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Et al.

Observational Study

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Paternal exposure to medical-related radiation associated with low birthweight infants

A large population-based, retrospective cohort study in rural China

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Abstract

Low birthweight (LBW) is closely associated with fetal and perinatal mortality and morbidity. We identified the risk factors of LBW and geographical differences in LBW incidence in 30 Chinese provinces in the present study.

This study was a population-based, retrospective cohort study performed in 30 Chinese provinces. We used data from the free National Pre-pregnancy Checkups Project, which is a countrywide population-based retrospective cohort study. To identify regional differences in LBW incidence, we used the Qinling-Huaihe climate line to divide China into northern and southern sections and the Heihe-Tengchong economic line to divide it into eastern and western sections. Multivariate unconditional logistic regression analysis with SAS 9.4 was used for data analysis. $P < .05$ was considered statistically significant.

LBW incidence was 4.54% in rural China. Southern China had a significantly higher incidence (4.65%) than northern China (4.28%). Our main risk factor for LBW is paternal exposure to radiation (odds ratio = 1.537), which has never been studied before.

This study identifies multiple risk factors of couples giving birth to LBW babies including paternal risk factors.

Abbreviations: BMI = body mass index, CIs = confidence intervals, CT = computed tomography, LBW = low birthweight, NBW = normal birthweight, NPCP = National Pre-pregnancy Checkups Project, ORs = odds ratios, PET-CT = positron emission tomography-computed tomography.

Keywords: incidence, low birthweight infants, paternal exposure to radiation, risk factors

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SC and YY contribute equally to this article.

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1. Introduction

Weight is an important indicator of infant health, and the mortality rate in low-weight infants is 40 times that of normal-weight infants.[1] According to the 2011 United Nations International Children's Emergency Fund report, an estimated 20 million low-birthweight (LBW) infants are born annually in developing countries, and LBW remains a significant public health problem in many developing countries. According to a study by Yi Chen et al, the incidence of LBW in mainland China was about 6.1%.[2] LBW infants are likely to have a high risk of infections, hospitalization, and physiological illness.[3] Further, they are more likely to develop atherosclerosis, hypertension, coronary artery disease, and chronic kidney disease later in life.[4–9] To lower the incidence of birth defects and improve the overall health of the population in China, the present study focused on the incidence and risk factors of LBW. Although similar studies of LBW have been performed in China, these studies seldom focus on the incidence of LBW because of the limited scope of population and most of them neglect the effects of paternal factors on LBW. Previous studies found some evidences that prenatal paternal factors can affect the offspring's physical characteristics and cause some diseases. A study of Bailey et al has shown that fathers who underwent more than one abdominal x-rays were more likely to give birth to children with acute lymphoblastic leukemia.[10] Other studies have proved that perceptional paternal exposure to radiation will cause the occurrence of other cancers like renal cancer and chondrosarcoma.[11] With the development of the medical technology, a report of United States indicated that the exposure to radiation has doubled during the past 3 decades, especially the medical radiation which is considered as small doses of radiation[12]; the link between medical radiation and radiation-related hereditary effects remains unclear. So many previous researches have evaluated the health effect of the offspring of atomic bomb survivors and occupational employees exposed to radiation. However, nobody focused on the relationship between parental pregestational exposure to radiation and LBW. We were the first to include the paternal exposure to medical radiation into our database to investigate whether it was related to LBW. Our study has large sample size since we used national data and received government support. In-depth research on LBW in China is still lacking, so our goal of this study was to identify those at risk for having a LBW baby. These families can focus on reducing their risk factors for LBW during prepregnancy and early pregnancy.

