The effects of work-related maternal risk factors on time to pregnancy, preterm birth and birth weight: the Generation R Study

Burdorf, A.; Brand, T.; Jaddoe, V.W.; Hofman, A.; Mackenbach, J.P.; Steegers, E.A.P.

DOI
10.1136/oem.2009.046516

Publication date
2011

Document Version
Final published version

Published in
Occupational and Environmental Medicine

The effects of work-related maternal risk factors on time to pregnancy, preterm birth and birth weight: the Generation R Study

A Burdorf,[1,2] T Brand,[3] V W Jaddoe,[1,4,5] A Hofman,[4] J P Mackenbach,[1] E A P Steegers[6]

[1]The Generation R Study Group, Erasmus MC, Rotterdam, The Netherlands
[2]Department of Public Health, Erasmus MC, Rotterdam, The Netherlands
[3]Coronel Institute, Netherlands Center for Occupational Diseases, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
[4]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[5]Department of Pediatrics, Erasmus MC, Rotterdam, The Netherlands
[6]Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands

Correspondence to
Alex Burdorf, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands; a.burdorf@erasmusmc.nl

The Generation R Study is conducted by Erasmus MC, University Medical Center Rotterdam in close collaboration with: Erasmus University Rotterdam, School of Law and Faculty of Social Sciences; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (STAR), Rotterdam.

Accepted 9 June 2010
Published Online First 20 December 2010

ABSTRACT

Objective To investigate the influence of maternal working conditions on fertility and pregnancy outcomes.

Methods 8880 women were enrolled in a large prospective birth cohort during early (76%), mid (21%) or late pregnancy (3%) (61% participation). Complete questionnaire information was available for 6302 women (71% response). Outcomes were prolonged time to pregnancy (TTP) (>6 months), preterm birth (<37 weeks) and decreased birth weight (<3000 g). Self-reported exposure to chemical agents was based on a limited list of chemicals. Physical load questions concerned manual materials handling, prolonged sitting and long periods of standing. A job-exposure matrix (JEM) linked reported job title to workplace chemical exposure within jobs according to expert judgement. Associations between maternal occupational exposure and fertility and pregnancy outcomes, adjusted for age, education, minority, parity, smoking and alcohol use, were studied using logistic regression analysis.

Results Women in jobs with regular handling of loads ≥5 kg had better fertility and pregnancy outcomes. No self-reported exposure to chemicals was associated with any outcomes and self-assessments had very low reliability compared with JEM-based assessments. JEM-based maternal occupational exposure to phthalates was associated with prolonged TTP (OR 2.16, 95% CI 1.02 to 4.57) and exposure to pesticides was associated with decreased birth weight (OR 2.42, 95% CI 1.10 to 5.34). The population attributable fractions were small at 0.7% for phthalates and 0.7% for pesticides.

Conclusion This birth cohort study presents evidence of health-based selection into the workforce and adverse effects of maternal occupational exposure to phthalates and pesticides on fertility and pregnancy outcomes.

What this paper adds

- Associations between maternal occupational exposure and adverse pregnancy outcomes are often based on retrospective studies with potential response bias.
- This prospective birth cohort study among pregnant women shows that occupational exposure, ascertained using a job–exposure matrix, to phthalates was associated with prolonged time to pregnancy and to pesticides with decreased birth weight.
- Self-reported exposure to chemical agents had very low reliability when compared with job–exposure matrix assessment.
- The population attributable fractions of phthalates and pesticides in fertility and pregnancy outcomes were small, illustrating the low prevalence of maternal occupational exposure in the general population.

INTRODUCTION

With growing labour force participation among women in Western countries, many women will work during their reproductive years. This will increase the likelihood that during pregnancy women will be exposed to a variety of risk factors at work that may affect pregnancy outcome and cause spontaneous abortion, stillbirth, preterm birth or low birth weight. Occupational exposure may also interact with fetal development, resulting in health effects in the offspring, such as congenital malformations and neurobehavioral disorders in childhood.[1–3] Timely recognition of the risks of hazardous agents will allow precautions to be taken to protect the reproductive health of women. For several work-related risk factors, the associations with reproductive effects are well established and have been translated into legislation, for instance providing mandatory protection for pregnant woman preparing antineoplastic drugs or exposed to lead.[4] However, the scientific evidence is less consistent for many other work-related risk factors.

Several reviews have summarised the epidemiological evidence on associations between maternal occupational exposure and adverse pregnancy outcomes. Figà-Talamanca presented evidence that several chemical agents, physical factors and physical load were associated with low birth weight, preterm birth and spontaneous abortion.[2] Mozurkewich and colleagues concluded in their meta-analysis that physically demanding work was associated with preterm birth and small-for-gestational age (SGA) newborns and that prolonged standing and shift work were risk factors for preterm birth.[5] Another systematic review reported the pooled relative risks of working hours, shift work, lifting at work and prolonged standing for pre-term delivery to be between 1.20 and 1.31, indicating at best only a moderate effect size. The evidence for low birth weight was much more limited.[6] Most chemical agents associated with adverse pregnancy outcomes also seem to affect fertility as expressed by time to pregnancy (TTP).[1]

Epidemiological studies have also presented contradictory findings. For example, a recent nested case–control study among pregnant women in Canada concluded that certain occupational conditions, including prolonged standing and lifting loads, increased the risk of having an SGA child,[7] whereas a similar study in the USA reported that physically demanding work was not associated with preterm delivery and SGA.[8] This contradictory evidence may be partly explained by the lack of studies that address the effects of a broad range of work-related risk factors on different fertility and pregnancy outcomes.

