zhu *et al.*, 2006; Spinder *et al.*, 2019).

Studies regarding maternal occupational exposure early in pregnancy in relation to CAKUT are limited. One study found an association between maternal occupational exposure to solvents and urinary tract malformations (Garlantézec *et al.*, 2009). However, only 13 cases were included in this prospective study. Another study found no association between solvent exposure and urinary tract malformations (Cordier *et al.*, 1997). Neither of these studies differentiated between specific subcategories of CAKUT. The aim of our study was thus to examine the association between maternal occupational exposure to EDCs early in pregnancy and subgroups of CAKUT and hypospadias in the offspring.

Materials and methods

Study design

This is a case–control study. Cases were selected from the European Concerted Action on Congenital Anomalies and Twins Northern Netherlands (Eurocat NNL) registry. Since 1981, this registry has been collecting data on children born with congenital anomalies in the northern Dutch provinces of Groningen, Friesland and Drenthe. Eurocat NNL registers live births (up to 10 years of age at notification), stillbirths, miscarriages and pregnancies terminated because of a congenital anomaly. After the parents have given informed consent, they are asked to complete a questionnaire that includes items on pregnancy characteristics, parental medical history, demographic and occupational characteristics, pre-pregnancy weight and height, and smoking, alcohol and medication use during the periconceptional period (3 months before pregnancy to the end of the first trimester).

Controls for this study were selected from the Lifelines cohort. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a three-generation design the health and health-related behaviours of 167 729 persons living in the same catchment region as Eurocat NNL. Participants were recruited through general practitioners in the study area. Children were invited to participate if one parent was already a participant in Lifelines. Children were included from 6 months of age until their 18th birthday after parents or the child has given informed consent. Parents of participating children received a questionnaire with questions on pregnancy, childbirth and health of the child in the first 6 months of life. Detailed information

about the Lifelines cohort study has been published previously (Scholtens *et al.*, 2015).

Ethical approval

Eurocat NNL and Lifelines operate within the scope of the Dutch data protection act according to the principles of the Declaration of Helsinki, and in accordance with the Code of Good conduct. Eurocat NNL did not require ethics committee approval to collect and store data according to the medical ethical committee of the University Medical Center Groningen, in line with the Dutch act Medical Research involving Human Subjects. Lifelines is approved by the medical ethical committee of the University Medical Center Groningen. All parents and participants of Eurocat NNL and Lifelines give informed consent before participation.

Case and control definition

Children, foetuses and terminated pregnancies affected by a major anomaly of the urogenital tract born between 1997 and 2013 were selected from Eurocat NNL. Coding and classification of congenital anomalies were performed according to EUROCAT guidelines (Greenlees *et al.*, 2011; EUROCAT, 2013). Since there are many different types of CAKUT, we classified cases into four groups of urinary tract anomalies: one, malformations of the renal parenchyma; two, anomalies of the urinary collecting system; three, abnormal embryonic migration of kidneys and other urinary tract anomalies; and four, combinations of urinary anomalies (Rosenblum, 2017; Bakker *et al.*, 2018). The anomalies included in these categories are listed in Table I. The primary urinary tract anomaly was used for categorisation. For example, if a child developed renal dysplasia as a consequence of an ureteropelvic junction stenosis (UPJ stenosis), the anomaly was classified as UPJ stenosis and categorised under 'anomalies of the urinary collecting system'. The only genital tract anomaly included in this study was hypospadias (Table I). Infants with both hypospadias and CAKUT were counted in both main categories (n = 7). Cases with a genetic or chromosomal anomaly were excluded. To avoid genetic correlation, we also excluded cases in which a sibling with the same defect was included.

Controls were defined as children without congenital anomalies born between 1997 and 2013. We only selected infants whose biological mother participated in Lifelines. Parents were asked if their child was born with a congenital anomaly. Since linkage with Eurocat NNL was not possible and parental descriptions of the congenital anomaly were poor, we could not include these infants as cases. Lifelines is a three-generation study, which aimed at including multiple family members, therefore, one infant per mother was included to avoid genetic correlation.

