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Occupational exposure to inorganic particles during pregnancy and birth outcomes – a nationwide cohort study in Sweden

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Abstract

Objectives: The aim of this study was to investigate if occupational exposure to inorganic particles or welding fumes during pregnancy is associated with negative birth outcomes.

Methods: This cohort study included all single births from 1994 to 2012 by occupationally active mothers in Sweden. Information on birth weight, preterm birth, small for gestational age, smoking habits, nationality, age, occupation, absence from work, and education was obtained from the nation-wide medical birth registry. Exposure to inorganic particles (mg/m^3) was assessed from a job exposure matrix.

Results: Mothers who had high exposure to inorganic particles and had less than 50 days (median) of absence from work during pregnancy showed an increased risk of preterm birth (OR = 1.18; 95% CI: 1.07– 1.30), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), as well as small for gestational age (OR = 1.20; 95% CI: 1.04– 1.39). The increased risks were driven by exposure to iron particles. No increased risks were found in association with exposure to stone and concrete particles. High exposure to welding fumes was associated with an increased risk of low birth weight (OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (OR = 1.24; 95% CI: 1.07–1.42).

Conclusions: The results indicate that pregnant women should not be exposed to high levels of iron particles or welding fumes.

Strengths and limitations of this study:

This register-based cohort study contains a vast amount of information with few missing observations about all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers, which make it possible to assess maternal occupational exposure to inorganic particle or welding fumes and adverse pregnancy outcome.

The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known.

The information about the exposure was assessed from the job-exposure matrix which can introduce non-differential misclassification even though it is assessed objectively and blinded from the outcome.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. In this study this issue was managed by the use of information on absence.

Introduction

Many studies have shown associations between exposure to traffic-related air pollution at the residence during pregnancy (including the combustion products SO_2, NO_X, and CO and particles ($PM_{2.5}$ and PM_{10})) and low birth weight, preterm birth, and small for gestational age [1, 2]. However, very few studies have assessed the association between occupational particle exposure during pregnancy and foetal effects, and no previous study has been done on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcomes. The levels of pollutants can be substantially higher at work than in the general outdoor environment, and it is therefore important to study occupational exposure to air pollution and its effect on pregnant workers. In a Swedish survey from 2009, 23% of occupationally active women in the age group 16 to 29 years and 16% in the age group 30 to 49 years reported exposure to air pollution at the workplace for at least a quarter of the working day [3].

Low birth weight (<2,500 g), small for gestational age (birth weight less than two standard deviations below the mean for gestational length), and preterm birth (<37 full weeks) are relatively common conditions among newborns. About 2.7%–4.4% of the children born in 1998–2007 in Sweden were born small for gestational age, and about 3.7%–5.1% were born with low birth weight [4]. The proportion of premature births has been quite constant in recent decades, and in 2013 about 5% of all single births were premature [5]. Low birth weight has been associated with an increased risk of asthma and respiratory problems [6] as well as increased risk of cardiovascular disease [7]. In addition, children with low birth weight have a higher mortality than children with normal birth weight [8], and low birth weight and preterm birth both might result in cognitive deficits later in life [9, 10].

The aim of this study was to investigate the relationship between the mothers' exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes: small for gestational age, low birth weight, and preterm birth.

Methods

The study population was selected among mother and child pairs with children born from January 1, 1994, to December 31, 2012. Only single births were included in the study (1,826,743 observations). Additional inclusion criteria were that the mother should have an occupation during pregnancy that could be coded into AMSYK or NYK 83 (1,148,312 observations) and that they also should work full-time or part-time at the beginning of pregnancy (995,843 observations).

The study was based on data from three Swedish registers – the Medical Birth Register at the National Board of Health and Welfare, the Longitudinal integration database for health insurance and labour market studies at Statistics Sweden, and the Register of sick leave and parental leave from the Swedish Social Insurance Agency.

The Medical Birth Register includes information about the mother's occupation in free-text (un-coded) and if the mother was working full-time, part-time, or not at all, which are reported during the registration interview at prenatal care facilities around week 10 of the pregnancy. It also includes important information about the outcome variables and potential confounders. The register includes in total about 98%–99% of all children born in Sweden [11].

To increase the specificity of the information on occupational exposures, information about absence from work for pregnancies between 1994 and 2012 was collected from the register of sick leave and parental leave and matched by birth date and gestational length, in order to assess the number of days of absence from the workplace during each pregnancy. Citizens report sick leave and parental leave in order to get social insurance benefits. The register does not cover short-term sick leave of less than 14 days (when the employer is responsible for the benefit), but it covers long-term sick leave, parental leave, and special sick leave related to the pregnancy from day 1.

The Longitudinal integration database for health insurance and labour market studies contains all persons in Sweden aged 16 and older who are registered in Sweden as of the 31st of December every year [12]. The information about the mother's highest level of the education from the register was used to adjust for socioeconomic status.

