The effect of prenatal TVOC exposure on birth and infantile weight: the Mothers and Children's Environmental Health study

Moonhee Chang[1], Hyesook Park[1], Mina Ha[2], Yun-Chul Hong[3], Youn-Hee Lim[3], Yangho Kim[4], Young Ju Kim[5], Dongheon Lee[6] and Eun-Hee Ha[7]

BACKGROUND: Volatile organic compounds (VOCs) might restrict prenatal and postnatal growth. However, the effect of the exposure of prenatal VOCs on postnatal growth has not been studied sufficiently. Thus, we investigated the relationship between the exposure of total volatile organic compounds (TVOCs) during pregnancy and its effects on postnatal growth.

METHODS: A total of 383 pregnant participants were enrolled from 2006 to 2008. We investigated maternal characteristics using a questionnaire. Personal air samples of TVOCs were obtained in mid or late pregnancy. After these mothers had given birth, 360 singleton newborns were selected and postnatal follow-up data were collected at 6, 12, 24, and 36 months, as well as anthropometric factors including body weight. Multiple general linear and mixed models were applied for statistical analyses.

RESULTS: The mean concentration of prenatal exposure to TVOCs was 284.2 μg/m^3 and that of formaldehyde was 81.6 μg/m^3. The birth weight of newborns decreased significantly with prenatal TVOC exposure ($\beta = -45.89$, $P = 0.04$). The adjusted mean body weight was 300 g lower in the high-TVOC group (⩾75th) compared with that in the low-exposure group (<75th).

CONCLUSION: These results indicate that elevated exposure to TVOCs during the prenatal period may adversely influence early postnatal growth.

Pregnant women tend to spend more time indoors during the latter part of pregnancy (1). During this period, activities such as papering or buying new items for their upcoming baby may lead to elevated exposure to air contaminants for pregnant women. Staying in the house and engaging in decorating activities increase exposure to volatile organic compounds (VOCs) such as formaldehyde (HCHO), benzene, toluene, xylene, and their totals (TVOCs) (2). The health risks of VOC exposure should receive more attention because of their ubiquitous prevalence, unintentionality of exposure, and greater concentration indoors than outdoors. Pregnant women and their fetuses are at higher risk, as they are more susceptible to environmental toxicants.

Recent public concerns about VOC-related health effects have arisen after several reports on sick building syndrome. In addition, evidence from epidemiological and experimental studies has shown that exposure to VOCs adversely affects birth outcomes and hinders infantile immunologic and neurologic functional development (3–6). HCHO was classified as a potential carcinogen by the International Agency for Research on Cancer (IARC), and a European study classified VOCs and HCHO as environmental risk factors with medium priority (7–9). However, there are still limited data on the link between prenatal exposure to VOCs and postnatal growth.

This study investigated the relationship between TVOC/HCHO exposure during the prenatal period and the newborn's postnatal growth, with a special focus on weight. We focused on two major research questions: (i) the relationship between prenatal environmental VOC exposure and birth weight as an indicator of harmful effects due to intrauterine exposure and (ii) the relationship between prenatal VOC exposure and postnatal infant weight at birth and at 6, 12, 24, and 36 months after birth.

METHODS

Study Population and Weight Growth Assessment

A subsample of 383 pregnant participants was chosen from a prospective birth cohort study (Mother and Children's Environmental Health Study) (10). The Mother and Children's Environmental Health Study was initiated in May 2006 to establish a mother–child cohort to examine how environmental exposures from the fetal period affect a newborn's growth, development, and susceptibility to disease. All study protocols were reviewed by the institutional review board of three collaborative centers at Ewha Womans University Hospital in Seoul, Dankook University Hospital in Choen-an, and Ulsan University in Ulsan. After participants had given their informed consent, trained nurses investigated the prenatal characteristics of the mothers using questionnaires on

[1]Department of Preventive Medicine and Medical Research Institute, School of Medicine, Ewha Womans University, Seoul, South Korea; [2]Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, South Korea; [3]Institute of Environmental Medicine, Seoul National University Medical Research Center, Seoul, South Korea; [4]Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; [5]Departments of Obstetrics and Gynecology and Medical Research Institute, School of Medicine, Ewha Womans University, Seoul, South Korea; [6]Department of Mathematics and Statistics, Williams College, Williamstown, Massachusetts; [7]Department of Occupational and Environmental Medicine and Medical Research Institute, School of Medicine, Ewha Womans University, Seoul, South Korea. Correspondence: Eun-Hee Ha (eunheeha@ewha.ac.kr)

