Exposure to benzene, occupational stress, and reduced birth weight

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Abstract

***Objectives*—The association between birth weight and exposure to benzene, work stress, and other occupational and environmental hazards was investigated.**

***Methods*—In a large petrochemical industry, 792 pregnant workers were enrolled and followed up through delivery between May 1996 and December 1998. Exposure to benzene and other solvents was assessed by an industrial hygienist based on each woman's job title and workplace information. Other occupational and environmental exposures and personal information, including perceived work stress, exposure to noise, physical exertion at work, and passive smoking, were obtained by an interview questionnaire. Univariate and multivariate regression models were used to examine the individual and combined associations of occupational and environmental exposures with birth weight, with adjustment for major confounders including gestational age.**

***Results*—In the univariate model, birth weight was negatively associated with exposure to benzene (−58 g (95% confidence interval (95% CI), −115 to −2)) and with work stress (−84 g (95% CI, −158 to −10)). In the multivariate model, there was a significant interaction between exposure to benzene and work stress relative to reduced birth weight, after adjustment for other environmental and occupational exposures and personal variables. Adjusted mean birth weight was 3445 g (95% CI 3401 to 3489) among those with neither exposure, 3430 g for those with exposure to benzene only, 3426 g for those with work stress only, and 3262 g (95% CI 3156 to 3369) for those with both exposures. In other words, there was 183 g (95% CI 65 to 301) reduction in birth weight among those with both exposure to benzene and work stress compared with those with neither exposure. Other work or environmental factors could not explain these findings.**

***Conclusions*—Low level exposure to benzene and work stress interact to reduce birth weight in this population.**

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With an increasing number of women entering the work force world wide, women are exposed to various reproductive toxins. A growing body of evidence shows an association between environmental and occupational exposures and adverse reproductive outcomes. Studies have examined exposures to cigarette smoke,[1 2] caffeine,[3] pesticides,[4 5] air pollution,[6 7] organic solvents,[8–13] and occupational stress.[14]

Exposure to solvents is ubiquitous in the general population. Ashley *et al*[15] measured the organic solvents in the blood of about 600 subjects without occupational exposure in the third national health and nutrition examination survey (NHANES III). Detectable concentrations of benzene, xylene, styrene, toluene, tricholoroethane, and other volatile organic chemicals were found in most of the blood samples. Organic solvents are also commonly used in the workplace. The National Institute for Occupational Safety and Health[16] estimated that 9.8 million workers in the United States were occupationally exposed to solvents. Organic solvents identified as potential reproductive toxins include benzene,[8 9 17] toluene,[10–12] and related compounds.[13] Although the level of exposure in most modern industrial working environments is far below the limit recommended by OSHA, studies have begun to suggest that even low level occupational exposure to organic solvents is linked to a broad range of adverse reproductive outcomes.[17–19] Furthermore, it is increasingly recognised that a person is usually exposed to many environmental and occupational hazards. Most previous studies examined a specific exposure without simultaneously considering other exposures. There is little information on how multiple environmental and occupational exposures interact and affect reproductive outcomes.

The purpose of this study was to investigate the association between reduced birth weight and prenatal exposure to low concentrations of benzene and a range of other common environmental and occupational hazards and to examine potential interactions among those exposures in a large cohort of female workers in a modern petrochemical plant in Beijing, China.

Methods

STUDY SITE

This study was conducted in Beijing Yanshan Petrochemical Corporation (BYPC), in a suburban area of Beijing, China. The BYPC, in operation since 1986, has over 47 000 employees and consists of 17 major production plants and institutes for petroleum and chemical processing. About 40% of its employees are women. The major occupational exposures are to benzene, toluene, styrene, and xylene. As BYPC is a modern industry, the level of exposure is very low. For example, the time weighted average (TWA) for benzene during the shift for exposed workers ranged from 0.017 ppm (rubber plant) to 0.191 ppm (chemical plant No 1)[20] with an overall mean of 0.112 ppm and a median of 0.033 ppm, a concentration far below the limit of 1 ppm as an 8 hour TWA recommended by OSHA.[21] Concentrations of other solvents, such as styrene, toluene, and xylene, were all below 1 ppm, far below the OSHA standard.[20] About 80% of local residents are employed at BYPC. In general, pregnant employees stop working at about 28 weeks of gestation.