Information on the mothers' occupation obtained during the registration interview was coded manually by occupational hygienists according to AMSYK/SSYK, the Swedish version of ISCO-88 (International Labour Office (ILO) 1990). A detailed description of the coding procedure has been published earlier by Selander et al. 2016 [13]. Exposure to air pollution at work was assessed by matching of the mother's occupational title during pregnancy to a job-exposure matrix, based on FINJEM and adopted to Swedish conditions by the research group [14]. The matrix included estimations for fourteen different types of particles for about one hundred different occupational groups and two time periods.

The mean value for exposure was divided into the following exposure groups based on percentiles: unexposed (0), low exposure (0 to 50th percentile), and high exposure (equal to or over the 50th percentile). The cut off value between low exposure and high exposure (50th percentile) was 0.09 mg/m^3 for both inorganic particles and welding fumes, with a range of 0.01 to 1.60 mg/m^3 for inorganic particles and 0.01 to 3.20 mg/m^3 for welding fumes. When the study participants were few, the exposure was dichotomized into unexposed or exposed.

The occupational exposures were further divided into three subgroups. The subgroup of iron dust included occupational exposure to iron dust or fumes from welding, smelting, grinding, or other processing of steel and other materials containing iron. The subgroup of concrete dust included dust from stone and concrete material, and the subgroup of other inorganic dust included dust from plaster and insulation.

The presence of the pregnant mother at the workplace was divided into three categories – i) working full-time with low absence from work (reported full-time work and with fewer than 50 days of absence from work (<50th percentile) during pregnancy), ii) working full-time or part-time with moderate absence from work (reported part-time work or with 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy), and iii) working full-time or part-time with high absence from work (reported full-time or part-time work and with 112 or more days of absence from work (≥75th percentile) during pregnancy).

Potential confounders were identified through a review of previous studies on small for gestational age, preterm birth, and low birth weight in association with exposure to residential or occupational air pollution [15, 16] and included the mother´s age (quartiles), current smoking habits (three categories: non-smokers, smokers of 1–9 cigarettes per day, and smokers of 10 cigarettes per day or more), highest completed educational level (three categories: high school 2 years or less, high school more than 2 years or university less than 3 years, and university 3 years or more or graduated), working at the beginning of pregnancy (three categories: full-time, part-time, and not at all), occupational exposure to noise (two categories: <75dB and ≥75dB), nationality measured as country of origin (three categories: Swedish, EU15/Nordic countries except Sweden, and outside Europe) and parity (three categories: first child, second child, and third child or more).

The selection of variables for confounding adjustment was based on the effect each potential confounder had on the association between occupational exposure and outcome. The inclusion criterion for the final model was a deviation >5% in the point estimate with the confounder in the model compared to the model without the confounder.

Outcome variables available through the Medical Birth Registry were small for gestational age (a calculated growth curve of weight and gestational age estimated by the National Board of Health and Welfare), birth weight, and gestational length. Preterm birth was defined by dichotomizing gestational length at gestational week 37, and low birth weight was defined by dichotomizing birth weight at 2,500 g. Small for gestational age was defined as birth weight below two standard deviations of the mean[17].

Analyses were done with logistic regression in STATA SE 13.1 (StataCorp LLC, Texas, USA) generating odds ratios (ORs) and 95% confidence intervals (CIs). The study was approved by the regional ethics committee in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

Results

In total, the study population included 1,826,743 single births, and out of these 995,843 had complete data on mother’s occupation. The study included 20,445 cases of small for gestational age, 28,272 cases of low birth weight, and 46,044 cases of pre-term birth.

Table 1. Baseline characteristics of the study participants [a] (995,843) in per cent (%) and number (n) of cases in relation to the adverse outcomes of SGA [b], LBW [c], and PTB [d].