The purpose of the current study was to investigate the influence of maternal working conditions on fertility and pregnancy outcomes in a large prospective prenatally recruited birth cohort. The specific aims of the study were (1) to analyse associations of chemical exposure and physical load with TTP, preterm birth and decreased birth weight, and (2) to estimate the impact of these associations on the occurrence of these health outcomes in the general population.

METHODS

Design and study population

The Generation R study is a population-based prospective cohort study on growth, development and health from early fetal life until young adulthood.[9 10] In total, 8880 pregnant women with a delivery date between April 2002 and January 2006 enrolled in the study with an estimated participation rate of approximately 61%. Enrolment was highest in early pregnancy (76%), lower in mid-pregnancy (21%) and lowest in late pregnancy (3%). Extensive assessments were carried out during early pregnancy (gestational age <18 weeks), mid-pregnancy (gestational age 18–25 weeks) and late pregnancy (gestational age ≥25 weeks), including physical examinations, questionnaires, interviews and biological samples at different stages during the pregnancy. Since Rotterdam is a city with large groups of immigrants, questionnaires were available in different languages and, when needed, interviews in the mother tongue of the main ethnic minorities could be conducted.[9] A more detailed description can be found elsewhere.[9–11] The current study focuses on the effects of maternal working conditions on fertility and pregnancy outcomes, collected primarily through the mid-pregnancy questionnaire, which was filled out by 6830 pregnant women (77% response rate). Due to incomplete or conflicting answers on work status, job description and working conditions (5.3%) and prenatal loss to follow-up until birth (0.7%), complete information was available for 6302 women (71% response rate). The study has been approved by the Medical Ethics Committee at Erasmus MC, University Medical Center Rotterdam, The Netherlands.

Time to pregnancy and pregnancy outcomes

Three outcome measures related to fertility and pregnancy were used: TTP, preterm birth and birth weight. Participants filled out a questionnaire during early pregnancy or thereafter at delayed enrolment, including a question whether the pregnancy was natural (yes/no) and, in case of a positive answer, women with a planned pregnancy were asked about the number of months it took the couple to conceive.[12] A TTP of 6 months or longer was considered a prolonged period.[13]

Date of birth and birth weight were obtained from mid-wife and hospital registries. Fetal ultrasound examinations were used to establish gestational age[10] and in this study preterm birth was defined as a gestational age of less than 37 weeks at delivery.[14] A reduced birth weight was defined as a birth weight below 3000 g.[15] For reasons of comparison and because of some highly skewed distributions, all three outcome measures were defined as dichotomous variables.

Occupation and working conditions

The questionnaire filled out during mid-pregnancy contained questions about work status, occupation and working conditions. Work status was based on a single question on current economic status with seven mutually exclusive categories: paid labour, self-employed, unemployed, disabled, homemaker, student or other. Subjects with paid employment were asked to answer open questions on job title, type of business, name of employer and activities in the job. For 97% of the subjects with a paid job, this information was sufficient to classify the occupation at a five digit level according to the current Dutch Classification of Occupations.[16] This classification is based on the level and field of required skills and closely mirrors the International Standard Classification of Occupations 1988.[17] The Dutch classification was also used to distinguish five skill levels within paid employment, reflecting the educational requirements for these occupations.[16]

Working conditions focused on exposure to chemical agents and on physical load. Pregnant mothers without paid employment were considered to have no occupational exposure. The selection of exposures of interest was guided by recent reviews on the effects of occupational exposure on the reproductive system.[1 2 5 6] With respect to chemical exposure, two approaches were used: a job–exposure matrix (JEM) and self-reported exposure. The first step in the JEM approach was to link job titles to a previously designed JEM for potential endocrine disrupting chemicals. This JEM was based on the judgement of occupational hygienists who estimated for particular jobs exposure to various categories of chemicals, five categories of which were selected (ie, pesticides, solvents, phthalates, alkylphenolic compounds and heavy metals).[18] A particular job title was assigned 'a possibility that some workers with this job title had exposure' (lenient definition) and 'the probability that a reasonable proportion of workers had exposure' (strict definition) and all workers with the same job title were regarded as similarly exposed.[19] Since this JEM was not suitable to identify relevant exposure to anaesthetics and cytostatics within or outside healthcare, the aforementioned JEM was expanded by the authors (AB) to include occupations with possible or probable exposure to anaesthetics and cytostatics as reported in the literature.[20 21]

The approach with self-reported exposure was based on a checklist of chemicals that have previously been described as male reproductive toxicants, including pesticides, anaesthetics and cytostatics, heavy metals, dry cleaning fluids and solvents.[1 19 22] Subjects were asked whether they dealt with these chemicals in the direct environment of their current job. Subjects were classified as being exposed to solvents when reporting contact in their job to industrial cleaning products (degreasers).[23]

The questions on physical work load were obtained from the Dutch Musculoskeletal Questionnaire and concerned manually handling loads of 5 kg or more, manually handling loads of 25 kg or more, prolonged sitting and long periods of standing. A four-point scale was used with the ratings 'seldom or never', 'now and then', 'often' and 'always' during a regular workday, and subjects with the answers 'often' or 'always' were classified as exposed.[24 25]

Potential confounders

Information on age, height, weight, education, country of origin, parity, smoking habits and alcohol use was collected from the first questionnaire available. Educational level was defined as the

highest educational program successfully completed and categorised as low (primary school up to 3 years of general secondary school), mid-low (>3 years of general secondary school, intermediate vocational training), mid-high (higher vocational training, Bachelor's degree) or high (higher academic education). The country of origin assigned to foreigners (defined as someone with at least one parent born abroad) was that of the mother if both parents were born abroad, otherwise it was the country of birth of the parent that was born abroad, as defined by Statistics Netherlands.[26] Three minority groups were defined: (1) Antilleans and Surinamese, both from former overseas Dutch colonies, (2) Turks and Moroccans who share a comparable migration history and (3) all other non-native groups. Smoking was assessed during mid-pregnancy by a dichotomous question on whether the subject had smoked in the past 2 months, implying that women with a positive answer had continued smoking after the pregnancy was known. Alcohol use was assessed in a similar manner by a question on whether the subject had drunk any alcohol in the past 2 months.[27]