Exposure assessment

Mothers were asked to report their occupation, including industry of employment, held during early pregnancy (first trimester). By restricting our analyses to employed women, we controlled for confounding by employment status and related factors. This is important because employment status is related to sociodemographic and (reproductive) health characteristics that are generally recognised risk factors for adverse pregnancy outcomes (Rocheleau *et al.*, 2017; Johnson *et al.*, 2019). The maternal job descriptions of children included from the Eurocat registry and Lifelines cohort were coded by two authors (N.S. and H.K.) into the International Standard Classification of Occupational 1988 (ISCO88; International Labor Office, 1988), without knowledge of case or study details. To translate the ISCO88 codes into occupational exposure, we used a job-exposure matrix (JEM) developed by van Tongeren *et al.* (2002). The original JEM was developed to study the risk of hypospadias after maternal exposure to EDCs (van Tongeren *et al.*, 2002) and later updated to improve its performance (Brouwers *et al.*, 2009). Chemicals incorporated in this JEM were identified from the literature and classified into nine chemical groups: polycyclic aromatic hydrocarbons (PAHs), polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants and a miscellaneous group (benzophenones, parabens and siloxanes). Three occupational experts scored the exposure to each chemical group as 'unlikely, possible or probable' using job titles from the Standard Occupation Classification (SOC). Two authors (N.S. and H.K.) translated SOC codes into the ISCO88 classification to make the JEM applicable to the data in this study. Owing to sparse data (<5 exposed cases), exposures to polychloride organic compounds, bisphenol A and flame retardants were not analysed. Detailed information on the JEM has been published elsewhere (Brouwers *et al.*, 2009).

Statistical analyses

The selection of covariates was based on associations observed in prior literature. Infant and maternal characteristics for cases and controls were tabulated. Variables registered in both Eurocat NNL and the Lifelines cohort were: child sex, birth year, maternal age at delivery, maternal body BMI—the self-reported pre-pregnancy weight and height for Eurocat NNL cases or objective measurement at baseline visit for Lifelines controls (underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) or obese (≥30 kg/m^2))—, maternal education level (low (primary school, lower vocational education, pre-vocational education), middle (secondary vocational education, general secondary education or pre-university education) or high (higher professional education or academic education)), maternal smoking (no, yes/some period during pregnancy), maternal alcohol use during pregnancy (no, yes/some period during pregnancy), folic acid use (no/wrong period, yes/sometime during periconceptional period) and fertility problems (no, yes (self-reported fertility problems or fertility treatment)) (Pierik *et al.*, 2004; Ormond *et al.*, 2009; Brouwers et al., 2010; Nicolaou et al., 2015) .

The correlation between EDC subgroups was explored in mothers of controls to determine the best modelling strategy. Owing to high correlation, organic solvents and alkylphenolic compounds were combined into a single exposure group (exposure to at least one exposure in this group), as were phthalates, benzophenones, parabens and siloxanes.

The association between maternal occupational exposures was assessed separately for the four classes of CAKUT and hypospadias. Because hypospadias is only present in boys, only boys were selected as controls for the hypospadias analyses. The associations between any occupational exposures (possible/probable) and CAKUT and hypospadias were assessed using univariate and multivariate logistic regression to estimate crude odds ratios (OR) and adjusted odds ratios

(aORs), respectively. Cases and controls with no occupational exposure to EDCs included in the analysis were used as the reference category. Multivariate logistic regression analyses were adjusted for birth year, maternal age at delivery, maternal BMI, and smoking and alcohol use during pregnancy, based on χ^2 tests (Supplementary Table SI). Multivariate logistic regressions regarding CAKUT were additionally adjusted for child sex, folic acid use and fertility problems. Stratified analyses were conducted for isolated urogenital defects and for urogenital defects co-occurring with congenital anomalies because these may differ in aetiology. To account for the likelihood of exposure, subgroup analyses were performed only including mothers who had a job 'probably' involving exposure to EDCs, meaning that exposure was likely to occur in more than 10% of workers with this job. We also performed analyses using 'no exposure' to any occupational EDCs as the reference category. Also, stratified analyses were performed for males and females. The Statistical Package for the Social Sciences version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA) was used to perform all analyses.

Results

We selected 1462 cases with urogenital defects from Eurocat NNL (Fig. 1). Cases were excluded because mothers had no job early in pregnancy (n = 176) or because job information was missing (n = 369). Fourteen cases were excluded because siblings with the same defect were included. We included 530 cases with CAKUT, 364 cases with hypospadias and 7 cases with both a urinary tract anomaly and hypospadias. For CAKUT cases, 12% were miscarriages, stillbirths or terminated pregnancies because of a congenital anomaly. All hypospadias cases were live births.