	SGA		LBW		PTB		All births
Per cent (%) and number (n) of cases.	%	n	%	n	%	n	n
Mother´s characteristics							
Age (quartiles)							
<20 years	3.42	111	4.41	143	6.37	207	3,259
≥20, <25 years	2.20	2,370	3.12	3,355	5.28	5,680	107,792
≥25, <30 years	1.96	6,433	2.73	8,936	4.69	15,398	328,776
≥30, <35	1.95	7,064	2.65	9,593	4.27	15,456	362,597
≥35 years	2.32	4,467	3.24	6,245	4.82	9,303	193,419
Missing							0%
Smoking							
Non-smokers	1.86	16,679	2.66	23,912	4.52	40,605	900,154
Smokers, 19 cig per day	3.91	2,331	4.39	2,620	5.45	3,252	59,874
Smokers, ≥10 cig per day	5.15	1,125	5.82	1,272	6.57	1,437	21,945
Missing							1%
Highest completed educational level							
High school ≤2 years (1)	2.44	6,525	3.23	8,635	5.02	13,395	267,775
University <3 years (2)	1.97	8,128	2.79	11,541	4.66	19,288	414,529
University ≥3 years or Graduate (3)	1.83	5,649	2.58	7,945	4.26	13,154	309,072
Missing							0%
Working at the beginning of pregnancy							
Full-time	2.21	14,295	3.03	19,574	4.86	31,437	648,050
Part-time	1.77	6,150	2.51	8,698	4.21	14,607	347,793
Missing							0%
Absence from work							
<50 days	2.36	12,209	3.57	18,458	5.73	29,613	518,275
≥50 days and < 120 days	1.87	5,164	2.00	5,511	3.13	8,642	276,789
≥120 days	1.53	3,072	2.15	4,303	3.89	7,789	200,779
Missing							0%
Occupational noise							
Unexposed	2.02	16,686	2.82	23,216	4.57	37,671	826,422
Exposed	2.23	3,759	2.99	5,056	4.95	8,373	169,421
Missing							0%
Nationality							
Swedish	1.97	17,469	2.77	24,508	4.61	40,863	887,847
EU15 and Nordic countries (except Sweden)	2.35	632	2.95	794	4.43	1,194	27,029
Outside Europe	2.91	2,339	3.68	2,963	4.93	3,973	80,711
Missing							0%
Child´s characteristics							
Parity							
First child	2.91	13,379	3.79	17,449	5.87	27,007	461,203
Second child	1.29	4,640	1.92	6,915	3.42	12,315	360,660
Third child or more	1.40	2,426	2.25	3,908	3.87	6,722	173,980
Missing							0%

- **a.** *Restricted to single births between 1994 and 2012 among mothers who worked full-time or part-time.*
- **b.** *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
- **c.** *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*
- **d.** *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

Baseline characteristics are presented in table 1 above. The risk for births with adverse outcome varied with the mother’s age and seemed to be higher for younger (26 years of age or younger) and older (34 years of age or older) mothers. Smokers had a higher percentage of adverse outcomes than non-smokers, and higher education was correlated with a lower prevalence of adverse birth outcomes. There also seemed to be a difference in percentage between nationalities, with a higher prevalence of cases in the group of mothers born outside Europe.

Table 2. Maternal occupational exposure [d] to inorganic particles and SGA [a], LBW [b], and PTB [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work [e]				Working full or part-time with moderate absence from work [f]				Working full or part-time with high absence from work [g]			
	Crude		Adjusted [h]		Crude		Adjusted [h]		Crude		Adjusted [h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,736	1	8,551	1	8,010	1	7,828	1	2,927	1	2,853
Low Exposure	.83 (.71–.97)	156	.88 (.75–1.03)	154	.75 (.58–.99)	54	.89 (.68–1.16)	54	.85 (.60–1.21)	32	1.02 (.72–1.46)	32
High Exposure	1.35 (1.17–1.55)	207	1.20 (1.04–1.39)	203	1.21 (1.05–1.39)	210	1.06 (.92–1.22)	204	1.19 (.98–1.44)	113	.97 (.80–1.17)	112
LBW												
No Exposure	1	13,085	1	12,838	1	9,975	1	9,742	1	4,119	1	3,999
Low Exposure	.84 (.73–.95)	236	.90 (.79–1.03)	230	.98 (.79–1.21)	87	1.11 (.89–1.38)	85	.73 (.53–1.01)	39	.84 (.61–1.16)	39
High Exposure	1.52 (1.36–1.70)	346	1.32 (1.18–1.48)	341	1.11 (.98–1.26)	240	1.02 (.90–1.17)	235	1.08 (.91–1.28)	145	.93 (.78–1.11)	141
PTB												
No Exposure	1	21,003	1	20,630	1	15,904	1	15,551	1	7,469	1	7,272
Low Exposure	.83 (.75–.92)	377	.89 (.80–.99)	366	.89 (.75–1.07)	127	.98 (.82–1.17)	125	.75 (.60–.95)	73	.82 (.65–1.04)	72
High Exposure	1.38 (1.26–1.51)	502	1.18 (1.07–1.30)	491	.99 (.89–1.10)	342	.93 (.83–1.04)	334	1.01 (.89–1.16)	247	.93 (.81–1.06)	243