2. Methods

2.1. Data acquisition

The Population and Family Planning Commission collaborated with the Ministry of Finance of China to start the first wave of free pre-pregnancy physical examinations in 60% of the pilot counties in China between January 2010 and December 2012. We used data from childbearing-aged couples who delivered babies from January 2010 to December 2013 in the 31 pilot counties of China. The data used in this study came from the database of the free National Pre-pregnancy Checkups Project (NPCP), which is a population-based, retrospective cohort study of free, preconception medical examinations and services for rural reproductive-age couples who are trying to conceive throughout the 30 provinces of China. By the end of 2013, 11.42 million families had participated in this project and they had given birth to a total of 248,501 babies. We included 192,492 records with complete weight information for single live babies in this study (Fig. 1). We have gained ethics approval with the ethics committee of Chinese Academy Medical School and Peking Union Medical College Hospital (the reference number: S-K132). We have also obtained the consent to participate under the "Ethics, consent and permissions" heading and the consent to publish from the participant by signing informed consent forms (Chinese Edition) before they filled in the questionnaire (Supplemental informed consent English Edition). All methods were performed in accordance with the relevant guidelines and regulations.

The clinical data were collected by professional medical staff and an application developer (somebody who programs apps for collecting information) during the preconception medical examination. After the examination, interviewers asked the couple questions which were planned in our study questionnaire. Newborn information was collected by a trained interviewer.

2.2. Data processing

2.2.1. Diagnosis and assignment to the LBW group.
According to a manual published by the World Health Organization, LBW means a birthweight <2500 g[9]. As a result, infants' weights were divided into 2 groups: a LBW (<2500 g) and a normal weight (2500–4000 g) group.

2.2.2. Variable grouping, assignment and definitions of variables.
The data of exposure to radiation in the residence before pregnancy, which may indicate the exposure of x-ray, computed tomography (CT), positron emission tomography-computed tomography(PET-CT) or other radionuclide imaging before pregnancy, were obtained by a "yes or no" question, namely "If any x-ray, CT, PET-CT or other radionuclide imaging was underwent in your residence or workplace within 6 months before you got pregnant?" All the mothers/fathers whose answers to this question were "yes" would be grouped as "exposed", and the rest ones were defined as "non-exposed." Oral contraception use means that mothers have used it within 6 months before pregnancy as well. We also asked the mothers to answer whether they take folic acid regularly within 1 month before pregnancy and during the previous 3 months, "Irregular" refers "No" in their answers. Stress statues and gum bleeding were recorded by their answers to "Do you feel stressed?" "Do you usually have gum bleeding?" on questionnaire as well, "Yes" means "Having stress" and "Having gum bleeding", "No" means "Not having stress" and "No gum bleeding." Table 2 shows how the variables were assigned to groups. In the table, "♂" means father of the baby and "♀" means mother. Chinese body mass index (BMI) classification standards were used in this study to classify different BMI groups.[13]

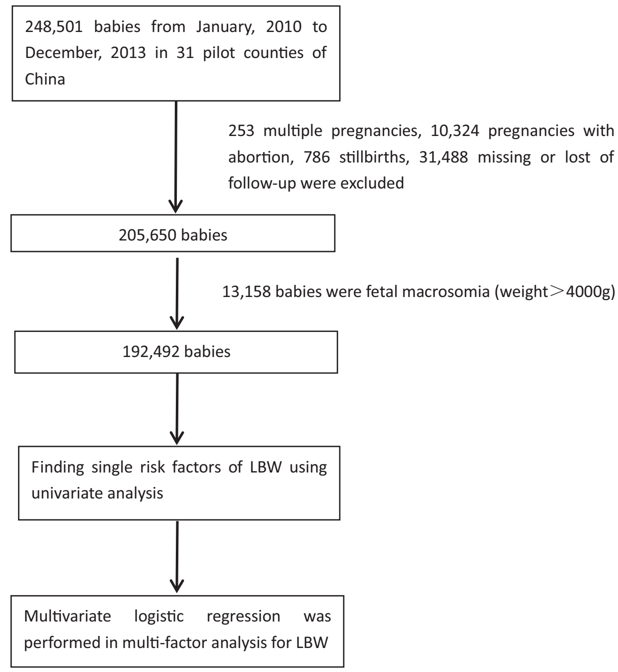

Figure 1. Study profile. A total of 192,492 pregnancies were analyzed after the missing or lost follow-up data, abortions, stillbirths, fetal macrosomia were excluded.