The Lifelines children's cohort consisted of 12 494 potentially eligible infants born from 1997 to 2013 (Fig. 2). From these, we excluded 163 non-biological infants. A further 814 children were excluded because their parents reported one or more congenital anomalies or it was unknown if the child was born with a congenital anomaly. Another 3029 children were excluded because their mother did not work early in pregnancy or job information was missing. One child per parent was selected, which resulted in the exclusion of another 2886 children. In total, 5602 children without congenital anomalies were selected as the control group.

Children affected by a urinary tract anomaly were more often boys (70.2% of Eurocat NNL cases were male versus 48.8% of the Lifelines cohort, Supplementary Table SI). For both CAKUT and hypospadias cases, the mothers appeared to be younger at delivery and had a lower BMI compared to controls. Mothers of cases were also more often smokers and more often used alcohol during pregnancy compared to controls. The mothers of CAKUT cases used folic acid less often and more often had fertility problems.

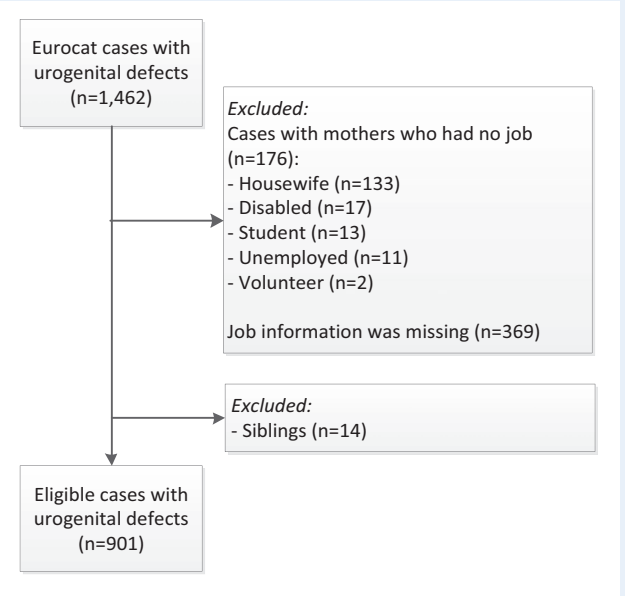

Figure 1 Flowchart for case selection from the European Concerted Action on Congenital Anomalies and Twins Northern Netherlands registry, 1997–2013.

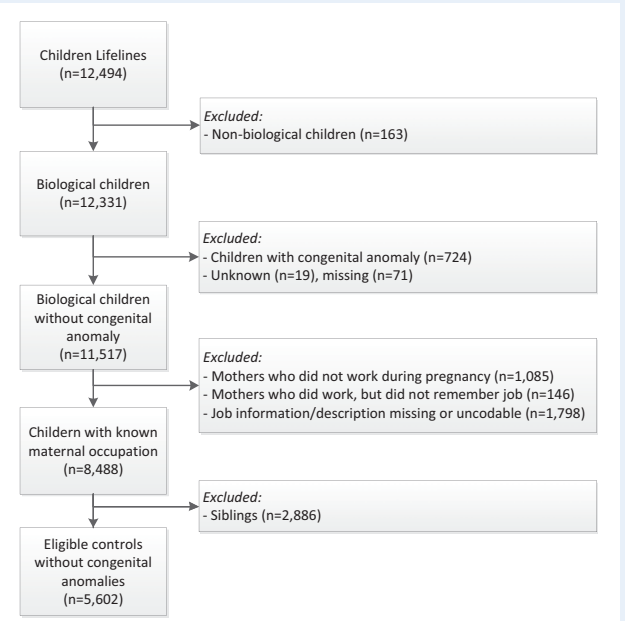

Figure 2 Flowchart for control selection from the Lifelines population-based cohort study Northern Netherlands, 1997–2013.