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m^3.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).*

g. *All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.*

h. *Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.*

Table 3. Maternal occupational exposure [d] to welding fumes and SGA [a], LBW [b], and PTB [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work[e]				Working full or part-time with moderate absence from work[f]				Working full or part-time with high absence from work[g]			
	Crude		Adjusted[h]		Crude		Adjusted[h]		Crude		Adjusted[h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,916	1	8,729	1	8,097	1	7,913	1	2,982	1	2,908
Low Exposure	1.63 (1.34–1.99)	106	1.45 (1.19–1.78)	103	1.29 (1.05–1.59)	94	1.14 (.92–1.40)	92	1.21 (.90–1.64)	44	1.03 (.76–1.40)	44
High Exposure	1.14 (.91–1.43)	77	1.05 (.83–1.32)	76	1.18 (.95–1.47)	83	1.07 (.86–1.34)	81	1.15 (.85–1.54)	46	.94 (.69–1.26)	45
LBW												
No Exposure	1	13,362	1	13,109	1	10,104	1	9,867	1	4,188	1	4,068
Low Exposure	1.75 (1.49–2.05)	168	1.52 (1.30–1.79)	166	1.13 (.93–1.38)	103	1.06 (.87–1.29)	102	1.00 (.75–1.32)	51	.87 (.65–1.16)	49
High Exposure	1.37 (1.15–1.63)	137	1.22 (1.02–1.45)	134	1.08 (.88–1.33)	95	1.00 (.81–1.23)	93	1.14 (.88–1.46)	64	.99 (.76–1.27)	62
PTB												
No Exposure	1	21,451	1	21,066	1	16,109	1	15,753	1	7,586	1	7,389
Low Exposure	1.36 (1.18–1.56)	211	1.16 (1.00–1.34)	205	.98 (.82–1.16)	142	.92 (.77–1.09)	138	1.08 (.89–1.33)	100	.99 (.81–1.22)	97
High Exposure	1.38 (1.20–1.58)	220	1.24 (1.07–1.42)	216	.87 (.72–1.04)	122	.82 (.68–.98)	119	1.01 (.83–1.23)	103	.93 (.76–1.14)	101

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m*^{3}*.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).*

g. *All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.*

h. *Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.*

ORs for the association between exposure to air pollution and birth outcomes subdivided by absence from work are presented in table 2 and 3 above. An elevated risk of small for gestational age, low birth weight, and preterm birth were indicated after exposure to inorganic particles during pregnancy (table 2). In the highest exposed group of mothers working full-time with a low absence from work < 50 days, a statistically significantly increased risk in all outcomes was shown, including small for gestational age (OR = 1.20; 95% CI: 1.04–1.39), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), and preterm birth (OR = 1.18; 95% CI: 1.07–1.30). An increased risk of adverse birth outcomes was not visible among mothers that had an exposed occupation, but were absent from work during pregnancy. Full-time working women who were exposed to high levels of welding fumes during pregnancy had a significantly increased risk of low birth weight (adjusted OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (adjusted OR = 1.24; 95% CI: 1.07–1.42) compared to the unexposed (table 3). Mothers with low exposure had a statistically significant increased risk of having children born small for gestational age (adjusted OR = 1.45; 95% CI: 1.19–1.78), but no dose-response was shown. Among exposed mothers with moderate or high absence from work, no increased risk for negative birth outcomes was shown.

Table 4. Maternal occupational exposure [d] to inorganic particles, subdivided into iron particles, stone and concrete particles, and other inorganic particles, and SGA [a], LBW [b], and PTB [c].

	Working full-time with low amount of absence from work [e]			
	Crude		Adjusted [f]	
	OR (95% CI)	n/cases	OR (95% CI)	n/cases
Iron particles				
SGA				
Unexposed	1	361,282 /8,916	1	354,903 /8,729
Exposed	1.38 (1.19–1.61)	5,361 /183	1.25 (1.07–1.46)	5,253 /179
LBW				
Unexposed	1	356,889 /13,362	1	350,574 /13,109
Exposed	1.55 (1.38–1.75)	5,239 /305	1.37 (1.22–1.54)	5,132 /300
PTB				
Unexposed	1	348,989 /21,451	1	342,797 /21,066
Exposed	1.37 (1.24–1.51)	5,119 /431	1.20 (1.08–1.33)	5,016 /421
Stone and concrete particles				
SGA				
Unexposed	1	358,427 /8,924	1	352,060 /8,735
Exposed	.86 (.74–1.00)	8,216 /175	.89 (.76–1.04)	8,096 /173
LBW				
Unexposed	1	354,007 /13,396	1	347,700 /13,145
Exposed	.88 (.78–1.00)	8,121 /271	.92 (.81–1.04)	8,006 /264
PTB				
Unexposed	1	346,142 /21,450	1	339,957 /21,068
Exposed	.88 (.79–.97)	7,966 /432	.91 (.82–1.00)	7,856 /419
Other inorganic particles				
SGA				
Unexposed	1	366,317 /9,089	1	359,836 /8,898
Exposed	1.24 (.66–2.32)	326 /10	1.07 (.57–2.02)	320 /10
LBW				
Unexposed	1	361,804 /13,655	1	355,388 /13,397
Exposed	.98 (.55–1.75)	324 /12	.77 (.43–1.37)	318 /12
PTB				
Unexposed	1	353,796 /21,858	1	347,507 /21,463
Exposed	1.25 (.82–1.89)	312 /24	.94 (.62–1.43)	306 /24

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed and exposed.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and who had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Odds Ratio (OR) adjusted for the confounders of the mothers' age, education, smoking habits, nationality, occupational exposure to noise, and the children's parity.*