Received 31 July 2016; accepted 6 February 2017; advance online publication 7 June 2017. doi:10.1038/pr.2017.55

maternal demographic factors, socioeconomic status, previous obstetric history, and residential factors including exposure to household products (air cleaner, humidifier, sofa, etc.), house age, and the number of cohabitants during pregnancy. After delivery, birth-related information, including gestational age, birth weight, gender, and current obstetric complications, was obtained from the delivery records. Infants were followed up at 6, 12, 24, and 36 months of age. The numbers of infants that participated in the physical examination at 6, 12, 24, and 36 months was 262, 234, 199, and 92, respectively. When participants visited the research hospital, mothers were asked to complete questionnaires on demographic characteristics, disease history, and environmental conditions surrounding the infants. At the same time, anthropometric factors such as body weight and height of infants were measured by trained staff. Age-specific weights by gender were calculated on the basis of the growth standard for Korean children developed by the Korean Pediatric Society and Ministry of Health and Welfare (11). Retention rates were 94% at birth, 72.8% at 6 months, 89.3% at 12 months, and 85.0% at 24 months; except for the cases aged under 36 months at final follow-up.

TVOC and HCHO Exposure Measurements During Pregnancy

Personal TVOC samples were collected using a passive sampler (3M 3500 OVM Badge, St. Paul, MN, USA) for 3 days in mid or late pregnancy of participants, which were analyzed using GC/MSD (Agilent, model 6890/5973N, Santa Clara, CA, USA). Simultaneously, personal HCHO levels were recorded by pulling air through a 2,4-dinitrohydrazine-coated silica gel cartridge (SKC UMEX 100, Eighty Four, PA, USA) with a flow rate of 0.2 l/min for 3 days. The 2,4-dinitrohydrazine-HCHO derivative eluted with acetonitrile was determined by reverse-phase high-performance liquid chromatography.

Covariates

Prenatal covariates and confounders were obtained from the questionnaires and medical records. We investigated demographic factors such as maternal age and pre-pregnancy body mass index, socioeconomic factors such as parental education level and family income, and obstetric factors such as parity (equal to birth order), gestational age, and the newborn's gender.

Postnatal covariates were obtained using a questionnaire after birth. Information on breastfeeding and family income was collected by interviewing the mothers.

Statistical Analysis

We used data on 360 singleton newborns born to an initial sample of 383 mothers. TVOC and HCHO concentrations were categorized into two groups at the 75th percentile (low vs. high), and continuous values were log-transformed to assume a normal distribution. We prepared models to measure the associations between TVOC/HCHO and birth weight: (i) a univariate model with simple regression; and (ii) a multivariate model adjusted for related confounders such as maternal age, pre-pregnancy body mass index, education level, parity, newborn's gender, gestational age at birth, and related residential factors. Second, we constructed a general linear model at each visit separately to explore the relationship between TVOC/HCHO and postnatal weight. Multiple linear mixed model analyses (12,13) were applied to repeated data of infantile weight measured at birth and at 6, 12, 24, and 36 months after adjusting for gender, birth order, breastfeeding, and education. In addition, calculated weight-for-age (Z score) was used in the same analysis. Bar plots were created to illustrate the least square estimates of weight scores at each visit. All statistical analyses were performed using the Statistical Analysis System, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows the general characteristics of the mothers and their newborns. The mean maternal age was 30 years, the mean pre-pregnancy body mass index was 21.3 kg/m^2, and 33.8% of mothers were working during pregnancy. A total of 65% of the women had a university-level education and 90.7% earned over two million Korean Won (1,800 USD) per month. No significant difference was observed between the high-exposure group and the low-exposure group regarding maternal demo-social characteristics; however, family income in the high TVOC exposure group was higher than that in the low-exposure group ($P = 0.03$).

Regarding the newborn's birth and infantile characteristics, 52.2% of the babies were female and 56.1% had no siblings. The mean birth weight was 3.3 kg, and nine cases (2.5%) were born with a low birth weight, defined as lower than 2.5 kg. The mean infantile body weight was 8.5, 10.1, 12.5, and 14.5 kg at 6, 12, 24, and 36 months of age, respectively.