Congenital anomalies of kidney and urinary tract

The percentage of women exposed to EDCs and the ORs for CAKUT are shown in Table II. For CAKUT, 23.1% of the cases and 19.8% of the controls were exposed to 'any' EDCs. After adjustment, an OR of 1.21 (95% CI 0.96–1.53) was observed between exposure to 'any' EDCs and CAKUT when comparing to non-exposed infants. When we looked into specific types of EDCs, we observed associations for exposure to organic solvents/alkylphenolic compounds (aOR 1.41, 95% CI 1.01–1.97) and exposure to phthalates/benzophenones/parabens/siloxanes (aOR 1.56, 95% CI 1.06–2.29). No associations

Table I Classes of urogenital anomalies.

Anomaly	Classes	Included urinary tract anomalies
Urinary anomalies	I Malformations of the renal parenchyma	Renal agenesis, renal hypoplasia, multicystic dysplastic kidneys, cystic kidney and renal dysplasia
	II Anomalies of the urinary collecting system	Hypdronephrosis (end stage of obstructive anomalies), ureteropelvic junction stenosis, megaloureter, hydroureter, duplication of ureter, vesico-uretero-renal reflux, epispadias, exstrophy of urinary bladder, OEIS complex, (posterior) urethral valves, stenosis, atresia of urethra and bladder neck, and absence of bladder and urethra
	III Abnormal embryonic migration of kidneys and other urinary tract anomalies	Pelvic kidney, horseshoe kidney, other malformations of the urinary system
	IV Combinations of urinary anomalies	Presence of at least two types of urinary tract anomalies, both considered to be primary anomalies and belonging to at least two categories
Genital anomalies	Hypospadias	Glandular,* coronal, penile, penoscrotal and perineal hypospadias

*Included from birth year 2005 onwards according to EUROCAT guidelines (Greenlees *et al.*, 2011; EUROCAT, 2013).
EUROCAT, the European Concerted Action on Congenital Anomalies and Twins Northern Netherlands registry; OEIS complex, omphalocele-exstrophy-imperforate anus-spinal defects.

were observed for exposure to PAHs or pesticides when comparing to non-exposed infants (aOR 1.06, 95% CI 0.73–1.53 and aOR 0.53, 95% CI 0.22–1.25, respectively).

Subgroup analyses for specific classes of CAKUT were performed (Table II). The aOR for anomalies of the urinary collecting system was higher compared to all urinary tract anomalies (aOR 1.29, 95% CI 0.98–1.69). The aORs for other subgroups anomalies were lower and ranged from 0.84 (95% CI 0.28–2.52) for abnormal embryonic migration of the kidneys to 1.10 (95% CI 0.51–2.35) for combinations of urinary tract anomalies. An association was found between occupational exposure to phthalates/benzophenones/parabens/siloxanes and anomalies of the urinary collecting system (aOR 1.62, 95% CI 1.03–2.54) and combinations of CAKUT (aOR 2.90, 95% CI 1.09–7.71). We found no associations with anomalies of the renal parenchyma and abnormal embryonic migration of the kidney.

When we performed a stratified analysis for isolated CAKUT (n = 420, Supplementary Table SII) and CAKUT co-occurring with other congenital anomalies (n = 117, Supplementary Table SIII), the association between occupational exposure to phthalates/benzophenones/parabens/siloxanes was stronger for isolated cases (aOR 1.63, 95% CI 1.07–2.49) than for CAKUT co-occurring with congenital anomalies (aOR 1.20, 95% CI 0.51–2.80), specifically for anomalies of the urinary collecting system (aOR 1.76, 95% CI 1.11–2.79). The association between exposure to organic solvents/alkylphenolic compounds and combinations of urinary tract anomalies became stronger when restricting the analysis to CAKUT co-occurring with congenital anomalies (aOR 7.51, 95% CI 2.41–23.43).

Stratified analyses for males and females affected by CAKUT were performed (n = 377 and n = 160, respectively, Supplementary Tables SIV and SV). The association between exposure to phthalates/benzophenones/parabens/siloxanes and anomalies of the urinary collecting system was only present in male offspring (aOR 1.85, 95% CI 1.06–3.23), whereas the association between organic solvents/alkylphenolic compounds and CAKUT was only present in females (aOR 1.87, 95% CI 1.11–3.14) .

Subgroup analyses performed for mothers with 'probable' exposure to EDCs according to the JEM and for women not exposed to any EDC (the reference category) did not materially change the results (Supplementary Tables SVI and SVII).