In table 4 exposure to iron particles showed statistically significantly increased risks of small for gestational age (OR = 1.25; 95% CI: 1.07–1.46), low birth weight (OR = 1.37; 95% CI: 1.22–1.54), and preterm birth (OR = 1.20; 95% CI: 1.08–1.33) in the exposed group that had been working full-time. There was no association between welding fumes and adverse birth outcomes among mothers who had high absence from work. Overall, the trend was that exposed mothers with less absence had higher risk of adverse birth outcomes. Examples of common occupations in the group exposed to iron particles were welders, car builders, flight engineers, metal workers, and plumbers. For stone and concrete and other inorganic dust, there was no statistically significant increase in the risk for any of the outcomes.

Discussion

Among the full-time working mothers with low absence from work and high exposure to inorganic particles during pregnancy, statistically significantly increased risks for small for gestational age, low birth weight, and preterm birth were observed. No previous studies have been found on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcome [18]. A statistically significantly increased risk for low birth weight and preterm birth was also found in children to mothers who were exposed to welding fumes during pregnancy and with a low absence from work. However, the analysis did not show a dose-response trend. This was in line with the only previous study made on maternal occupational exposure to welding fumes, metal dust, and adverse birth outcome [19]. A few previous studies have shown that exposure to welding fumes in general is associated with negative health effects, and there are already reasons to protect pregnant women from several compounds related to welding, including lead, cobalt, hexavalent chromium, nickel, and carbon monoxide [20]. Also, polycyclic aromatic hydrocarbons that are prevalent in welding fumes have been associated with adverse pregnancy outcomes [21]. In the present study, there was no information on relocation or change of work task within the workplace in order to avoid exposure during pregnancy; therefore, some of the women might have been misclassified regarding exposure, and this might be the reason for the OR being lower than expected in the group of working women with low absence from work and high exposure to welding fumes.

The mechanism behind the association between exposure to air pollution during pregnancy and foetal health effects is not yet fully understood [2]. Several plausible pathways have been suggested [22], where oxidative stress is one putative mechanism [23]. Low birth weight could possibly be caused by cardiovascular mechanisms related to oxidative stress, inflammation, coagulation, disturbed endothelial function, and hemodynamic responses [22]. Preterm delivery and intrauterine growth retardation could by themselves or together be the underlying cause of low birth weight. Adverse effects in the development of the foetus during pregnancy, such as intrauterine growth restriction [24, 25], have previously been associated with low birth weight, and stress during pregnancy has been shown to lead to preterm birth [26].

Oxidative stress occurs when the capacity of the antioxidant system cannot keep up with the generated reactive oxygen species (ROS). Both chronic oxidative stress as well as acute exposure to high levels of ROS can be harmful and can damage proteins, lipids, and DNA [27] as detected through biomarkers in blood and urine. This is a process that might be reinforced by different exposures, and in high quality studies, exposures to particles and welding fumes have been associated with oxidative

DNA damage [28, 29]. Graczyk et al. found an association between welding and the biomarker 8-OHdG in plasma and urine, and there was an exposure response with the number of fine particles but not when particles were measured gravimetrically [30]. Associations between welding fumes and indications of ROS, increased oxidative stress, and lipid peroxidation have also been seen [30, 29].

The size distribution of the particles and the toxicity of the substances are important to know in order to interpret the results. Inorganic particles (such as iron, concrete, plaster, and insulation material) mostly contain coarse particles and are therefore likely to deposit in the nasopharyngeal region [31], even if there is also a smaller fraction with finer particles that might deposit farther down in the tracheobronchial and alveolar regions of the lung. Particle size can explain the distribution and where in the respiratory system the particles deposit, but not the toxicity to lung tissue among different substances [32, 33]. Welding fumes are difficult to define because they contain both small and large particles as well as many different compounds [20]. However, among the three subgroups of inorganic particles, only iron particles showed an increased risk of adverse outcomes.

Measured gravimetrically, most of the iron particles are coarse and deposit mainly in the upper airways and thus can be transported out of the airways. Measurements of blood markers for cardiovascular disease and inflammation indications in subway platform workers – who are exposed to high levels of iron particles in the underground system – showed only slightly increased levels [34]. Even so, measured in numbers there could also be a large amount of fine particles, especially if the iron particles are derived from welding. The translocation of carbon particles from the lung to the systemic circulation in humans has been shown to be low [35, 36], but inhalation of iron particles in rats has been shown to lead to oxidative stress [37].

It is also interesting that a synergistic interaction between soot and iron particles regarding oxidative stress has been shown in rats [38]. All of the occupations in the group exposed to iron particles listed above have one or more other exposures in addition to iron particles, and thus the observed effect cannot with certainty be attributed solely to iron.