The mean concentration of prenatal exposure to TVOCs was 284.2 μg/m^3 and that of HCHO was 81.6 μg/m^3. The 75th percentile value of TOVC exposure was 374.0 μg/m^3 and that of HCHO exposure was 105.7 μg/m^3 (**Table 2**).

Table 3 shows the relationship between prenatal exposure to TVOCs and HCHO and the newborn's birth weight, after adjusting for maternal age, body mass index, education level, parity, infant's gender, and gestational age at delivery. Prenatal exposure to TVOCs significantly and adversely affected the newborn's birth weight ($\beta = -45.89$, $P = 0.04$ with a log 1 unit increase). HCHO also tends to show a negative relationship with birth weight; however, no statistical significance was found.

Visit-time-varying association between TVOCs and postnatal weight was explored by comparing adjusted body weights of the high-exposure group with those of the low-exposure group. We also compared age-specific standardized weight values (Z score) of the high-exposure group with those of the low-exposure group (**Figure 1**). The high-exposure group showed a lower weight than that in the high-exposure group at each time point from birth to 36 months. The adjusted mean body weight (0–36 months) was 224 g lower in the high-TVOC group (≥75th) compared with that in the low-exposure group (<75th).

When using age–gender-specific weights, the adjusted mean Z score was 0.15 points in the low-exposure group and −0.05 points in the high-exposure group; however, it was not statistically significant.

DISCUSSION

In this study, we observed associations between high TVOC exposure during pregnancy and reduced body weight at birth and during the infantile period.

To prevent the risk of high indoor VOC exposure, the Korean Ministry of Environment has provided recommended values named "Indoor air quality control in public use facilities, etc.", which are 120 μg/m^3 for HCHO and 500 μg/m^3 for TVOCs. In particular, a stronger recommended value of 400 μg/m^3 was applied for TVOCs in medical facilities, including maternity facilities. On the basis of these values, 22.9% of participants exceeded the current reference value for

Table 1. General characteristics of the participants according to their ambient personal exposure level to total volatile organic compounds (TVOCs) and formaldehyde (HCHO) during pregnancy

Characteristics			TVOC (μg/m^3)		HCHO (μg/m^3)	
	Total		Low (<75th)	High (⩾75th)	Low (<75th)	High (⩾75th)
	N	Mean ± SD (%)	Mean ± SD (%)	Mean ± SD (%)	Mean ± SD (%)	Mean ± SD (%)
Maternal						
Age	364	30.30 ± 3.29	30.34 ± 3.31	29.83 ± 3.10	30.41 ± 3.31	29.86 ± 3.11
Pre-pregnancy BMI (kg/m^2)	334	21.27 ± 3.02	21.41 ± 3.06	20.81 ± 3.04	21.12 ± 2.90	21.66 ± 3.35
Obese (⩾23)	79	(23.65)	(26.05)	(15.19)	(21.90)	(28.05)
Occupation						
Having	223	(66.17)	(64.26)	(75.00)	(65.73)	(70.37)
Not having	114	(33.83)	(35.74)	(25.00)	(34.27)	(29.63)
Education						
⩽High school	88	(24.58)	(24.21)	(28.74)	(25.57)	(23.26)
University	243	(67.88)	(67.86)	(64.37)	(66.41)	(70.93)
⩾Graduated school	27	(7.54)	(7.94)	(6.90)	(8.02)	(5.81)
Family income (USD)						
<2,000	33	(9.32)	(11.69)	(3.45)*	(9.69)	(9.30)
2,000–4,000	238	(67.23)	(67.74)	(68.97)	(68.99)	(62.79)
⩾4,000	83	(23.48)	(20.56)	(27.59)	(21.32)	(27.91)
Secondhand smoke						
Exposed	161	(49.54)	(48.23)	(53.66)	(51.91)	(45.00)
Non-exposed	164	(50.46)	(51.77)	(46.34)	(48.09)	(55.00)
Newborn's						
Birth order						
First (no sibling)	171	(56.07)	(51.07)	(47.62)	(49.61)	(51.81)
Gender						
Male	172	(47.28)	(46.27)	(53.49)	(49.43)	(43.53)
Female	188	(52.22)	(53.73)	(46.51)	(50.57)	(56.47)
Gestation age (weeks)	360	39.11 ± 1.71	39.17 ± 1.74	38.98 ± 1.68	39.14 ± 1.73	39.04 ± 1.73
<37	13	(3.61)	(3.14)	(4.65)	(3.02)	(5.88)
Weight (kg)						
At birth	360	3.28 ± 0.43	3.30 ± 0.40	3.23 ± 0.49	3.29 ± 0.40	3.26 ± 0.51
<2.5	9	(2.50)	(1.57)	(3.49)	(2.26)	(3.53)
At 6 months	262	8.47 ± 1.02	8.51 ± 1.02	8.36 ± 1.70	8.50 ± 1.02	8.36 ± 1.03
At 12 months	234	10.09 ± 1.12	10.14 ± 1.14	9.89 ± 1.07	10.14 ± 1.16	9.89 ± 0.97
At 24 months	199	12.50 ± 1.33	12.53 ± 1.35	12.22 ± 1.20	12.48 ± 1.38	12.48 ± 1.19
At 36 months	92	14.46 ± 1.53	14.52 ± 1.56	14.14 ± 1.32	14.41 ± 1.52	14.49 ± 1.66