Hypospadias

The exposure rates and ORs for hypospadias are shown in Table III. For hypospadias, 22.9% of the cases and 18.9% of the controls were exposed to 'any' EDCs. We observed no association between EDCs in general and hypospadias in offspring (aOR 1.26, 95% CI 0.95–1.65), nor did we observe an association between subcategories of EDCs and hypospadias.

We performed stratified analyses of isolated hypospadias (n = 341) and hypospadias co-occurring with other congenital anomalies (n = 30; Supplementary Table SVIII). An increased aOR was found for 'any' EDCs exposure and hypospadias that co-occurred with another congenital anomalies (aOR 1.46, 95% CI 0.63–3.39) compared to isolated hypospadias (aOR 1.23, 95% CI 0.92–1.64). Subgroup analyses for mothers with 'probable' exposure to EDCs or using women not exposed to any EDC as reference category did not materially change the results (Supplementary Tables SIX and SX).

Discussion

In this study, we found an association between maternal occupational exposure to organic solvents/alkylphenolic compounds and phthalates/benzophenones/parabens/siloxanes and CAKUT, specifically for anomalies of the urinary collecting system when more than one urinary tract anomaly was present. Women exposed to organic solvents/alkylphenolic compounds were working in the agricultural sector or as life-science technicians. Women exposed to phthalates/benzophenones/parabens/siloxanes worked mainly as cleaners, hairdressers or beauticians.

Strengths and weaknesses of the study

For this case–control study, we used case data from the high-quality population-based Eurocat NNL registry. Detailed medical information

Table II Prevalence, crude and adjusted odds ratios of maternal occupational exposure to endocrine-disrupting chemicals, and the risk of urinary anomalies in the offspring (Eurocat) compared to non-malformed controls (Lifelines), Northern Netherlands, 1997–2013.Organic solvents/alkylphenolic compounds[c]

Occupational exposure	Total	Unexposed		Exposed[a]		Unadjusted		Adjusted[b]	
	n	n	(%)	n	(%)	OR	95% CI	OR	95% CI
Any EDC									
Controls	5602	4491	(80.2)	1111	(19.8)	1.00		1.00	
Urinary anomalies	537	413	(76.9)	124	(23.1)	1.21	(0.98–1.50)	1.21	(0.96–1.53)
Malformations of the renal parenchyma	109	85	(78.0)	24	(22.0)	1.14	(0.72–1.80)	1.04	(0.64–1.69)
Anomalies of the urinary collecting system	360	274	(76.1)	86	(23.9)	1.27	(0.99–1.63)	1.29	(0.98–1.69)
Abnormal embryonic migration of kidneys	25	20	(80.0)	5	(20.0)	1.01	(0.38–2.67)	0.84	(0.28–2.52)
Combination of urinary tract anomalies	43	34	(79.1)	9	(20.9)	1.07	(0.51–2.24)	1.10	(0.51–2.35)
PAHs									
Controls	5602	5251	(93.7)	351	(6.3)	1.00		1.00	
Urinary total	537	498	(92.7)	39	(7.3)	1.17	(0.83–1.65)	1.06	(0.73–1.53)
Malformations of the renal parenchyma	109	104	(95.4)	5	(4.6)	0.72	(0.29–1.78)	0.51	(0.18–1.41)
Anomalies of the urinary collecting system	360	330	(91.7)	30	(8.3)	1.36	(0.92–2.01)	1.28	(0.84–1.94)
Abnormal embryonic migration of kidneys	25	<5				NC		NC	
Combination of urinary tract anomalies	43	<5				NC		NC	
Pesticides									
Controls	5602	5486	(97.9)	116	(2.1)	1.00		1.00	
Urinary total	537	531	(98.8)	6	(1.1)	0.53	(0.23–1.22)	0.53	(0.22–1.25)
Malformations of the renal parenchyma	109	<5				NC		NC	
Anomalies of the urinary collecting system	360	355	(98.6)	5	(1.4)	0.67	(0.27–1.64)	0.65	(0.25–1.66)
Abnormal embryonic migration of kidneys	25	<5				NC		NC	
Combination of urinary tract anomalies	43	<5				NC		NC	
Organic Solvents/Alkylphenolic compounds[c]									
Controls	5602	5220	(93.2)	382	(6.8)	1.00		1.00	
Urinary total	537	486	(90.5)	51	(9.5)	1.43	(1.06–1.95)	1.41	(1.01–1.97)
Malformations of the renal parenchyma	109	100	(91.7)	9	(8.3)	1.23	(0.62–2.45)	1.17	(0.58–2.38)
Anomalies of the urinary collecting system	360	326	(90.6)	34	(9.4)	1.43	(0.99–2.06)	1.39	(0.93–2.06)
Abnormal embryonic migration of kidneys	25	<5				NC		NC	
Combination of urinary tract anomalies	43	37	(86.0)	6	(14)	2.22	(0.93–5.28)	2.16	(0.88–5.30)
Phthalates/benzophenones/parabens/siloxanes[c]									
Controls	5602	5348	(95.5)	254	(4.5)	1.00		1.00	
Urinary total	537	500	(93.1)	37	(6.9)	1.56	(1.09–2.23)	1.56	(1.06–2.29)
Malformations of the renal parenchyma	109	104	(95.4)	5	(4.6)	1.01	(0.41–2.51)	0.92	(0.36–2.32)
Anomalies of the urinary collecting system	360	334	(92.8)	26	(7.2)	1.64	(1.08–2.49)	1.62	(1.03–2.54)
Abnormal embryonic migration of kidneys	25	<5				NC		NC	
Combination of urinary tract anomalies	43	38	(88.4)	5	(11.6)	2.77	(1.08–7.10)	2.90	(1.09–7.71)