Statistical analysis

The agreement between self-reported exposure and the exposure classification derived from the JEM was determined by the weighted Cohen's kappa. A κ value below 0.4 was considered as poor agreement, 0.4–0.6 as moderate agreement, and above 0.6 as good agreement.[28]

Logistic regression analysis was used, starting with univariate associations of individual characteristics and occupational exposures as independent variables with the three dichotomous outcomes of interest: prolonged TTP, preterm birth and decreased birth weight. All independent variables were assessed directly at categorical or ordinal scale, except for the continuous variable age which was reclassified into four categories for ease of interpretation. In order to arrive at a multivariable model for each outcome, univariate risk factors with a significance level of $p<0.20$ were considered and retained in the final multivariable model when reaching a significance level of 0.05. For reasons of comparison, age and education were included by default, independent of their level of statistical significance, as well as individual factors of statistical significance in the univariate analyses for any of the three outcome measures. In addition, exposure variables of interest were also included in a multivariable model when this factor caused a change of 15% or more in the coefficient of other risk factors in the model.[19] Interactions of all variables were also tested for statistical significance. The 95% confidence intervals around the odds ratios were derived from the individual Wald's statistics, except for variables with cell frequencies of five or fewer in which case likelihood-based confidence intervals were used. All logistic regression analyses were performed using the procedure Logistic in SAS V.8.2 (SAS Institute).

The results from these multivariate analyses were used to estimate population attributable fractions (PAFs), expressing the proportion of adverse health outcomes in the general population that is attributable to exposure to the risk factors of interest. The PAF is a function of both the relative risk and the proportion of exposed persons in the population.[29] Given the low prevalence of the three dichotomous health outcomes of interest, odds ratios were used in the calculation of the PAFs.

RESULTS

The characteristics of the study population of pregnant women are shown in table 1. In this cohort age ranged from 15.8 to 46.3 years with a mean age of 30.2 years. The largest minorities were Turkish and Moroccan women (12%) and Surinamese and Dutch Antillean women (10%), apart from a large group of miscellaneous minorities (24%). About 72% of the women held a paid job during early pregnancy and the skill level requirements of the occupation were strongly associated with the educational level attained ($p<0.001$).

The question on planned pregnancy was completed by 5730 women (91%), of whom 4256 (68%) answered in the affirmative. Among these women, 3719 (87%) provided information on TTP. A prolonged TTP of 6–12 months or >12 months was reported by 15% and 10% of these women, respectively. Average

Table 1 Characteristics of pregnant women (n=6302) enrolled in a prospective prenatally recruited birth cohort, 2002–2006

Variables	n	%
Individual characteristics		
Age at enrolment in study		
<25 years	1066	17%
25–30 years	1690	29%
30–35 years	2530	40%
≥35 years	1016	16%
Educational level		
Low	1355	22%
Mid-low	2016	32%
Mid-high	1277	20%
High	1654	26%
Country of origin		
Netherlands	3412	54%
Surinam and Dutch Antilles	658	10%
Morocco and Turkey	752	12%
Other	1480	24%
Parity		
First child	3689	58%
Second child and higher	2613	42%
Smoker during mid-pregnancy	827	13%
Alcohol use during mid-pregnancy	2046	32%
Occupational characteristics		
Paid employment	4556	72%
Skill level		
Elementary education	134	3%
Lower secondary education	975	22%
Higher secondary education	1397	31%
Tertiary education	1283	29%
Academic education	643	15%
Outcome measures		
Live birth	6282	99.7%
Preterm birth		
<34 weeks	78	1.2%
<37 weeks	346	5.5%
Birth weight (n=6201)		
<2500 g	285	5%
2500–3000 g	926	15%
3000–3500 g	2175	35%
3500+ g	2817	45%
Time to pregnancy (n=3719)		
≤6 months	2796	75%
6–12 months	536	15%
>12 months	387	10%

birth weight was 3440 g (SD 548) with an average gestational age of 39.9 weeks (SD 1.7). About 5.5% of the pregnant women had a preterm birth (<37 weeks) and 1.2% of the women gave birth before 34 weeks. Birth weight was not available for approximately 1%. Fifteen per cent of the infants had a birth weight below 3000 g and 5% a low birth weight.

The univariate analyses in table 2 show that women having their second child or higher were consistently at lower risk for all three outcome measures. Older age was associated with prolonged TTP and less often decreased birth weight. A higher educational level showed strong trends with lower TTP, less preterm birth and higher birth weight. Compared to Dutch mothers, Surinamese and Dutch Antillean mothers more often had a preterm birth (7.1% vs 4.9%) and a child with reduced birth weight (36% vs 16%). Alcohol use was positively associated with the health outcomes but odds ratios became close to unity when alcohol use was at least four glasses per week. Women with paid employment during early pregnancy had reduced risk of prematurity and decreased birth weight.