BMI, body mass index.
*$P < 0.05$.

Table 2. Distribution of prenatal exposure to TVOCs and HCHO

Exposure (μg/m^3)	*N*	Mean	SD	GM	Q3	Correlation[a]	%⩾Ref[b]
TVOCs	341	284.18	334.65	169.00	374.00	0.22 $P < 0.01$	(22.87)
HCHO	350	81.57	51.88	67.36	105.70		(28.57)

GM, geometric mean; HCHO, formaldehyde; Q3, 3rd quartile (75th); TVOC, total volatile organic compound.
[a]Correlation between TVOCs and HCHO.
[b]Current indoor guidance value for TVOCs (40 μg/m^3) and reference value for HCHO (100 μg/m^3).

Table 3. Associations between ambient personal TVOC and HCHO exposure during pregnancy and postnatal weight at each time point

Outcome exposure	Crude model β (SE)	*P* value	Adjusted model[a] β (SE)	*P* value
Birth weight (g)				
TVOCs (log)	−30.13 (21.25)	0.16	−45.89 (22.36)	0.04
HCHO (log)	−11.21 (36.43)	0.76	−37.98 (39.55)	0.34
Postnatal weight (kg)	(mean differences[b])		(mean differences[b])	
TVOCs				
At 6 months	−0.15	0.316	−0.26	0.080
At 12 months	−0.25	0.163	−0.32	0.066
At 24 months	−0.31	0.176	−0.28	0.079
At 36 months	−0.38	0.305	−0.40	0.345
HCHO				
At 6 months	−0.14	0.329	−0.09	0.529
At 12 months	−0.25	0.157	−0.25	0.149
At 24 months	<0.01	0.988	−0.04	0.860
At 36 months	0.38	0.420	0.22	0.702

BMI, body mass index; HCHO, formaldehyde; TVOC, total volatile organic compound.
Generalized linear model used to calculate the mean differences between the high-exposed group and the low-exposed (cutoff point at 75th percentile of TVOCs or HCHO) for postnatal weight.
Adjusted for postnatal weight with gender, birth order, breastfeeding and educational level.
Linear regression analysis performed to estimate beta coefficients and its standard errors.
[a]Multiple linear regression analysis performed and adjusted for birth weight with maternal age, gestational age at delivery, pre-pregnancy BMI, educational level, parity, and infant's gender plus, existence of kitchen door (TVOCs); air cleaner use and house age (HCHO).
[b]Mean difference = high-expose group – low-expose group (cutoff at 75th).

TVOCs and 19.7% exceeded that for HCHO. Compared with the current TVOC and HCHO exposures in other studies conducted in Korea, TVOC exposure in this study was lower than that in other indoor housing air quality assessments in pregnant women (429 μg/m^3; (ref. 14)). HCHO exposure was higher in Korea than in Japan (37.5 μg/m^3) but lower than that in Hong Kong (112.3 μg/m^3; (ref. 15)). There is a limitation comparing our personal exposure results directly with those of other studies' indoor exposure; however, it is noteworthy that we observed a reduction in infantile growth in babies who were exposed to higher prenatal TVOCs even at low concentrations.