[a]Possible or probable exposure.
[b]Adjusted for child sex, birth year, maternal age and BMI, smoking, alcohol, and folic acid use during pregnancy and fertility problems.
[c]Exposure to at least one exposure in this group.
OR, odds ratio; EDCs, endocrine-disrupting chemicals; PAHs, polycyclic aromatic hydrocarbons; NC, not calculated owing to sparse data (<5 exposed cases).

was available for each case, and all cases were coded by trained registry staff according to international coding guidelines (EUROCAT, 2013). These factors made it possible to distinguish between classes of urinary tract anomalies and between isolated defects and urinary tract defects that co-occurred with other anomalies. A major strength of this study is that we used non-malformed controls. We selected controls from Lifelines, a large population-based cohort that recruited its participants from the same region as Eurocat. The Lifelines cohort is representative for the population in the Northern Netherlands (Klijs *et al.*, 2015). Another strength is that we used a JEM for occupational exposure assessment. When compared to self-reported exposures, the use of a JEM limits the effect of recall bias on exposure estimates

Table III Prevalence, crude and adjusted OR of maternal occupational exposure to EDCs and the risk of hypospadias in the offspring (Eurocat) compared to non-malformed controls (Lifelines), Northern Netherlands, 1997–2013.

Occupational exposure	Total	Unexposed		Exposed[a]		Unadjusted		Adjusted[b]	
	n	n	(%)	n	(%)	OR	95% CI	OR	95% CI
Any EDC									
Controls[c]	2731	2214	(81.1)	517	(18.9)	1.00		1.00	
Hypospadias	371	286	(77.1)	85	(22.9)	1.27	(0.98–1.65)	1.26	(0.95–1.65)
PAHs									
Controls[c]	2731	2560	(93.7)	171	(6.3)	1.00		1.00	
Hypospadias	371	340	(91.6)	31	(8.4)	1.37	(0.92–2.03)	1.37	(0.91–2.07)
Pesticides									
Controls[c]	2731	2685	(98.3)	46	(1.7)	1.00		1.00	
Hypospadias	371	366	(98.7)	5	(1.3)	0.80	(0.32–2.02)	0.76	(0.30–1.98)
Organic solvents/alkylphenolic compounds[d]									
Controls[c]	2731	2560	(96.7)	171	(3.3)	1.00		1.00	
Hypospadias	371	347	(93.5)	24	(6.5)	1.02	(0.66–1.59)	0.94	(0.59–1.48)
Phthalates/benzophenones/parabens/siloxanes[d]									
Controls[c]	2731	2620	(95.9)	111	(4.1)	1.00		1.00	
Hypospadias	371	351	(95.6)	20	(5.4)	1.35	(0.83–2.19)	1.21	(0.73–2.01)

[a]Possible or probable exposure.
[b]Adjusted for birth year, maternal age and BMI smoking and alcohol use during pregnancy.
[c]Only boys are selected as controls.
[d]Exposure to at least one exposure in this group.
EDC, endocrine-disrupting chemical; PAHs, polycyclic aromatic hydrocarbons.

as well as the differential misclassification of exposure compared to self-reported exposure (Kromhout and Vermeulen, 2001; Mannetje and Kromhout, 2003).