This register-based cohort study has several strengths, and it is in many ways unique in a global perspective. First, it contained a vast amount of material with information about all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers. The variables from the Medical Birth Register and the Longitudinal integration database for health insurance and labour market studies are of high quality with few missing observations (see table 1). The free text data on occupations from the Medical Birth Register have been manually coded (blinded), which ensures accuracy, and even if some misclassification cannot be ruled out, these are most likely non-differential misclassifications. The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known. The information about the exposure was assessed from the job-exposure matrix objectively and blinded from the outcome.

There are also some weaknesses in this kind of study design. Job-exposure matrices were used, which can introduce non-differential misclassification [39]. The job-exposure matrices were based on measurements among workers in different occupations, and based on those measurements a mean value for the occupational group was calculated. This way of classifying exposure is valid, but is not equal to individual measurements throughout the pregnancy for each participant. Therefore it could introduce a misclassification, but the misclassification would not likely be differential and would therefore only push the risk towards null in the middle and high-exposure groups [13]. The risks might therefore in reality be higher than we found in the present study.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. To manage this issue, information on absence can be used. If the exposed groups (according to job title) have high amounts of absence, they would not have been exposed and thus should not have an increased risk of adverse outcome. In this study, there were no statistically significantly increased risks among the exposed women with high absence from work, which indicates no or little residual confounding regarding socioeconomic factors related to the occupational title among the study participants.

Conclusion

Maternal exposure to air pollution from iron particles and welding fumes in the work environment during pregnancy was associated with negative health effects in the children. No increased risk was found in association with exposure to stone and concrete or other inorganic dust. The results emphasise that women should not be exposed to high levels of iron particles and welding fumes during pregnancy. However, since so few studies have been made in this area, these results need confirmation in future studies.

Compliance with Ethical Standards

Source of Funding: The results reported herein correspond to specific aims of grant no 2013-1438 from Swedish Research Council for Health, Working life and Welfare.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. The study was approved by the regional ethics committee in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Occupational exposure to inorganic particles during pregnancy and birth outcomes – a nationwide cohort study in Sweden

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Original Research Article for the BMJ Open.

Occupational exposure to inorganic particles during pregnancy and birth outcomes – a nationwide cohort study in Sweden

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Abstract

Objectives: The aim of this study was to investigate if occupational exposure to inorganic particles or welding fumes during pregnancy is associated with negative birth outcomes.

Methods: This cohort study included all single births from 1994 to 2012 by occupationally active mothers in Sweden. Information on birth weight, preterm birth, small for gestational age, smoking habits, nationality, age, occupation, absence from work, and education was obtained from the nation-wide medical birth registry. Exposure to inorganic particles (mg/m^3) was assessed from a job exposure matrix.

Results: Mothers who had high exposure to inorganic particles and had less than 50 days (median) of absence from work during pregnancy showed an increased risk of preterm birth (OR = 1.18; 95% CI: 1.07– 1.30), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), as well as small for gestational age (OR = 1.20; 95% CI: 1.04– 1.39). The increased risks were driven by exposure to iron particles. No increased risks were found in association with exposure to stone and concrete particles. High exposure to welding fumes was associated with an increased risk of low birth weight (OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (OR = 1.24; 95% CI: 1.07–1.42).

Conclusions: The results indicate that pregnant women should not be exposed to high levels of iron particles or welding fumes.

Strengths and limitations of this study:

This register-based cohort study contains a vast amount of information with few missing observations about all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers, which make it possible to assess maternal occupational exposure to inorganic particle or welding fumes and adverse pregnancy outcome.

The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known.

The information about the exposure was assessed from the job-exposure matrix which can introduce non-differential misclassification even though it is assessed objectively and blinded from the outcome.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. In this study this issue was managed by the use of information on absence.

Introduction

Many studies have shown associations between exposure to traffic-related residential air pollution during pregnancy (including the combustion products SO_2, NO_X, and CO and particles ($PM_{2.5}$ and PM_{10})) and low birth weight, preterm birth, and small for gestational age [1, 2]. However, few studies have assessed the association between occupational exposure to particles and adverse pregnancy outcomes, even though the levels of pollutants can be substantially higher at work than in the general outdoor environment.

A majority of Swedish women are in the active work force, 64% of women in ages 20-64 are employed or self-employed. In a Swedish survey from 2009, 23% of occupationally active women in the age group 16 to 29 years and 16% in the age group 30 to 49 years reported exposure to air pollution at the workplace for at least a quarter of the working day [3]. Most women continue to work during pregnancy. Women in physically very demanding work can apply for pregnancy benefit during the last 60 days of pregnancy. A few occupations/exposures are not allowed for pregnant women: lead exposure, diving, fire-fighting with smoke helmet, underground mining work, and work involving exposure to certain microbiological agents [4]. Women exposed to substances or physical conditions that may affect pregnancy negatively can apply for pregnancy benefit during the whole pregnancy, but this is rare. Thus, a large number of Swedish women keep working during pregnancy.