Many epidemiological studies have investigated residential risk factors in houses with elevated VOC levels from decorative activities such as painting, wall papering, and living in a new house (16–18). Elevated TVOCs showed a significant relationship with the number of cohabitants (more than two people), build year (within 3 years), and the presence of an air conditioner. Furthermore, HCHO was higher in newly built houses and in those without air conditioners, sofas, and beds (data not shown).

Cigarette smoking has been known to be related to VOC concentration as well as being a risk factor for low birth weight (15,19). The smoking rate in Korean women during pregnancy has been reported to be 0.5–3.0% (ref. 20). In this study, participants also showed low smoking rate: three pregnant women were current smokers (0.88%) and 34 women were past smokers (9.97%). Jaddoe *et al.* (19) also reported that active smoking in late pregnancy was associated with adverse effects on birth weight. Thus, we considered using exposure to secondhand smoking instead of maternal active smoking during pregnancy; however, we could not find any significant relationship between secondhand smoking and infantile growth.

As a part of national-level action, the United States and Canadian governments have released information on how to reduce HCHO by controlling sources that emit HCHO to help the public manage a safe home environment (21,22). Suggested methods of controlling exposure to pollutants include source control (minimizing the emission), ventilation, and air cleaning control (23).

Adverse birth outcomes such as preterm births, low birth weight, or lower birth weight have been associated with higher VOC exposure, not just in the occupational setting but also in the general population (5,24–26).

A growing number of studies have hypothesized that developmental origins of health and disease determine the risk of postnatal diseases or altered growth and function. Those studies also suggested that fetal environment might have a long-term effect on the onset of postnatal diseases, such as metabolic syndrome, and stress the importance of the fetal environment (27). Those results have significant public implications in that a harmful fetal environment provides a rather long-lasting influence.

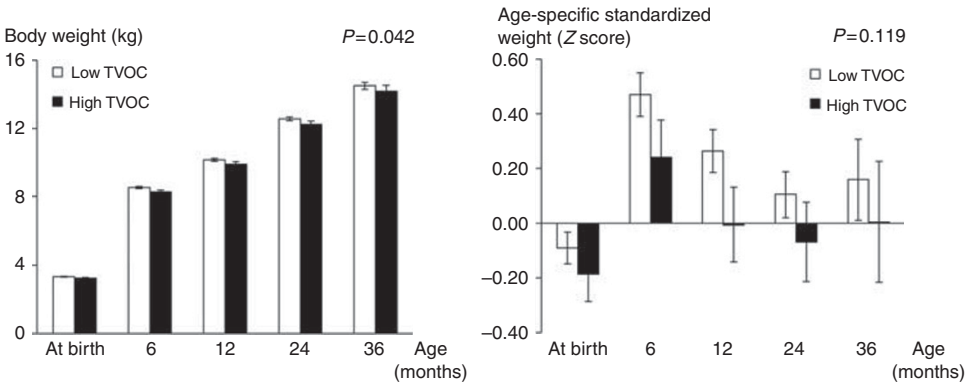

Figure 1. Associations between ambient personal total volatile organic compound (TVOC) exposure during pregnancy and body weight growth in infants (time-varying model). Linear mixed model applied to assess exposure effect at each time point and over time using repeatedly measured weight growth after controlling for gender, birth order, breastfeeding, and educational level. *P value of weight difference between high- and low-exposure groups in the time-varying model.

It is difficult to achieve a valid confirmation of the causal association between environmental exposure and health outcomes using cross-sectional studies; thus, birth cohort studies, in which explanatory variables precede results in time, are regarded as a more proper and powerful method of identifying these associations (28). A number of birth cohort studies were conducted several decades ago, but these studies were mainly carried out in western countries (29–31). This research is unique because it was an environmental health birth cohort study conducted in Asia. Furthermore, as far as we know, this is the first report on the influence of prenatal exposure to TVOCs on postnatal growth that was longitudinally measured.