The BYPC Staff Hospital is the only regional hospital that serves the local community and the employees of BYPC. It is a large hospital affiliated with Beijing Medical University. The obstetrics department of the hospital has 50 delivery beds. All BYPC female workers are entitled to receive free medical care including routine health examination, family planning counselling, prenatal care, delivery service, and neonatal care. On confirmation of pregnancy, each prospective mother is scheduled for antenatal visits and is given a maternity notebook to record examination findings at each visit and the dates of subsequent visits.

STUDY POPULATION AND PROCEDURE

Eligible women were current BYPC employees who had a single live birth at the BYPC staff hospital between May 1996 and December 1998. Those who had multiple gestation, births with major congenital defects, or a medically diagnosed gynaecological or endocrine disorder were excluded from the study. Among eligible subjects, participation rate was over 92%. The study protocol was approved by the institutional review boards of Harvard School of Public Health and Beijing Medical University. A total of 1237 eligible women were enrolled on confirmation of a clinical pregnancy. After informed consent was obtained, a previously validated questionnaire[17] was administered by trained interviewers to obtain information on demographic characteristics, cigarette smoking, alcohol consumption, diet, physical activity, occupational exposure, and medical and reproductive history. Clinical data including prepregnancy weight and height, the first day of the last menstrual period, findings of each prenatal visit, and birth outcomes (including the infant's sex, gestational age, and birth weight) were recorded by a trained nurse.

ASSESSMENT OF EXPOSURE TO BENZENE AND OTHER SOLVENTS

We based maternal exposure to benzene on a specialised industrial hygiene method developed in three steps. Firstly, a walk through field study was conducted by an industrial hygienist to obtain detailed information on the production processes in each of the plants. Information was obtained on different sections of the plant known as workshops, including raw materials, end products, chemical reaction processes, and the job titles involved in the production. Location maps and flow charts of the chemical reaction processes were also prepared for each workshop. A qualitative description of typical job tasks was provided for major production workshops. Each of the plants had a different number of workshops. In total, 218 workshops were identified, and a list of 104 job titles was constructed.

Secondly, on a subset of 132 workers, two different methods of assessment of exposure were compared. For each woman in this subgroup, personal air sampling was conducted on a randomly chosen workday. Quantitative chemical measurements were performed for benzene, toluene, styrene, and xylene. If a detectable concentration of any chemical was measured, the woman was classified as exposed to the specific solvent. The second method was based on an industrial hygienist's assessment of each woman's plant, workshop, and job title information. A standardised algorithm was developed to classify each worker into either exposed or unexposed to each of the four solvents, respectively. For example, in the workshops where benzene was present as a raw material or end product, all the workers were classified as exposed to benzene. If a woman did not work primarily in such a workshop, but had a job title that required tasks in the exposed areas, she was also rated as exposed to benzene. Thus, operators who worked in such facilities as refinery, rubber plant, oil blending workshop, benzene tank farm, or phenol production workshop, were rated as exposed, and workers in the electricity control room, packing workshop, workers' union, administration office, information centre, or the library, were considered to be unexposed. The industrial hygienist's assessment was compared with the classification based on detection of chemicals from air samples. The sensitivity and specificity of the hygienist's qualitative assessment was reasonably high for benzene (0.70 and 0.62, respectively). However, sensitivity was below 0.4 for toluene, styrene, and xylene.

Thirdly, a trained interviewer obtained information on plant, workshop, and job title from all women participants. Based on the standardised algorithm developed in the validation stage, an industrial hygienist classified each woman's exposure into three categories without knowledge of birth outcomes. Women who were exposed to benzene with or without other exposures were classified as exposed to benzene. Women who were not exposed to benzene but potentially to other solvents were grouped as exposed to other solvents. Finally, women who were not exposed to any solvents were classified as unexposed. Further details of the exposure assessment method and validation results are described elsewhere.[20 22]