The univariate associations of working conditions with fertility and pregnancy outcomes are described in table 3. Regular manual materials handling of loads of 5 kg or more was consistently associated with all outcomes with ORs varying between 0.43 and 0.74. Exposure to high physical work load, as characterised by lifting loads of 25 kg or more, long periods of walking or long periods of standing, was not associated with any of the health measures. The prevalence of self-reported exposure to chemicals was consistently higher than the exposure prevalences identified in the JEM. The agreement between self-reports and the JEM (lenient definition) was low with κ values for pesticides, anaesthetic gases and cytostatics, heavy metals and solvents of 0.22 (95% CI 0.09 to 0.36), 0.25 (95% CI 0.17 to 0.34), 0.24 (95% CI 0.10 to 0.38) and 0.11 (95% CI 0.06 to 0.15), respectively. There were no associations between self-reported chemical exposure and health outcomes, although one association was of borderline statistical significance (industrial solvents OR 1.35). With respect to the JEM approach, odds ratios for a prolonged TTP were elevated for solvents (OR 1.96) and phthalates (OR 2.70). Exposure to pesticides also had an increased likelihood for decreased birth weight (OR 2.40).

In the multivariable logistic regression analyses, the effects of smoking and alcohol use were largely unchanged after adjustment for other determinants (table 4). Self-reported manual handling of loads of 5 kg or more remained associated with pregnancy outcomes but was no longer statistically significant for TTP. Maternal occupational exposure to pesticides was

Table 2 Univariate logistic regression analyses of the effects of individual characteristics on time to pregnancy (>6 months), preterm birth (<37 weeks) and decreased birth weight (<3000 g) among women in a birth cohort study

Variables	Prolonged time to pregnancy (n=3719), OR (95% CI)	Preterm birth (n=6302), OR (95% CI)	Decreased birth weight (n=6201), OR (95% CI)
Individual characteristics			
Age at enrolment in study			
<25 years	1.00	1.00	1.00
25–30 years	0.94 (0.71 to 1.23)	1.02 (0.74 to 1.41)	0.72 (0.60 to 0.87)*
30–35 years	1.06 (0.82 to 1.37)	0.88 (0.65 to 1.21)	0.61 (0.51 to 0.72)*
≥35 years	1.72 (1.30 to 2.29)*	0.89 (0.61 to 1.30)	0.65 (0.52 to 0.80)*
Educational level			
Low	1.00	1.00	1.00
Mid-low	0.83 (0.67 to 1.02)	0.81 (0.61 to 1.08)	0.80 (0.68 to 0.94)*
Mid-high	0.56 (0.44 to 0.71)*	0.63 (0.45 to 0.89)*	0.58 (0.47 to 0.70)*
High	0.57 (0.46 to 0.71)*	0.71 (0.52 to 0.96)*	0.51 (0.43 to 0.62)*
Country of origin			
Netherlands	1.00	1.00	1.00
Surinam and Dutch Antilles	1.26 (0.94 to 1.68)	1.50 (1.08 to 2.10)*	2.85 (2.37 to 3.43)*
Morocco and Turkey	1.00 (0.79 to 1.27)	1.04 (0.73 to 1.49)	1.05 (0.85 to 1.30)
Other	1.04 (0.85 to 1.26)	1.18 (0.89 to 1.57)	1.29 (1.10 to 1.53)*
Parity			
First child	1.00	1.00	1.00
Second child and higher	0.66 (0.57 to 0.78)*	0.63 (0.50 to 0.80)*	0.51 (0.45 to 0.59)*
Smoker during mid-pregnancy	1.65 (1.32 to 2.06)*	1.10 (0.80 to 1.50)	1.77 (1.49 to 2.09)*
Alcohol use during mid-pregnancy	0.78 (0.65 to 0.90)*	0.85 (0.67 to 1.08)	0.80 (0.70 to 0.92)*
Occupational characteristics			
Paid employment	0.94 (0.78 to 1.13)	0.76 (0.60 to 0.95)*	0.78 (0.68 to 0.89)*
Job skill level			
Elementary education	1.00	1.00	1.00
Lower secondary education	0.74 (0.42 to 1.31)	2.36 (0.85 to 6.58)	0.85 (0.57 to 1.28)
Higher secondary education	0.69 (0.40 to 1.21)	1.74 (0.63 to 4.84)	0.59 (0.39 to 0.89)*
Tertiary education	0.52 (0.29 to 0.90)*	1.37 (0.49 to 3.86)	0.49 (0.32 to 0.73)*
Academic education	0.57 (0.32 to 1.03)	1.65 (0.57 to 4.74)	0.48 (0.31 to 0.74)*

*p<0.05.

Table 3 Univariate logistic regression analyses of the effects of maternal occupational exposure during pregnancy on time to pregnancy (>6 months), preterm birth (<37 weeks) and decreased birth weight (<3000 g) among women in a birth cohort study