The different study designs of Eurocat and Lifelines could have introduced differential information bias. Eurocat aimed to conduct research specifically to identify risk factors for congenital anomalies, whereas Lifelines aimed to collect data that could be used to examine diseases in general. Eurocat questionnaires therefore focused specifically on risk factors for congenital anomalies, whereas the Lifelines questionnaire included a wide variety of risk factors for neonatal and childhood diseases such as low birthweight, asthma, allergies and congenital anomalies. This is of particular importance when assessing our confounder variables because questions were asked with different intentions. An example that illustrates the difference in study design is BMI. In Eurocat, weight was self-reported, whereas in Lifelines, participants' weight was measured at the study clinic. It is likely that self-reported weight is underestimated for overweight women, which could have an impact on our results. Questions regarding smoking and drinking alcohol were very similar in Eurocat and Lifelines (self-reported), limiting the introduction of differential information bias. However, recall bias could have been an issue. There was also a lack of detailed information for several covariates. For example, if women smoked during the first trimester, there was no detailed information on how many cigarettes women were smoking at that time. Furthermore, not all the data on potential covariates were available. For example, there were no data on maternal medication use for infants from Lifelines. Previous literature showed that maternal medication use, such as hormones for fertility treatment, increases the risk of hypospadias (Raghavan *et al.*, 2018). In addition, supplementation with multivitamins was not studied and, although a previous study showed that intake of multivitamins can decrease the risk of CAKUT (Groen In 't Woud et al., 2016), it is possible that residual confounding was introduced.

Bias was unlikely for our main risk factor of interest: maternal occupational exposure early in pregnancy. In both questionnaires, the mothers were asked to report their job during pregnancy. In addition, recall bias could have been introduced, as the time between birth and notification was 16 months for Eurocat cases and 7.5 years for Lifelines controls. An underestimation of the effect between occupational exposure and urogenital anomalies owing to recall bias is expected to be small, because exposure is assigned based on job description/industry of employment, and recall bias for self-reported job description has been reported to be limited (Teschke *et al.*, 2002). A limitation of JEMs in general is that they assign exposure at job level, which under normal conditions will result in a Berkson type error resulting in unbiased, but less precise, risk estimates. Another limitation is that the JEM estimates exposure as possible exposed (involves <10% of workers with this job title) and probably exposed (exposure was likely to occur in more than 10% of workers with this job; Brouwers *et al.*, 2009). No studies have evaluated how the exposure assigned by the JEM relates to the actual exposures of the females involved. Non-differential misclassification could be introduced in three different ways. First, the JEM does not account for the years in which the job was performed, and previous studies have shown that occupational exposure can vary over time (Burstyn and Kromhout, 2002; Peters

et al., 2011). Second, circumstances at the workplace are often unpredictable and can vary within a job and between companies (Teschke et al., 2002). Finally, the JEM does not account for the possibility that women avoided certain exposures because of their pregnancy, which could have led to bias towards the null. We have no information regarding the number of hours per week mothers worked early in pregnancy or other characteristics regarding employment. Therefore, it is possible that the actual exposure is lower or absent than the exposure estimated by the JEM. Besides the variability of exposures assessed by the JEM, women could also have been exposed to other exposures not included in the JEM. This could have resulted in residual confounding by co-exposures. One other limitation is that the JEM assigns a probability of exposure rather than a level of exposure, which precludes performing dose–response analyses.

Interpretation

Studies regarding occupational exposure and urinary anomalies are scarce and only performed for maternal occupational exposure to solvents. One earlier study also found an association between solvent exposure and urinary tract anomalies (Garlantézec et al., 2009), but the results of two other studies were not in line with our finding (Cordier et al., 1997, 2001). However, one of these studies did find an association between glycol ethers (a specific group of organic solvents) and multiple congenital anomalies (Cordier et al., 1997), which is in line with the association we found in our subgroup analysis for cases with a combination of urinary tract anomalies co-occurring with congenital anomalies. We did not observe a specific pattern of co-occurring congenital anomalies in the five exposed cases that could explain the association between solvents and multiple anomalies. The number of included CAKUT cases in those previous studies (Cordier et al., 1997, 2001; Garlantézec et al., 2009) was low compared to the present study (n = 12–76 versus n = 537), and therefore no subgroup analyses were performed.