This study has some limitations. Recruitment was mainly conducted in hospitals, and hence selection bias was inherent. We could not calculate specific risks because of the small number of adverse birth outcome events such as low birth weight and preterm births. Therefore, we applied a mixed model to maximize the data utilization by repeatedly measuring newborns' growth. Consequently, we were able to obtain meaningful results despite the small sample size. We used a standardized weight-for-age value (Z score) based on Korean growth from the Society of Pediatrics.

We found that prenatal exposure to TVOCs was related to reduced postnatal growth. Although the underlying mechanism of how hazardous indoor air pollutants affect the fetus and reduce infantile growth has not been elucidated, oxidative stress, which is induced by VOCs such as benzene or toluene (32–34), is one of the mechanisms that explain poor fetal development (35,36). Kim *et al.* (37) suggested significant association between urinary 8-hydroxydeoxyguanosine and malondialdehyde as biomarkers of oxidative stress and reduced birth weight. Furthermore, free radicals produced by hazardous chemicals may cause an inflammatory response (38–40). Thus, an altered immune system might affect fetal and infantile growth development. However, there are still limitations to revealing the mechanism of fetal toxicity by VOCs, and almost nothing is known about infantile growth. Supportive studies are needed to deepen our knowledge in both experimental and epidemiological settings.

CONCLUSION

This study provided evidence of adverse association between prenatal exposure to TVOCs and postnatal weight. The results suggest that prenatal exposure to TVOCs as well as their household environment should be considered as possible factors that hinder infant development. Precautionary and preventive actions should be taken to avoid hazardous toxicants as well as reduce the potential for adverse health effects.

ACKNOWLEDGMENTS

We thank Young-Man Roh for providing expertise in the exposure assessment, and all mothers for permitting researchers to measure their home environmental TVOCs.

STATEMENT OF FINANCIAL SUPPORT

This study was supported by the National Institute of Environmental Research, Korea.

Disclosure: The authors declare no conflict of interest.

REFERENCES

1. Nethery E, Brauer M, Janssen P. Time-activity patterns of pregnant women and changes during the course of pregnancy. J Expo Sci Environ Epidemiol 2009;19:317.
2. Stock T, Mendez S. A survey of typical exposures to formaldehyde in Houston area residences. Am Ind Hyg Assoc J 1985;46:313–7.
3. Hougaard KSØ, Hass U, Lund SØP, et al. Effects of prenatal exposure to toluene on postnatal development and behavior in rats. Neurotoxicol Teratol 1999;21:241–50.
4. Collins JJ, Ness R, Tyl RW, et al. A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. Regul Toxicol Pharmacol 2001;34:17–34.
5. Maroziene L, Grazuleviciene R. Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. Environ Health 2002;1:6.
6. Duong A, Steinmaus C, McHale CM, et al. Reproductive and developmental toxicity of formaldehyde: A systematic review. Mutat Res 2011;728:118–38.