Occupational exposure	n	Prolonged time to pregnancy (n=3719), OR (95% CI)	Preterm birth (n=6302), OR (95% CI)	Decreased birth weight (n=6201), OR (95% CI)
Self-reported occupational exposure				
Manual materials handling ≥5 kg	580	0.74 (0.57 to 0.97)*	0.43 (0.26 to 0.72)*	0.66 (0.52 to 0.84)*
Manual materials handling ≥25 kg	68	1.17 (0.56 to 2.44)	0.48 (0.12 to 1.98)	1.43 (0.82 to 2.50)
Prolonged sitting	2758	0.90 (0.77 to 1.04)	0.94 (0.76 to 1.17)	0.96 (0.84 to 1.09)
Prolonged standing	871	1.01 (0.81 to 1.25)	0.86 (0.62 to 1.18)	1.12 (0.94 to 1.34)
Pesticides	43	1.23 (0.48 to 3.18)	1.27 (0.39 to 4.11)	1.19 (0.57 to 2.50)
Anaesthetic gases, cytostatics	127	1.17 (0.73 to 1.88)	0.66 (0.27 to 1.62)	0.74 (0.45 to 1.22)
Heavy metals	38	1.53 (0.65 to 3.60)	0.89 (0.21 to 3.72)	1.75 (0.86 to 3.55)
Industrial solvents	218	1.22 (0.81 to 1.83)	1.02 (0.58 to 1.81)	1.35 (0.98 to 1.86)**
Common household cleaning materials	937	1.08 (0.87 to 1.33)	0.72 (0.52 to 1.00)**	0.94 (0.79 to 1.13)
Dry cleaning (tetrachloroethylene or trichlroethylene)	43	0.97 (0.39 to 2.43)	0.78 (0.19 to 3.24)	1.06 (0.49 to 2.32)
Ionising radiation	108	0.79 (0.44 to 1.40)	0.30 (0.07 to 1.32)	1.04 (0.64 to 1.68)
Job–exposure matrix approach				
Possible exposure to				
Pesticides	32	2.04 (0.73 to 5.76)	1.67 (0.51 to 5.52)	2.40 (1.14 to 5.05)*
Anaesthetic gases, cytostatics	57	0.98 (0.46 to 2.09)	1.22 (0.44 to 3.39)	1.06 (0.54 to 2.05)
Heavy metals	27	0.41 (0.09 to 1.78)	1.20 (0.28 to 5.05)	1.12 (0.46 to 2.78)
Solvents	227	1.23 (0.83 to 1.83)	1.15 (0.67 to 1.96)	1.21 (0.88 to 1.66)
Phthalates	117	1.51 (0.92 to 2.47)	1.19 (0.58 to 2.45)	1.15 (0.73 to 1.80)
Alkylphenolic compounds	233	1.33 (0.90 to 1.96)	0.79 (0.43 to 1.47)	1.20 (0.88 to 1.65)
Probable exposure to				
Pesticides	32	2.04 (0.73 to 5.76)	1.67 (0.51 to 5.52)	2.40 (1.14 to 5.05)*
Anaesthetic gases, cytostatics	48	1.20 (0.55 to 2.60)	1.47 (0.53 to 4.12)	1.15 (0.57 to 2.32)
Heavy metals	27	0.44 (0.10 to 1.92)	1.29 (0.31 to 5.48)	1.24 (0.50 to 3.09)
Solvents	69	1.96 (1.10 to 3.49)*	1.55 (0.66 to 3.59)	1.05 (0.58 to 1.90)
Phthalates	41	2.70 (1.31 to 5.55)*	1.28 (0.39 to 4.15)	0.71 (0.30 to 1.68)
Alkylphenolic compounds	185	1.11 (0.70 to 1.76)	0.72 (0.35 to 1.48)	1.36 (0.96 to 1.92)**

*p<0.05; **p<0.10.

associated with decreased birth weight (OR 2.42) and exposure to phthalates was associated with prolonged TTP (OR 2.16). The PAFs were 0.7% for pesticides and 0.7% for phthalates. Several occupational exposures had increased odds ratios, but failed to reach the significance level of p<0.05, most notably JEM-defined exposure to pesticides (OR 1.75) for a prolonged TTP and preterm birth (OR 2.10). When restricting the analysis to primiparous mothers and their offspring (n=3689), the associations between occupational exposures and outcome measures had comparable odds ratios, but confidence intervals were much wider: phthalates and TTP (OR 1.84), manual materials handling and preterm birth (OR 0.31) and decreased birth weight (OR 0.74), and pesticides and decreased birth weight (OR 2.23).

DISCUSSION

This population-based prospective birth cohort study showed that self-reported manual handling of loads of 5 kg or more was associated with a lower probability of preterm birth and with higher birth weight. Mothers in early pregnancy occupationally exposed according to the JEM to phthalates and pesticides showed an increased risk for delayed pregnancy and a newborn with decreased birth weight, respectively. The self-reported exposures to chemical agents had very low reliability when compared with JEM-based assessments. None of the self-assessments of chemical exposure was associated with any of the fertility and pregnancy outcomes. Age, education, parity, ethnicity, smoking and alcohol use were the factors that influenced fertility and pregnancy outcomes.

The strengths of this study are its population-based cohort approach with recruitment during the prenatal period and the availability of a large number of potential confounders. Since subjects were included from early pregnancy onwards and the information on occupation and potential confounders was collected during mid-pregnancy, information bias in risk factors can largely be ruled out.

A limitation of the study is the initial participation rate of 61% and the 77% response rate to the mid-pregnancy questionnaire. Selective participation was present with lower enrolment among women below age 25, women with lower education, and in minority groups. These selection patterns may have influenced the occurrence of (self-reported) exposure to chemicals in the workplace, since women with jobs requiring lower and intermediate skill levels reported higher prevalences of exposure to manual materials handling, industrial solvents and dry cleaning fluids, but lower prevalences for anaesthetics and cytostatics and ionising radiation. It is expected that the selective response in this study will not have biased the findings to a large extent, since exposure status was reported before pregnancy outcomes were available. In theory, differential misclassification could be present among mothers of parity two or higher, but the magnitude of the observed associations were largely unchanged when restricting the analysis to mothers of higher parity.