It is known that EDCs can interfere with hormone levels during foetal development, and hormones such as gonadotrophins, oestrogen and androgens play an important role in the development of many tissues during foetal growth. Therefore, it seems possible that maternal occupational exposure to solvents increases the risk of multiple, co-occurring congenital anomalies. Additionally, it has been suggested that exposure to EDCs is associated with inappropriate modulation of hormone receptors and can, therefore, interfere with the development of the (male) reproductive tract (Yoon et al., 2014). The development of the urinary tract system is closely related to that of the reproductive tract.

However, despite the hypothesis that EDCs can interfere with the development of the reproductive tract, we did not find an association between maternal occupational exposure to EDCs and hypospadias, nor did we find one with specific groups of EDCs. Previous studies have reported contradictory results. Four studies found an association between maternal occupational exposure to EDCs in general and hypospadias (Giordano et al., 2010; Morales-Suárez-Varela et al., 2011; Kalfa et al., 2015; Haraux et al., 2016), but several other studies and the present study found no association (Vrijheid et al., 2003; Pierik et al., 2004; Carbone et al., 2007; Nassar et al., 2010). A few studies performed subgroup analysis for specific EDCs (Vrijheid et al., 2003; Pierik et al., 2004; Ormond et al., 2009; Giordano et al., 2010; Nassar et al., 2010; Morales-Suárez-Varela et al., 2011) . One study that found an effect for EDC exposure in general, found that specifically phthalates and other compounds (e.g. parabens) had an effect (Morales-Suárez-Varela et al., 2011). However, another study that found an association, did not find an effect for specific EDC subgroups (Giordano et al., 2010). Two studies that found no association between EDC exposure and hypospadias, also found no specific subgroup effects (Pierik et al., 2004; Carbone et al., 2007). Only one study found an association between maternal occupational exposure to metals and mild hypospadias (Nassar et al., 2010). Two studies showed an association between maternal occupational exposure to phthalates and hypospadias (Vrijheid et al., 2003; Ormond et al., 2009). Two studies showing an association between EDC exposure and hypospadias included a small number of cases (n = 57–80), which could have resulted in imprecise estimates (Giordano et al., 2010; Haraux et al., 2016). As studies were conducted in different countries, it is possible that exposure levels varied over time and by country owing to (pregnancy) policy differences. The difference in results could not be explained by exposure assessment methods as all studies used the same JEM produced by van Tongeren et al. (2002).

The association between maternal occupational exposure to pesticides and hypospadias has been examined in several studies. This study did not show an association between maternal occupational exposure to pesticides and hypospadias. This is in line with two published reviews, including previous studies with comparable exposure assessment methods to this study (Rocheleau et al., 2009; Spinder et al., 2019).

Conclusion

This study showed an association between maternal occupational exposure to organic solvents/alkylphenolic compounds and phthalates/benzophenones/parabens/siloxanes early in pregnancy and CAKUT in offspring. We also found some indication that exposure to those specific EDCs is associated with a combination of urinary tract anomalies that co-occur with other congenital anomalies. In the Netherlands, since 1997, employers have been obliged by law to identify occupational risks for pregnant employees by carrying out risk assessments at the workplace (Wetboek, 1997). Women, their healthcare providers and their employers need to be aware that occupational exposure to specific EDCs early in pregnancy may be associated with CAKUT in offspring. An occupational hygienist should be consulted to take exposure to those specific EDCs into consideration when risk assessments are carried out at the workplace.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The Eurocat Northern Netherlands data underlying this article will be shared on reasonable request to the corresponding author. The

Lifelines data underlying this article were provided by Lifelines Biobank under licence.

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Authors' roles

N.S.: study design, congenital anomaly classification, job coding, data analysis and manuscript drafting. J.E.H.B.: study design, Eurocat NNL data collection and congenital anomaly classification. M.v.T.: job-exposure matrix designer. H.M.B.: study design and statistical expertise. H.K.: job coding, study design and statistical expertise. H.E.K.d.W.: study design and Eurocat NNL data collection. All authors contributed to the interpretation of the results, revision of the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors report no conflict of interest.

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