2.2.3. Description of region designation.
The 30 provinces included in the study were: Beijing, Hebei, Jiangsu, Anhui, Jilin, Zhejiang, Fujian, Jiangxi, Henan, Hubei, Guangdong, Sichuan, Chongqing, Yunnan, Shanxi, Tianjin, Shanghai, Guangxi, Hunan, Shandong, Hainan, Heilongjiang, Qinghai, Tibet, Inner Mongolia, Shanxi, Liaoning, Ningxia, Guizhou, and Gansu. In this study, we divided China geographically into 4 regions with the Qinling-Huaihe line, which bisects China into North and South regions based on climate and the Heihe-Tengchong line, which divides China into east and west regions based on economic development. Eastern China is more economically developed than western China as most of its cities are coastal cities (Fig. 2).

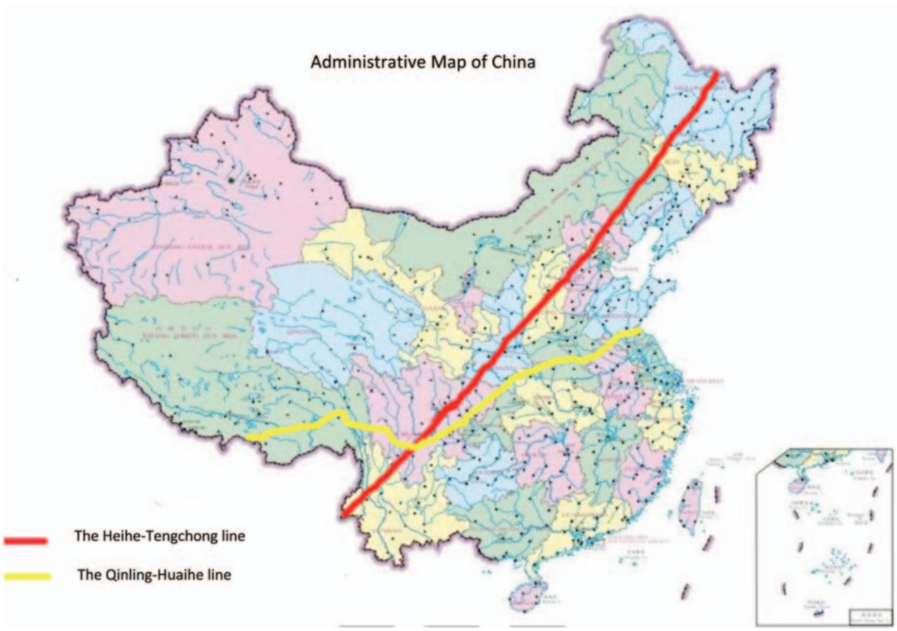

Figure 2. The map was created by Photoshop CS6 (URL: adobeid-na1.services.adobe.com) made by author CS, which is permitted to publis under an Open Access license by its copyright owner (Permission Document). The Heihe-Tengchong line and the Qinling-Huaihe line. The Heihe-Tengchong line is a line from Heihe in Heilongjiang province to Tengchong in Yunnan province. China was divided into south and north by the Heihe-Tengchong line. It was raised by geographer Weiyong Hu in 1935. The east has a more developed economy and degree of civilization than west. The Qinling-Huaihe line is along the Qinling Mountains.The Qinling Mountains are the barrier and boundary separating the climates of both northern and southern China; they are the highest mountains in central-western China. Natural conditions, agricultural production mode, geographical features and people's life styles greatly differ between the south and north of the Qinling-Huaihe line.

2.2.4. Statistical analyses. In our study, LBW was a dependent variable. In single-factor analysis, the χ^2 test was used to analyze qualitative data, the independent sample *t* test and 1-way analysis of variance were used for quantitative data analysis. We also calculated the Spearman rank correlation coefficient for correlation analyses. Stepwise multivariate logistic regression was performed in multifactor analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by use of both univariate and multivariate analyses. $P<.05$ was considered statistically significant. SAS 9.4 statistical packages were used for data analysis.

3. Results

Of the 192,492 infants in our study, 9,275 of them were LBW with a mean weight of 2088.8±407.4g. There were 183,217 infants with a normal birthweight (NBW) and the mean NBW was 3311.3±340.2g ($P<.001$). Our results indicate that the incidence of LBW in mainland rural area of China was 4.54% with south China having a higher incidence of LBW (4.65%) compared with north China (4.28%, $P<.001$). There were little differences between the distribution of LBW incidences in eastern (4.55%) and western China (4.42%, $P=.848$) (Table 1).