Another limitation of this population-based cohort study is the qualitative assessment of exposure to chemical agents, which was done either by means of self-reports in a questionnaire or by using a JEM. The observed κ values between the

Table 4 Multivariable logistic regression analysis of the effects of individual characteristics and maternal occupational exposure during pregnancy on time to pregnancy (>6 months), preterm birth (<37 weeks) and decreased birth weight (<3000 g) among women in a birth cohort study

Variables	Prolonged time to pregnancy (n=3719), OR (95% CI)	Preterm birth (n=6302), OR (95% CI)	Decreased birth weight (n=6201), OR (95% CI)
Individual characteristics			
Age at enrolment in study			
<25 years	1.00	1.00	1.00
25–30 years	1.33 (0.99 to 1.78)**	1.27 (0.88 to 1.84)	1.04 (0.85 to 1.29)
30–35 years	1.97 (1.47 to 2.65)*	1.39 (0.95 to 2.04)	1.17 (0.94 to 1.46)
≥35 years	3.90 (2.79 to 5.44)*	1.51 (0.96 to 2.38)	1.37 (1.06 to 1.78)*
Educational level			
Low	1.00	1.00	1.00
Mid-low	0.75 (0.60 to 0.94)*	0.68 (0.50 to 0.93)*	0.78 (0.65 to 0.93)*
Mid-high	0.47 (0.36 to 0.61)*	0.60 (0.41 to 0.88)*	0.62 (0.50 to 0.78)*
High	0.47 (0.36 to 0.60)*	0.68 (0.47 to 0.99)*	0.60 (0.48 to 0.75)*
Country of origin			
Netherlands	1.00	1.00	1.00
Surinam and Dutch Antilles	1.19 (0.87 to 1.61)	1.38 (0.96 to 1.98)**	2.60 (2.12 to 3.19)*
Morocco and Turkey	0.96 (0.73 to 1.27)	0.93 (0.62 to 1.40)	0.93 (0.73 to 1.19)
Other	1.00 (0.82 to 1.23)	1.12 (0.84 to 1.51)	1.26 (1.06 to 1.49)*
Parity			
First child	1.00	1.00	1.00
Second child and higher	0.50 (0.42 to 0.60)*	0.56 (0.43 to 0.72)*	0.48 (0.41 to 0.55)*
Smoker during mid-pregnancy	1.49 (1.17 to 1.89)*	1.02 (0.73 to 1.43)	1.64 (1.37 to 1.98)*
Alcohol use during mid-pregnancy	0.77 (0.64 to 0.92)*	0.93 (0.71 to 1.21)	0.90 (0.77 to 1.05)
Paid employment	0.94 (0.76 to 1.17)	0.82 (0.61 to 1.10)**	0.99 (0.83 to 1.18)
Occupational exposure			
Manual materials handling ≥5 kg (self-report)	0.82 (0.61 to 1.09)†	0.55 (0.32 to 0.95)*	0.75 (0.58 to 0.98)*
Pesticides (strict JEM definition)	1.75 (0.59 to 5.18)†	2.10 (0.61 to 7.24)†	2.42 (1.10 to 5.34)*
Phthalates (strict JEM definition)	2.16 (1.02 to 4.57)*	1.28 (0.39 to 4.20)†	2.42 (1.10 to 5.34)†
Solvents (strict JEM definition)	1.09 (0.43 to 2.78)†	1.28 (0.51 to 3.23)†	0.93 (0.51 to 1.69)†

*p<0.05; **p<0.10.
†Included in final multivariable model for comparison.
JEM, job–exposure matrix.

questionnaire and JEM for four groups of chemical agents were around 0.20, close to the previously published agreement between this questionnaire and actual measurement in urine samples.[23] Therefore, the reliability of the self-reported exposure to chemicals at the workplace in this survey was disappointingly low and will have resulted in a large misclassification. In community-based studies with a low prevalence of exposure, it is of critical concern to avoid classifying unexposed subjects as exposed and the low specificity of our assessment strategy will have resulted in a considerable attenuation of true associations between self-reported chemical exposure and reproductive effects.[30 31] It must be concluded that a questionnaire with a limited list of potential exposures to chemicals in the workplace as a single means of exposure assessment is not a suitable approach to characterise exposure in a community-based study.[23 32] The JEM approach resulted in several associations between maternal occupational exposure and fertility and pregnancy outcomes. The JEM was developed and successfully used in a study on occupational risk factors for hypospadias, with a focus on endocrine disrupting chemicals.[33 34] The inter-expert agreement among the industrial hygienists developing the JEM was moderate for most substance categories (κ around 0.36) but good for pesticides (κ 0.77). This demonstrates that the JEM approach is also subject to misclassification and therefore cannot be regarded as the gold standard in this study. External validation with quantitative measurement of exposure in the workplace is advised.[18] Under the assumption of non-differential misclassification in the JEM scores, the presented odds ratios are attenuated to an unknown extent.[31]

This population-based prospective birth cohort study showed that after adjustment for other risk factors, paid employment had no effect on pregnancy outcomes. Relatively healthy women are more likely to gain employment and remain employed.[35] Several studies have reported that women who are employed have a lower risk of preterm birth than women without paid employment,[36–38] but other studies could not corroborate this observation.[11 39] An alternative approach in the statistical analysis may be warranted whereby the risk factors for pregnancy outcomes are evaluated among economically active women and women without paid employment separately. Within the group of working women, the associations between occupational risk factors and pregnancy outcomes closely resembled the reported associations in the total study population, although the confidence intervals around the odds ratios became larger due to a smaller reference base in the analysis. Thus, the assumption that pregnant women without paid employment were non-exposed to occupational risk factors has not influenced the results to a large extent.

Self-reported manual handling of loads of 5 kg or more was consistently associated with reduced TTP, less preterm birth, and higher birth weight (table 3) and these associations remained largely unchanged when adjusted for other factors (table 4). An explanation for this finding cannot be sought in differential misclassification of the exposure parameter. It may be hypothesised that jobs with handling of materials weighing 5 kg or more during a regular workday require a certain physical health and, thus, may be prone to the healthy worker effect with women with less good health not entering these jobs or moving to other, less strenuous jobs. Alternatively, the definition of lifting loads of 5 kg or more may not sufficiently capture high levels of physical load, such as regularly lifting loads of 25 kg or more. However, the latter factor was not associated with pregnancy outcomes. Recent reviews have presented contradictory findings and concluded that physically demanding work has at best only a moderate effect on preterm birth and SGA newborns.[5 6] The fact that manual handling of loads of 25 kg or more did not present a moderately increased odds ratio may be partly attributed to the low prevalence of this risk factor (1.6%) and subsequent lack of power in this study.