OTHER OCCUPATIONAL EXPOSURES AND PERSONAL INFORMATION

To identify each woman's exposures to reproductive hazards other than solvents, a trained interviewer used a detailed checklist constructed from toxicology literature. Exposures to 26 different chemical and physical hazards were reported by 108 participants (86 exposed to benzene, 22 unexposed). The frequency of exposure to each specific hazard was low, ranging from 1 to 11. Therefore, a combined variable was formed as exposure to other reproductive hazards. Information on other occupational exposures such as noise (yes/no), vibration (yes/no), dust/fumes (yes/no), rotating shift work (yes/no), main work posture (sitting, standing, squatting, mobile, and other), frequency of lifting work (never, sometimes, always), physical exertion (light, moderate, heavy), and perceived work stress (no or low, moderate, high) were also obtained from the questionnaire interview. Perceived work stress was assessed by a person's response to the question "How stressed do you feel at your workplace? (1=no or low, 2=moderate, 3=high)." Data were also collected on personal variables including maternal age, education, date of marriage, weight and height before pregnancy, general health, medical history, use of contraceptives, reproductive history, active and passive smoking at home and at work, alcohol consumption, use of herbal medicines, and indoor air pollution. Passive smoking at work and at home was based on a person's response to the question "Do your colleagues in your office or work room smoke while they are on duty?" and "Are there any people who live with you who smoke?", respectively. To the extent that these factors relate to exposure to benzene and birth weight, adjustment was made for these factors in the data analysis. It is noted that many workers reported a rotating shiftwork, but in fact, most of them were able to sleep during their shift. As there is considerable misclassification of this variable, we decided not to include it in the data analysis.

ASSESSMENT OF BIRTH OUTCOMES

In this study, birth weight was measured in the delivery room by a trained nurse and was accurate to 10 g. The first day of the last menstrual period recorded on the first prenatal visit was used to estimate the gestational age. It was accurate in this population for several reasons. In China, married couples who plan to have a child need to apply for birth permission at the local family planning administration. In essence, all births are planned, and couples will try to conceive once they have obtained birth permission. Due to the one child policy, families are highly concerned about healthy pregnancy and healthy babies. All the women in our study population sought prenatal care and had a pregnancy test soon after missing a menstrual period. Furthermore, the gestational age was calculated in exact days instead of rounded completed weeks as in most epidemiological studies.

STATISTICAL ANALYSIS

Among 1237 eligible women enrolled, the sample for the analysis consisted of 825 women with well defined exposure: those who were exposed to benzene (n=366) and those who were not exposed to any organic solvents (n=459). Women who were exposed to other solvents (n=412) were excluded due to the concern of exposure misclassification. Among 825 women included in the analyses, a small number of women who smoked (n=2) or drank (n=22) during the pregnancy were excluded. Another nine women were excluded because of missing information on smoking or alcohol use during pregnancy. The final sample size for the analysis includes 792 women (354 benzene exposed, and 438 non-exposed).

Birth weight is the primary outcome of interest. It represents an end point of fetal growth. Reduced birth weight can result from preterm delivery, retardation of intrauterine growth, or both. This study specifically focused on adverse effects of environmental and occupational hazards on intrauterine growth; therefore, all the regression models adjusted for gestational age. To adequately adjust for gestational age, we examined the functional relation between gestational age and birth weight, and found that inclusion of both linear and quadratic terms fitted the model best.

We used linear regression models to examine the individual and combined associations between birth weight and major occupational and environmental exposures including benzene, noise, vibration, dust, perceived work stress, exposure to reproductive toxins other than solvents, lifting, physical exertion, main work posture, and passive smoking. All the exposure variables were treated as binary or dummy variables. Perceived work stress and physical exertion were dichotomised (low *v* moderate or high) because the highest category contained fewer than 20 subjects. We also investigated potential interactions of multiple occupational exposures on birth weight. Inclusion of exposure to benzene, stress, and the interaction of the two significantly contributed to the basic model as did gestational age ($p=0.03$, partial F test). None of the other interactions were detectable. None of the covariates examined changed the effect estimate for the interaction term between benzene and stress by more than 5%. The addition of the variable "working mainly in a sitting posture" changed the main effect of exposure to benzene by more than 15%; therefore this variable was included in the final model.

All the multivariate models adjusted for known or potentially important confounders,[23 24] including maternal age (categorised into 20–25, 26–29, and 30–40), height and body mass index (BMI) tertiles before pregnancy, education (college *v* lower), parity (≥1 *v* none), infant sex, exposure to noise, physical exertion, and exposure to other hazard". The final model showed a good fit with the residuals showing no significant departure from normal distribution ($p>0.10$, Shapiro-Wilk test).