7. Cogliano VJ, Grosse Y, Baan RA, et al. Meeting report: summary of IARC monographs on formaldehyde, 2-butoxyethanol, and 1-tert-butoxy-2-propanol. Environ Health Perspect 2005;113:1205–8.
8. Wilbourn J, Heseltine E, Møller H. IARC evaluates wood dust and formaldehyde. International Agency for Research on Cancer. Scand J Work Environ Health 1995;21:229–32.
9. Zuurbier M, Lundqvist C, Salines G, et al. The environmental health of children: priorities in Europe. Int J Occup Med Environ Health 2007;20: 291–308.
10. Kim B, Ha M, Park H, et al. The Mothers and Children's Environmental Health (MOCEH) study. Eur J Epidemiol. 2009;24:573–83.
11. The Korean pediatric society and Ministry of Health and Welfare. The Development of Growth Standard for Korean Children and Adolescents 2007.
12. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
13. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology: a Practical Guide. Cambridge University Press: Cambridge, 2003.
14. Hwang Y, Lee K, Kim S, et al. Measurement of residential volatile organic compound exposure through a participant-based method. J Environm Health Sci 2011;37:369–75.
15. Guo H, Kwok N, Cheng H, et al. Formaldehyde and volatile organic compounds in Hong Kong homes: concentrations and impact factors. Indoor air 2009;19:206–17.
16. Dingle P, Franklin P. Formaldehyde levels and the factors affecting these levels in homes in Perth, Western Australia. Indoor Built Environ 2002;11:111.
17. Sakai K, Norbäck D, Mi Y, et al. A comparison of indoor air pollutants in Japan and Sweden: formaldehyde, nitrogen dioxide, and chlorinated volatile organic compounds. Environ Res 2004;94:75–85.
18. Gilbert NL, Gauvin D, Guay M, et al. Housing characteristics and indoor concentrations of nitrogen dioxide and formaldehyde in Quebec City, Canada. Environ Res 2006;102:1–8.
19. Jaddoe VWV, EJWM Troe, Hofman A, et al. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr Perinat Epidemiol 2008;22:162–71.
20. Jhun HJ, Seo HG, Lee DH, et al. Self-reported smoking and urinary cotinine levels among pregnant women in Korea and factors associated with smoking during pregnancy. J Korean Med Sci 2010;25: 752–7.
21. Health Canada Environmental and Workplace Health: Formaldehyde. Secondary Environmental and Workplace Health: Formaldehyde. Available at http://www.hc-sc.gc.ca/ewh-semt/air/in/poll/construction/formaldehyde-eng.php (assessed 28 July 2016).
22. EPA. US An Introduction to Indoor Air Quality (IAQ) Formaldehyde. Secondary An Introduction to Indoor Air Quality (IAQ) Formaldehyde. Available at http://www.epa.gov/iaq/formalde.html (assessed 28 July 2016).
23. Bluyssen P. The Indoor Environment Handbook: how to make Buildings Healthy and Comfortable. Earthscan James & James: London, UK, 2009.
24. Chen D, Cho SI, Chen C, et al. Exposure to benzene, occupational stress, and reduced birth weight. Occup Environ Med 2000;57:661–7.
25. Slama R, Thiebaugeorges O, Goua V, et al. Maternal personal exposure to airborne benzene and intrauterine growth. Environ Health Perspect 2009;117:1313.
26. Aguilera I, Garcia-Esteban R, Iñiguez C, et al. Prenatal exposure to traffic-related air pollution and ultrasound measures of fetal growth in the INMA Sabadell cohort. Environ Health Perspect 2010;118:705.
27. Barker D. The developmental origins of adult disease. J Am Coll Nutr 2004;23 (suppl 6): 88S–595S.
28. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002;31:285–93.
29. Landrigan PJ, Trasande L, Thorpe LE, et al. The National Children's Study: a 21-year prospective study of 100 000 American children. Pediatrics 2006;118:2173–86.
30. Guxens M, Ballester F, Espada M, et al. Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. Int J Epidemiol 2011;41:930–40.
31. Vrijheid M, Casas M, Bergström A, et al. European birth cohorts for environmental health research. Environ Health Perspect 2012;120:29–37.
32. Moro AM, Brucker N, Charão M, et al. Evaluation of genotoxicity and oxidative damage in painters exposed to low levels of toluene. Mutat Res 2012;746:42–8.
33. Lagorio S, Tagesson C, Forastiere F, et al. Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. Occup Environ Med 1994;51:739–43.
34. Moro AM, Charão M, Brucker N, et al. Effects of low-level exposure to xenobiotics present in paints on oxidative stress in workers. Sci Total Environ 2010;408:4461–7.
35. Karowicz-Bilińska A, Suzin J, Sieroszewski P. Evaluation of oxidative stress indices during treatment in pregnant women with intrauterine growth retardation. Med Sci Monit 2002;8:CR211.
36. Biri A, Bozkurt N, Turp A, et al. Role of oxidative stress in intrauterine growth restriction. Gynecol Obstet Invest 2007;64:187–92.
37. Kim YJ, Hong YC, Lee KH, et al. Oxidative stress in pregnant women and birth weight reduction. Reprod Toxicol 2005;19:487–92.
38. Baiz N, Slama R, Bene MC, et al. Maternal exposure to air pollution before and during pregnancy related to changes in newborn's cord blood lymphocyte subpopulations. The EDEN Study Cohort. BMC Pregnancy Childbirth 2011;11:87.
39. Hong YC, Lee JT, Kim H, et al. Effects of air pollutants on acute stroke mortality. Environ Health Perspect 2002;110:187.
40. Lehmann I, Thoelke A, Rehwagen M, et al. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. Environ Toxicol 2002;17:203–10.