Mothers occupationally exposed to pesticides (n=32) had an increased risk of prolonged TTP with an OR of 1.75 but a large 95% CI of 0.59 to 5.18. This illustrates the lack of power in this study to identify occupational risk factors with moderate effects on fertility and pregnancy outcomes, thus failing to corroborate previous findings.[40] Paternal exposure to monobutyl phthalate has been associated with altered semen quality[41] and there is substantial evidence that occupational exposure to several organic solvents affects semen quality.[42] These effects on male fertility may have contributed to subfertility among couples, as assessed by TTP in this study.[43] Occupational exposure to pesticides, as established by the JEM, was associated with a decreased birth weight (OR 2.42) and this association was not influenced by adjustment for other significant risk factors. Jurewicz and colleagues have described this association among greenhouse workers and estimated that exposure to pesticides reduced mean birth weight by about 70 g.[44] However, a recent study among Danish greenhouse workers failed to show any effect on birth weight.[45]

The observed associations between maternal occupational exposure to phthalates and pesticides with TTP and reduced birth weight cannot be explained by recall bias, since exposure status was ascertained by the JEM, independently of knowledge on pregnancy outcomes. Since the exposure assessment was limited to the presence of exposure based on job title, no information was available on the frequency and duration of exposure in order to estimate the magnitude of exposure. In addition, the exposure assessment strategy does not allow identification of the role of specific phthalates or pesticides. Although the observed associations are based upon occupational exposure among pregnant women, a possible role of paternal exposure cannot be ruled out. Thus, the current study cannot establish with certainty whether the observed associations are due to maternal or paternal occupational exposure.

In summary, this population-based birth cohort study has presented evidence of health-based selection within paid jobs, as was illustrated by the positive effects of regularly handling of loads of 5 kg or more on fertility and pregnancy outcomes. Maternal occupational exposure to phthalates was associated with prolonged TTP (OR 2.16) and maternal occupational exposure to pesticides was associated with decreased birth weight (OR 2.42). The PAFs were small with an estimated contribution of phthalates to prolonged TTP of 0.7% and pesticides to decreased birth weight of 0.7%, primarily due to the very low occurrence of these occupational exposures in the study population.

Acknowledgements We gratefully acknowledge the contribution of general practitioners, hospitals, mid-wives and pharmacies in Rotterdam.

Funding The first phase of the Generation R Study is made possible by financial support from Erasmus MC, University Medical Centre Rotterdam, Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development (ZonMw). The present study was commissioned by the Netherlands Center for Occupational Diseases (NCVB) in Amsterdam, supported by a grant from the Ministry of Social Affairs and Employment of the Netherlands.

Competing interests None.

Ethics approval This study was conducted with the approval of Erasmus MC, Rotterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Burdorf A,** Figà-Talamanca I, Jensen TK, *et al*. Effects of occupational exposure on the reproductive system: core evidence and practical implications. *Occup Med* 2006;**56**:516–20.
2. **Figà-Talamanca I.** Occupational risk factors and the reproductive health of women. *Occup Med* 2006;**56**:521–31.
3. **Laslo-Baker D,** Barrera M, Knittel-Keren D, *et al*. Child neurodevelopmental outcome and maternal occupational exposure to solvents. *Arch Pediatr Adoslesc Med* 2004;**158**:956–61.
4. **Commision of the European Communities.** Council Directive 92/85/EEC concerning the implementation of measures to encourage improvements int he safety and health of pregnant workers, women workers who have recently given birth and women who are breastfeeding. Official Journal L 348. Vol. 28.11.1992.
5. **Mozurkewich EL,** Luke B, Avni M, *et al*. Working conditions and adverse pregnancy outcome: a meta-analysis. *Obstet Gynecol* 2000;**95**:623–35.
6. **Bonzini M,** Coggon D, Palmer T. Risk of prematurity, low birth weigth, and pre-eclampsia in relation to working hours and physical activities: a systematic review. *Occup Environ Med* 2007;**64**:228–43.
7. **Croteau A,** Marcoux S, Brisson C. Work activity in pregnancy, preventive measures, and the risk of delivering a small-for-gestational-age infant. *Am J Public Health* 2006;**96**:846–55.
8. **Pompeij LA,** Savitz DA, Evenson KR, *et al*. Physical exertion at work and the risk of preterm delivery and small-for-gestational-age birth. *Obstet Gynecol* 2005;**106**:1279–88.
9. **Hofman A,** Jaddoe VW, Mackenbach JP, *et al*. Growth, development and health from early fetal life until young adulthood: the Generation R study. *Paediatr Perinat Epidemiol* 2004;**18**:61–72.
10. **Jaddoe VW,** Mackenbach JP, Moll HA, *et al*. The Generation R study: design and cohort profile. *Eur J Epidemiol* 2006;**21**:475–84.
11. **Jansen PW,** Tiemeier H, Verhulst FC, *et al*. Employment status and the risk of pregnancy complications: the Generation R Study. *Occup Environ Med* 2010;**67**:387–94.
12. **Bonde JP,** Joffe M, Sallmén M, *et al*. Validity issues relating to time-to-pregnancy studies of fertility. *Epidemiology* 2006;**17**:347–9.
13. **Joffe M,** Bisanti L, Apostoli P, *et al*. Time To Pregnancy and occupational lead exposure. *Occup Environ Med* 2003;**60**:752–8.
14. **Kristensen P,** Irgens LM, Bjerkedal T. Environmental factors, reproductive history, and selective fertility in farmers' sibships. *Am J Epidemiol* 1997;**145**:817–25.
15. **Niedhammer I,** O'Mahony D, Daly S, *et al*. Occupational predictors of pregnancy outcomes in Irish working women in the Lifeways cohort. *BJOG* 2009;**116**:943–52.
16. **Statistics Netherlands.** *Dutch classification of occupations*. Voorburg: Statistics Netherlands, 1992.
17. **International Labour Office.** *International standard classification of occupations 1988*. Genève: International Labour Office, 1990.
18. **Van Tongeren M,** Nieuwenhuijsen MJ, Gardiner K, *et al*. A job-exposure matrix for potential endocrine-disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias. *Ann Occup Hyg* 2002;**46**:465–77.
19. **Pierik FH,** Burdorf A, Deddens JA, *et al*. Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys. *Environ Health Perspect* 2004;**112**:1570–6.
20. **Fransman W,** Vermeulen R, Kromhout H. Dermal exposure to cyclophosphamide in hospitals during preparation, nursing, and cleaning activities. *Int Arch Occup Environ Health* 2005;**78**:403–12.
21. **Meijster T,** Fransman W, Veldhof R, *et al*. Exposure to antineoplastic drugs outside the hospital environment. *Ann Occup Hyg* 2006;**50**:657–64.
22. **Tielemans E,** Burdorf A, te Velde ER, *et al*. Occupationally related exposures and reduced semen quality: a case-control study. *Fertil Steril* 1999;**71**:690–6.
23. **Tielemans E,** Heederik D, Burdorf A, *et al*. Assessment of occupational exposures in a general population: comparison of different methods. *Occup Environ Med* 1999;**56**:145–51.
24. **Hildebrandt VH,** Bongers PM, van Dijk FJ, *et al*. Dutch Musculoskeletal Questionnaire: description and basic qualities. *Ergonomics* 2001;**44**:1038–55.