Results

Maternal and infant characteristics by maternal exposure to benzene are presented in table 1. This is an overall low risk population, with most women at their optimal reproductive ages, most being the ideal weight for height, non-smokers, and non-alcohol drinkers. The overall mean (SD) birth weight for this sample was 3427 (441) g. The gestational age had a

Table 1 Characteristics of the study population, Beijing Yanshan Petrochemical Corporation, China

	No exposure (n=438) mean (SD)	Exposure to benzene (n=354) mean (SD)
Age (y)	27.0 (2.4)	26.7 (1.9)
Duration of employment (y)	5.7 (3.0)	6.3 (2.7)
Weight before pregnancy (kg)	57.8 (9.3)	58.3 (9.7)
Height before pregnancy (cm)	161.5 (5.0)	161.0 (4.7)
BMI before pregnancy (kg/m^2)	22.2 (3.5)	22.5 (3.6)
Birth weight (g)	3464 (429)	3382 (451)
Gestational age (weeks)	40.0 (1.3)	39.8 (1.5)
	n (%)	n (%)
Age (y):		
20–25	94 (21.5)	70 (19.8)
26–29	276 (63.0)	250 (70.6)
30–40	68 (15.5)	34 (9.6)
Education:		
Middle school or lower	45 (10.3)	33 (9.3)
High school	217 (49.5)	247 (69.8)
College or above	176 (40.2)	74 (20.9)
Passive smoking at home or work	239 (55.6)	218 (61.8)
Parity (one or more)	18 (4.1)	14 (4.0)
Female baby	215 (49.1)	171 (48.7)
Work stress	85 (19.4)	57 (16.1)
Noise	56 (13.0)	151 (42.8)
Physical exertion	105 (24.0)	89 (25.1)
Other hazards	22 (5.0)	86 (24.3)
Work mainly in a sitting posture	250 (57.1)	245 (69.2)

Table 2 Crude association of birth weight with environmental and occupational exposures and maternal and infant characteristics

Variable	n	Estimated* change in birth weight	p Value	(95% CI)
Maternal characteristics:				
Age (y):				
20–25	164	Referent		
26–29	526	21	0.559	(−50 to 91)
30–40	102	167	0.001	(68 to 266)
Height tertile before pregnancy (cm):				
1st (147–159)	244	Referent		
2nd (160–163)	314	24	0.478	(−43 to 92)
3rd (164–180)	234	112	0.003	(40 to 184)
BMI tertile before pregnancy (kg/m^2):				
1 (14.17–20.31)	264	Referent		
2 (20.32–23.42)	260	64	0.068	(−5 to 133)
3 (23.43–37.46)	268	100	0.004	(31 to 168)
College education or above	250	89	0.004	(28 to 149)
Passive smoking	457	−53	0.066	(−109 to 4)
Infant characteristics:				
Parity (one or more)	32	83	0.257	(−60 to 25)
Female baby	386	−97	0.001	(−153 to −40)
Occupational exposures:				
Exposure to benzene	354	−58	0.044	(−115 to −2)
Perceived work stress	142	−84	0.026	(−158 to −10)
Noise at work	207	−36	0.275	(−100 to 29)
Physical exertion	194	−32	0.337	(−98 to 33)
Other hazards	108	−30	0.471	(−112 to 52)
Work mainly in a sitting posture	495	18	0.552	(−41 to 76)

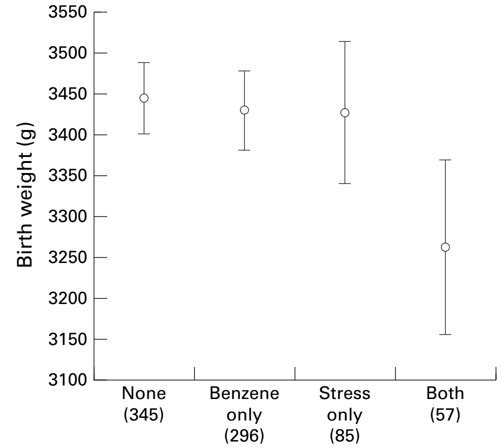
*All the estimates were derived from a linear regression model with adjustment for a linear and a square terms of gestational age.