Several factors were found significant by univariate analysis. These factors included: weight (♂, ♀), height (♂, ♀), age of menarche (♀), age (♀), BMI (♀), exposure to poisonous materials and radiation (♀), blood pressure (♂), gum bleeding (♂), stress, use of a contraceptive drugs (♂), folic acid intake (♂), uterine activity, infant's sex, BMI(♀), and red blood cell count (♂) ("♂" means man, "♀" means woman) (Table 2). Factors found significant by multivariate analysis which were adjusted for age, occupation, education, sex of baby, parity were: hypertension (odds ratio [OR]=2.326, [1.349,4.013], paternal exposure to radiation (OR=1.537, [1.083,2.181]), contraceptive drug use (OR=2.318, [1.059,5.074]), both parents with stress (OR=1.146, [1.047,1.255]), irregular use of folic acid (OR=1.121, [1.001,1.255]), maternal BMI <24 (OR=1.113, [1.030,1.202]) (Fig. 3). Table 3 showed the comparison of both paternal and neonatal characteristics between fathers exposed to radiation and unexposed to radiation. The average infant birthweight in the group of fathers exposed to radiation was 3239.5g, whereas it was 3252.5g in the population who wa not exposed to radiation ($P=.032$). Additionally, fathers who were exposed to radiation were likely to give birth to premature infants ($P=.006$).

4. Discussion

LBW is common worldwide, especially in developing countries. The percent of LBW in developing countries is far higher than in developed countries.[14,15]Therefore, it is especially important to find as many as risk factors of LBW. The data for this study came from the free NPCP. Our study had a large number of samples and this kind of large sample research has not happened in previous studies. Our data indicated that the incidence of LBW in

Table 1

The distribution of LBW in different regions of China.

Area	NBW, N (%)	LBW, N (%)	Odds ratio (95% CI)
North	53,370 (95.42%)	2,563 (4.58%)	1.0761 (1.0270, 1.1275)
South	128,663 (95.09%)	6,649 (4.91%)	
East	174,621 (95.17%)	8,854 (4.83%)	0.9706 (0.8743, 1.0775)
West	7,823 (95.31%)	385 (4.69%)	

LBW=low birthweight, NBW=normal birthweight.

Table 2

Factors found significant by univariate analysis.

	NBW	LBW	P
Weight (♀)	53.3024±7.1921	53.2331±7.5442	.3983
Height (♀)	159.1±4.8251	159.0±4.9788	.0040
BMI (♀)	21.0604±3.5806	21.0842±3.9370	.5778
Age of menarche (♀)	13.8452±1.2782	13.8183±1.2380	.0470
Age (♀)	25.1603±3.8737	25.1379±3.7951	.6653
Age (♂)	27.289±4 4.37	27.3490±4.3533	.3190
Height (♂)	171.1±5.1371	171.0±5.0945	.0061
Weight (♂)	65.5706±9.0949	65.4170±9.1613	.1297
BMI (♂)	22.3890±3.4355	22.3704±3.0784	.5893
Blood pressure (♀)			.1264
Normal	172,417 (95.22)	8649 (4.78)	
High	1794 (94.47)	105 (5.53)	
Gum bleeding(♀)			.1100
No	167,273 (95.22)	8391 (4.78)	
Yes	8095 (94.84)	440 (5.16)	
Stress			.0238
No	145,961 (95.26)	7257 (4.74)	
♂/♀	18,401 (94.96)	976 (5.04)	
Both	14,141 (94.86)	766 (5.14)	
Contraceptive drug use (♀)			.0311
No	183,119 (95.18)	9265 (4.82)	
Yes	98 (90.74)	10 (9.26)	
Taking folic intake acid (♀)			.0131
Regular	130,527 (95.25)	6505 (4.75)	
Irregular	7994 (94.66)	451 (5.34)	
Sex (infant)			.0045
Male	96,162 (95.31)	4728 (4.69)	
Female	86,950 (95.04)	4542 (4.96)	
BMI groups (♀)			.0001
BMI <24	23,193 (94.77)	1279 (5.23)	
BMI=24–28	133,101 (95.33)	6515 (4.67)	
BMI=28–32	16,237 (94.91)	870 (5.09)	
BMI ≥32	3015 (94.63)	171 (5.37)	
Blood red cell (♀)			.0841
Normal	152,719 (95.22)	7667 (4.78)	
Low	11,316 (94.88)	611 (5.12)	
High	10,722 (94.89)	577 (5.11)	

♂=man, ♀=woman, BMI=body mass index, LBW=low birthweight, NBW=normal birthweight.