25. **Elders LA,** Burdorf A. Interrelationships of risk factors and low back pain in scaffolders. *Occup Environ Med* 2001;**58**:597—603.
26. **Keij I.** Number of foreigners according to various definitions (in Dutch). Index (*Journal of Statistics Netherlands*) 2000;**10**:24—5.
27. **Jaddoe VW,** Verburg BO, de Ridder MA, *et al*. Maternal smoking in pregnancy and fetal growth characteristics in different periods of pregnancy: the Generation R study. *Am J Epidemiol* 2007;**165**:1207—15.
28. **Landis JR,** Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159—74.
29. **Last JM.** *A dictionary of epidemiology*. Oxford: Oxford University Press, 4th edn, 2001.
30. **Stewart WF,** Correa-Villaseñor A. False positive exposure errors and low exposure prevalence in community-based studies. *Appl Occup Environ Hyg* 1991;**6**:534—40.
31. **Armstrong BG.** Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;**55**:651—6.
32. **Özkaynak H,** Whyatt RM, Needham L, *et al*. Exposure assessment implications for the design and implementation of the National Children's Study. *Environ Health Perspect* 2005;**113**:1108—15.
33. **Vrijheid M,** Armstrong B, Dolk H, *et al*. Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. *Occup Environ Med* 2003;**60**:543—50.
34. **Ormond G,** Nieuwenhuijsen MJ, Nelson P, *et al*. Endocrine disruptors in the workplace, hair spray, folate supplementation, and risk of hypospadias: case-control study. *Environ Health Perspect* 2009;**117**:303—7.
35. **Schuring M,** Burdorf A, Kunst A, *et al*. The effects of ill health on entering and maintaining paid employment: evidence in European countries. *J Epidem Commun Health* 2007;**61**:597—604.
36. **Stengel B,** Saurel-Cubizolles MJ, Kaminksi M. Healthy worker effect and pregnancy: role of adverse obstetic history and social characteristics. *J Epidem Commun Health* 1987;**41**:312—20.
37. **Murphy JF,** Dauncey M, Newcombe R, *et al*. Employment in pregnancy: prevalence, maternal characteristics, perinatal outcome. *Lancet* 1984;**8387**:1163—6.
38. **Rodrigues T,** Barros H. Maternal employment status: an indicator of spontaneous preterm delivery risk. *Eur J Epidemiol*. 2007. In press.
39. **Saurel-Cubizolles MJ,** Zeitlin J, Lelong N, *et al*. Employment, working conditions, and preterm birth: results from the Europop case-control survey. *J Epidem Commun Health* 2004;**58**:395—401.
40. **Bretveld R,** Zielhuis GA, Roeleveld N. Time to pregnancy among female greenhouse workers. *Scand J Work Environ Health* 2006;**32**:359—67.
41. **Hauser R,** Meeker JD, Duty S, *et al*. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiology* 2006;**17**:682—91.
42. **Jensen TK,** Bonde JP, Joffe M. The influence of occupational exposure on male reproductive function. *Occup Med* 2006;**56**:544—53.
43. **Bretveld R,** Brouwers M, Ebisch I, *et al*. Influence of pesticides on male fertility. *Scand J Work Environ Health* 2007;**33**:13—28.
44. **Jurewicz J,** Hanke W, Makowiec-Dabrowska T, *et al*. Exposure to pesticides and heavy work in greenhouses during pregnancy: does it effect birth weight? *Int Arch Occup Environ Health* 2005;**78**:418—26.
45. **Andersen HR,** Schmidt IM, Grandjean P, *et al*. Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. *Environ Health Perspect* 2008;**116**:566—72.

The effects of work-related maternal risk factors on time to pregnancy, preterm birth and birth weight: the Generation R Study

A Burdorf, T Brand, V W Jaddoe, et al.

Occup Environ Med 2011 68: 197-204 originally published online December 20, 2010
doi: 10.1136/oem.2009.046516