Adverse birth effects, such as low birth weight (<2,500 g), small for gestational age (birth weight less than two standard deviations below the mean for gestational length), and preterm birth (<37 full weeks) are relatively common conditions among new-born’s. About 2.7%–4.4% of the children born in 1998–2007 in Sweden were born small for gestational age, and about 3.7%–5.1% were born with low birth weight [5]. The proportion of premature births has been quite constant in recent decades, and in 2013 about 5% of all single births were premature [6]. Low birth weight has been associated with an increased risk of asthma and respiratory problems [7] as well as increased risk of cardiovascular disease [8]. In addition, children with low birth weight have a higher mortality than children with normal birth weight [9], and low birth weight and preterm birth both might result in cognitive deficits later in life [10, 11]. The mechanism behind the association between exposure to air pollution during pregnancy and foetal health effects is not yet fully understood [2]. Several plausible pathways have been suggested [12], where oxidative stress is one putative mechanism [13]. Low birth weight could possibly be caused by cardiovascular mechanisms related to oxidative stress, inflammation, coagulation, disturbed endothelial function, and hemodynamic responses [12]. Preterm delivery and intrauterine growth retardation could by themselves or together be the underlying cause of low birth weight. Adverse effects in the development of the foetus during pregnancy, such as intrauterine growth restriction [14, 15], have previously been associated with low birth weight, and stress during pregnancy has been shown to lead to preterm birth [16].

One epidemiological study has assessed the association between occupational particle exposure in form of welding fumes and metal dust during pregnancy and foetal effects [17]. The Finnish cross-sectional study showed a 78% non-significant increased risk of small for gestational age in relation to welding fumes and threefold significant increased risk of small for gestational age in relation to a combination of welding fumes and metal dust [17]. However, the study was retrospective which gives an increased risk of recall bias. No previous study has been found on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcomes. There is therefore a strong need for a prospective cohort study in this area of research.

The aim of this cohort study was to investigate the relationship between the mothers' exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes: small for gestational age, low birth weight, and preterm birth.

Methods

Study setting and dataset

The study population was selected among mother and child pairs with children born from January 1, 1994 to December 31, 2012. Only single births were included in the study (1,826,743 observations). Additional inclusion criteria were that the mother should have an occupation during pregnancy that could be coded into Arbetsmarknadsstyrelsens yrkesklassificering (AMSYK) or Nordisk yrkesklassificering 1983 (NYK 83) (1,148,312 observations) and that they also reported working full-time or part-time at the beginning of pregnancy (995,843 observations).

The study was based on data from three Swedish registers – the Medical Birth Register at the National Board of Health and Welfare, the Longitudinal integration database for health insurance and labour market studies at Statistics Sweden, and the Register of sick leave and parental leave from the Swedish Social Insurance Agency.

The Medical Birth Register includes information about the mother's occupation in free-text (un-coded) and if the mother was working full-time, part-time, or not at all, which is reported during the registration interview at prenatal care facilities around week 10 of the pregnancy. It also includes important information about the outcome variables and potential confounders. The register includes in total about 98%–99% of all children born in Sweden [18].

To increase the specificity of the information on occupational exposures, information about absence from work for pregnancies between 1994 and 2012 was collected from the register of sick leave and parental leave and matched by birth date and gestational length, in order to assess the number of days of absence from the workplace during each pregnancy. Citizens report sick leave and parental leave in order to get social insurance benefits. The register does not cover short-term sick leave of less than 14 days (when the employer is responsible for the benefit), but it covers long-term sick leave, parental leave, and special sick leave related to the pregnancy from day 1.

The Longitudinal integration database for health insurance and labour market studies contains all persons in Sweden aged 16 and older who are registered in Sweden as of the 31st of December every year [19]. The information about the mother's highest level of education from the register was used to adjust for socioeconomic status.

Exposure

Information on the mothers' occupation obtained during the registration interview was coded manually by occupational hygienists according to AMSYK/Standard för svensk yrkesklassificering (SSYK), the Swedish version of ISCO-88 (International Labour Office (ILO) 1990). A detailed description of the coding procedure has been published earlier by Selander et al. 2016 [20]. Exposure to air pollution at work was assessed by matching of the mother's occupational title during pregnancy to a job-exposure matrix, based on Finnish Information System on Occupational Exposure (FINJEM) and adopted to Swedish conditions by the research group [21]. The matrix included estimations for fourteen different types of particles for about one hundred different occupational groups and two time periods.

The mean value for exposure was divided into the following exposure groups based on percentiles: unexposed (0), low exposure (0 to 50th percentile), and high exposure (equal to or over the 50th percentile). The cut off value between low exposure and high exposure (50th percentile) was 0.09 mg/m^3 for both inorganic particles and welding fumes, with a range of 0.01 to 1.60 mg/m^3 for inorganic particles and 0.01 to 3.20 mg/m^3 for welding fumes. When the study participants were few, the exposure was dichotomized into unexposed or exposed.