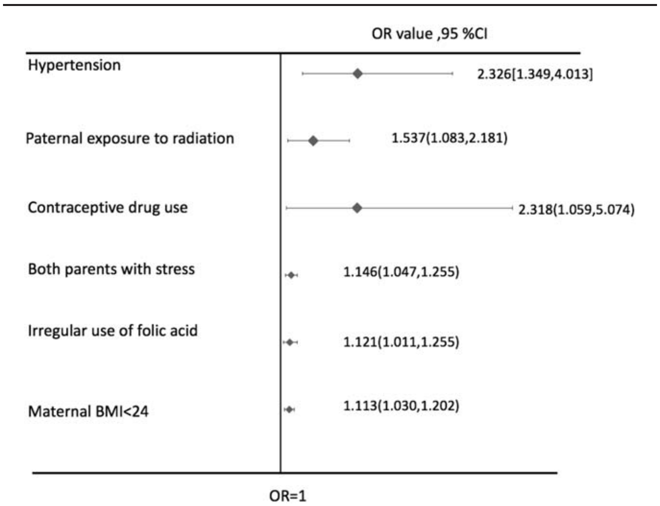

Figure 3. Risk factors found significant by multivariate analysis. These risk factors were adjusted for age, occupation, education, sex of baby, and parity.

Table 3

The comparison of both paternal and neonatal characteristics between fathers exposed to radiation and unexposed to radiation.

Comparison	Paternal exposure to radiation (N=876)	Paternal unexposure to radiation (N=191,616)	P
Spontaneous abortion	23	5713	.536
Induced abortion	1	432	.488
Birth defect	2	164	.151
Stillbirth	1	611	.283
Premature birth*	22	8467	.006
Cesarean delivery	375	83058	.749
Infant sex(man)	476	103832	.929
Neonatal body weight	3239.5 (433.21)	3252.5 (431.83)	.032
Paternal weight	65.58 (9.83)	65.76 (9.13)	.996
Paternal height	170.96 (5.87)	171.13 (5.14)	.344
Paternal BMI	22.51 (4.63)	22.39 (3.37)	.282

* $P<.05$ means significant difference.

rural areas of China was 4.54%. Southern China had a higher incidence of LBW ($P<.05$). There were no significant differences in LBW between eastern and western China. Climate and eating habits may play a critical role in the reason for the regional differences and similarities. People in the north are generally taller and heavier than those in the south, and the winter is much colder in the north than in the south. Therefore, people living in the north have diet that is high in calories; it may be the reason for the lower incidence of LBW in north.

Among the studies of LBW worldwide, the significant maternal risk factors for LBW contained abnormal weight gain during pregnancy, low family functioning, stressful events, cigarette smoking, a previous preterm or LBW baby, anemia, and having a female baby.[16–18] Significant paternal factors related to LBW including paternal age, height, weight, birthweight, occupation, education, parental smoking, and alcohol use. In China, several similar researches have been concerned about the risk factors of LBW, but their samples and variables were limited and most of them focused on the maternal factors without including paternal risk factors. So we reviewed all studies covering the mainland China for the risk factors of LBW in China. Their studies covered the population between 869 and 111187. Only one of them contained the paternal risk factors of LBW (Table 4).

In our study, we found the following to be significant risk factors for LBW (using multivariate analysis): paternal exposure to radiation, hypertension, use of contraceptive drugs, presence of pressure in both parents, irregular use of folic acid, and maternal BMI <24 kg/m^2.