Table 3 Adjusted association of birth weight with selected environmental and occupational exposures

Variable	Estimated* change in birth weight	p Value	(95% CI)
Benzene exposure	−15	0.655	(−82 to 52)
Work stress	−19	0.702	(−115 to 78)
Benzene-stress interaction	−149	0.048	(−296 to −1)
Noise exposure	14	0.697	(−55 to 82)
Physical exertion	−10	0.767	(−58 to 78)
Other hazards	−16	0.711	(−101 to 69)
Work mainly in a sitting posture	12	0.701	(−50 to 73)
Passive smoking at home or work	−36	0.200	(−92 to 19)

*All the estimates were derived from a multiple linear regression model including maternal age, education, parity, height and body mass index before pregnancy, infant sex, linear and quadratic terms of gestational age, and the other listed variables.

near normal distribution, with a mean (SD) of 39.9 weeks (1.4) and a range from 33 to 44 weeks. The women in the exposed and non-exposed groups were similar for age distribution, years of employment, stress, maternal weight and height before pregnancy, parity, and infant sex. However, the women in the exposed group were less likely to have a college education and more likely to be exposed to noise and passive smoke. The mean birth weight was 82 g lighter and the mean gestational age 0.2 weeks shorter for the group exposed to benzene than for the unexposed group.



Birth weight by exposure to benzene and stress. Adjusted birth weight (g) for four subgroups defined by maternal exposure to benzene and work stress: group 1 has no exposure to benzene and no work stress (none); group 2 (stress only); group 3 (benzene only); and group 4 (both). The numbers in parentheses indicate the number of women in each category (see table 3 for the list of variables adjusted for).

Table 2 presents the association between birth weight and each personal, environmental, and occupational factor, with adjustment for gestational age. Consistent with the available literature, taller stature, larger BMI, higher parity, and higher education were each associated with increased birth weight, whereas female sex and passive smoking were associated with decreased birth weight. Although the exposure to benzene was low in this population, it was significantly associated with reduced birth weight (−58; 95% confidence interval (95% CI) −115 to −2). Perceived work stress was also significantly associated with reduced birth weight (−84; 95% CI −158 to −10). Exposure to noise, other hazards, physical exertion, and work posture were not significantly associated with birth weight.

These associations were further evaluated by multivariate analysis. The multivariate regression model included exposure to benzene, work stress, and the variables listed in table 2. The interaction term was also included in the model (table 3) because there was a significant interaction between exposure to benzene and perceived work stress. The figure illustrates the interactive relation: the adjusted mean birth weight was 3445 g (95% CI 3401 to 3489) among those without exposure to benzene and work stress, 3430 g (95% CI 3382 to 3477) for those with only exposure to benzene, 3426 g (95% CI 3340 to 3513) for those with only work stress, and 3262 g (95% CI 3156 to 3369) for those with exposure to both benzene and work stress. The group with both exposures showed a 183 g reduction (95%

CI 65 to 301) in birth weight compared with those with neither exposure.

Discussion

In both developed and developing countries, low birth weight (<2500 g) is the single most important predictor of neonatal mortality and is a major determinant of post-neonatal mortality and morbidity.[25] There is growing evidence that many environmental and occupational factors are associated with reduced birth weight.[23 24] In this study, we investigated the association between birth weight and a range of potential environmental and occupational hazards, in particular, exposure to benzene and work stress. After adjusting for gestational age and other major maternal and infant covariates, we found that low exposure to benzene was significantly associated with reduced birth weight. More remarkably, there was a significant interaction between exposure to benzene and work stress, resulting in a much greater reduction in birth weight among those with both exposure to benzene and work stress, than among those without either.

This study has several characteristics. It is one of the few studies to examine low exposure to benzene relative to birth weight; it is based on many female workers from a modern petrochemical plant, where epidemiological and clinical data were collected with a validated questionnaire and consistent methods were used by trained research staff and where occupational exposure was measured by objective exposure assessment; and it is overall a low risk and relatively homogeneous population in terms of sociodemographic factors, which offers an opportunity to examine exposure to low concentrations of organic solvents and other occupational hazards relative to birth weight without many influential confounders. Assessment of exposure to low concentrations of organic solvents poses a challenge in epidemiological studies. In the current study, an extensive effort was made to develop an objective and cost efficient method with reasonable sensitivity and specificity.

This study examined a large range of occupational and environmental exposures and potential interactions. Especially, we examined whether any other personal, occupational, or environmental variables could explain the reduced birth weight among women with exposure to both benzene and stress. None of the factors substantially changed the effect of the benzene-stress interaction term by inclusion in or exclusion from the model. As production processes and work environments have been well characterised in our study population, it is not very likely that there was an unrecognised environmental or occupational exposure that could significantly alter our study findings.