It is generally known that maternal exposure to radiation before pregnancy can increase the possibility of fetal malformations including LBW. However, our results indicated that paternal history of exposing to radiation (OR=1.329) was related to LBW and nobody has reported a relationship between paternal radiation exposure and LBW. Human studies showed that fathers who were exposed to the nuclear plant or medical radiation were prone to give birth to children with leukemia or defect. Recent studies proved that paternal exposure to radiation could cause gene instability, especially for those cancer-related genes. Many such genes suppressed or overexpressed in the next generations of irradiated mice 23. Another animal experiment showed that paternal irradiation would disturb the expression of circadian genes in offspring. They found that gene involved in rhythmic process overpresented in irradiated male mice 24. Besides, transgenerational instability of the next generation was

Table 4

Studies covering the mainland China for the risk factors of LBW.

Studies	N	Maternal risk factors	Paternal risk factors
Bian et al (2013)[20]	55,633	Low primary education, anemia, hypertensive disorders, placental previa, oligohydramnios and premature rupture of membrane, primary education, anemia, and hypertensive disorders	N
Liu et al[19]	111,181	Being female infant, preterm delivery, lower educational level of mothers, antenatal care times <4, antenatal care times ≥8, gestational hypertension, being multipara, taking no folic acid during pregnancy	N
Zhang et al (2002)[21]	999	Multiparity, preterm birth, abnormal maternal health status and maternal malnutrition, maternal medical conditions during pregnancy, maternal schooling	N
Fan et al (2015)[22]	829	Maternal lower education, lower gestational weight gain, being primipara and shorter gestational age, mothers with the history of chronic disease, women who increased non-staple food consumption. Lifestyle factors including diet, exercise, screen time, drinking and smoking from both maternal and paternal exhibited little influence on fetal birthweight.	Fathers living in the rural area
Chen et al (2013)[2]	101,163	Maternal age of <20 years, low level of maternal education, previous histories of adverse pregnancies, hypertensive disorders during pregnancy, anemia, oligohydramnios, premature rupture of membranes, and gestational diabetes.	N

observed in Mughal et al' study[22] because of a threshold dose of acute paternal irradiation. But the reasons why paternal exposure to radiation was associated with LBW still needs further study. We hypothesize that the similar mechanism may act during the process of LBW formation. Several studies have been carried out on the gene etiology of LBW. Among them, Buschdorf et al's study found that gene expressed on hippocampal participated in the fetal development since 4% of genes expression of their study co-varied with DNA methylation levels in the tissue of nonhuman during this process 25. Recent research conducted by Rumbajan et al compared the placental DNA methylation levels between LBW and NBW; they finally detected low level of methylation in the promotor area of *HUSB* gene, which changed the placental gene expression, and thus may play a role in the pathogenesis of LBW 26. More investigations need to be done to establish this question.

Other risk factors including prepregnancy BMI, hypertension, oral contraceptive exposure, parental stress, and taking folic acid or used it irregularly were found to be significantly associated with LBW babies in other researches as well.[20–24]They are associated with maternal nutritional status, blood circulation, and the placental blood supply, which are related to many perinatal complications that may contribute to LBW incidence. Similar to Chen et al, our study also indicated an association between and LBW. We speculate that progesterone and E3 play a central role in pregnancy physiology, and maternal hormones are strongly correlated with birthweight and placental weight.

This study is the first to demonstrate that paternal exposure to radiation influences LBW incidence. These paternal risk factors need to be taken into consideration during conception and pregnancy. A limitation of this study is that some risk factors were only identified by questionnaires with a "Yes" or "No" question. A lot of variables were only qualitative indicators such as those variables that reflect the parents' social and mental state and we were unable to provide correct and quantifiable outcomes. In addition, we are not able to build an effective risk prediction model to show a relatively sensitive and specific way to calculate relative risk.

5. Conclusions

We showed that the incidence of LBW in rural areas of China is 4.54%, and that south China has a higher incidence of LBW than north China ($P < .05$). Our work is the first to show the relationship between paternal exposure to radiation and LBW. The risk factors for LBW identified in this study are modifiable and preventable. To reduce LBW incidence in China, holistic approaches such as health education, maternal nutrition, improvement in socioeconomic indices, and increasing the quality and quantity of antenatal care services are of paramount importance.

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