Our findings are consistent with previous epidemiological studies. Benzene and other organic solvents have been identified as potential reproductive toxins.[8–13 17] Wilkins and Steele[26] reported that the risk of preterm delivery was increased among female veterinarians exposed to solvents. Witkowski and Johnson[27] noted an increased risk of low birth weight among women who consumed drinking water polluted by benzene or other solvents. In a recent study of 125 women exposed to solvents and 125 matched controls,[28] an increased frequency of birth defects was found in the exposed group. As a secondary result, birth weight was also significantly lower among the exposed group. There have been strong suggestions that maternal stress is associated with preterm birth and low birth weight. A prospective study of 90 women showed that episodic and chronic stress factors were significantly associated with reduced birth weight and shortened gestational age at birth.[29] In a larger prospective study among 2593 women, stress measured by a 28 item Likert scale was significantly associated with preterm birth and low birth weight.[30] The results of our study are consistent with the previous studies for the effect of exposure to benzene and maternal stress separately. However, in our study the effect was most distinct among women who had both factors.

The biological mechanisms by which benzene and work stress affect birth weight remain to be determined. Benzene is known to produce several toxic metabolites that affect rapidly growing cells such as bone marrow, cause oxidative damage in the cells, and suppress cell growth.[31 32] In animal studies benzene and other aromatic organic solvents have consistently been shown to be fetotoxic, resulting in delayed fetal development and reduced birth weight.[33–35] The mechanism by which maternal stress affects birth outcome was thought to be through stress dependent hormones or immunological pathways.[36] Stress results in the release of various adrenal and hypothalamic stress hormones, which enhance placental, decidual, and amniochorionic expression of corticotropin releasing hormone.[37] McLean *et al*[38] found that, compared with women delivering at term, women delivering preterm had significantly increased plasma corticotropin releasing hormone between 16 and 30 weeks of gestation, whereas women delivering post-term had significantly decreased plasma concentrations of corticotropin releasing hormone. Our study suggests that there may be biological synergism between the causal pathways of benzene and stress relative to birth weight.

Our study findings have the following implications. As exposure to organic solvents is prevalent in the general population, even a small amount of shift in the mean birth weight distribution curve towards the left among those exposed may translate into a significantly increased number of low birth weight infants, thus contributing to a significant aetiological fraction of low birth weight. This study documents that exposure to benzene even at a concentration five times below the limit recommended by OSHA is significantly associated with reduced birth weight, which raises the occupational health issues for women of reproductive age even in a modern petrochemical industry. The finding of significant benzene and work stress interaction suggests the importance of assessing potential multiple exposure interactions for future assessment of reproductive risk among women workers.

When the results of this study are interpreted, several methodological limitations should be taken into account. We studied a low risk population with low exposure to benzene as the major occupational exposure, so the generalisability of our findings to women in other populations is unknown. A dose-response relation between exposure to benzene and birth weight could not be examined due to a lack of data on individual cumulative exposures. The main occupational exposure in this study population was benzene. Our analysis excluded those women who were exposed to other organic solvents but not to benzene. However, among women exposed to benzene, we could not completely exclude the possibility that they might be exposed to very low concentrations of other organic solvents as well. Nevertheless, the observed association should be largely attributed to benzene. Our assessment of perceived stress was based on a simple question to classify the level of stress into three categories: no or low, moderate, and high. This is a subjective measure. However, the data were obtained without the knowledge of the birth weight of the infant and the misclassification is expected to be non-differential, likely resulting in a conservative effect estimate. Previous studies by other investigators[39 40] have linked self perceived stress with adverse pregnancy outcomes. The measure of stress used in the current study has been validated in our earlier studies. In a retrospective study of 3343 women workers in BYPC,[19] we found a significant exposure-response relation between the three levels of perceived stress and the frequency of abnormal duration of the menstrual cycle, a result consistent with the studies that used more detailed assessment of perceived stress.[39] In another study of 1035 women working in textile mills in Anhui, China, we found a similar pattern of significant exposure-response relations between the levels of perceived stress and the frequency of dysmenorrhoea.[14] Finally, this is the first report of an interaction between benzene and work stress affecting birth weight. Further studies are clearly needed to corroborate our findings.

In summary, this study has shown that exposure to benzene at a low concentration, well below 1 ppm, was associated with reduced birth weight. More importantly, this study has shown a significant interaction between exposure to benzene and work stress in relation to reduced birth weight. Future assessment of reproductive risk among women workers should not only examine the dose-response relation of a particular exposure, but also take into consideration coexistent exposures as well as interactions among these exposures.

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