The occupational exposures were further divided into three subgroups. The subgroup of iron dust included occupational exposure to iron dust or fumes from welding, smelting, grinding, or other processing of steel and other materials containing iron. The subgroup of concrete dust included dust from stone and concrete material, and the subgroup of other inorganic dust included dust from plaster and insulation.

The presence of the pregnant mother at the workplace was divided into three categories – i) working full-time with low absence from work (reported full-time work and with fewer than 50 days of absence from work (<50th percentile) during pregnancy), ii) working full-time or part-time with moderate absence from work (reported part-time work or with 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy), and iii) working full-time or part-time with high absence from work (reported full-time or part-time work and with 112 or more days of absence from work (≥75th percentile) during pregnancy).

Confounders

Potential confounders were identified through a review of previous studies on small for gestational age, preterm birth, and low birth weight in association with exposure to residential or occupational air pollution [22, 23] and included the mother´s age (five categories: <20 years, ≥20-<25 years, ≥25-<30 years, ≥30-<35, ≥35 years), current smoking habits (three categories: non-smokers, smokers of 1–9 cigarettes per day, and smokers of 10 cigarettes per day or more), highest completed educational level (three categories: high school 2 years or less, high school more than 2 years or university less than 3 years, and university 3 years or more or graduated), working at the beginning of pregnancy (three categories: full-time, part-time, and not at all), occupational exposure to noise (two categories: <75dB and ≥75dB), nationality measured as country of origin (three categories: Swedish, EU15/Nordic countries except Sweden, and outside Europe (EU15)) and parity (three categories: first child, second child, and third child or more).

The selection of variables for confounding adjustment was based on the effect each potential confounder had on the association between occupational exposure and outcome. The inclusion criterion for the final model was a deviation >5% in the point estimate with the confounder in the model compared to the model without the confounder. The mother´s BMI, physical strenuous work and psychosocial stress, family structure and the children's gender and birth year were also tested, but since they affected the point estimate of the crude analysis 5 % or less, they were excluded from the final model.

Outcome

Outcome variables available through the Medical Birth Registry were small for gestational age (a calculated growth curve of weight and gestational age estimated by the National Board of Health and Welfare), birth weight, and gestational length. Preterm birth was defined by dichotomizing gestational length at gestational week 37, and low birth weight was defined by dichotomizing birth weight at 2,500 g. Small for gestational age was defined as birth weight below two standard deviations of the mean[24].

Statistical analysis

Analyses were done with logistic regression in STATA SE 13.1 (StataCorp LLC, Texas, USA) generating odds ratios (ORs) and 95% confidence intervals (CIs). All the confounders listed in table 1 have been tested with chi-square, and show a statistically significant difference, p-value <0.05. The study was approved by the regional ethics committee in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

Patient and Public Involvement

The research question and outcome measures have been developed through questions by occupational active women to Karolinska Institutet and Stockholm county council about risks with exposure during pregnancy, as well as a review of previous studies and literature. Formal consent is not obligated in this register based cohort study; therefore, neither patients/study participants nor the public were involved in the recruitment to or conduct of the study. The study participants have been interviewed in about week 10 and the information has been added to the Medical birth register. All the registries involved have done a confidentiality control on the behalf of the study participants. The study does not include publication of results on or to individual study participants. The results will be published through this paper and maybe alter the recommendations to pregnant women at antenatal clinics in Sweden.

Results

In total, the study population included 1,826,743 single births, and out of these 995,843 had complete data on mother's occupation. The study included 20,445 cases of small for gestational age, 28,272 cases of low birth weight, and 46,044 cases of pre-term birth.

Table 1. Baseline characteristics of the study participants [a] (995,843) in per cent (%) and number (n) of cases in relation to the adverse outcomes of small for gestational age (SGA) [b], low birth weight (LBW) [c], and preterm birth (PTB) [d].

	SGA		LBW		PTB		All births
Per cent (%) and number (n) of cases.	%	n	%	n	%	n	n[e]
Mother´s age							
<20 years	3.42	111	4.41	143	6.37	207	3,259
≥20, <25 years	2.20	2,370	3.12	3,355	5.28	5,680	107,792
≥25, <30 years	1.96	6,433	2.73	8,936	4.69	15,398	328,776
≥30, <35	1.95	7,064	2.65	9,593	4.27	15,456	362,597
≥35 years	2.32	4,467	3.24	6,245	4.82	9,303	193,419
Smoking							
Non-smokers	1.86	16,679	2.66	23,912	4.52	40,605	900,154
Smokers, ≥1, ≤9 cig per day	3.91	2,331	4.39	2,620	5.45	3,252	59,874
Smokers, ≥10 cig per day	5.15	1,125	5.82	1,272	6.57	1,437	21,945
Highest completed educational level							
High school ≤2 years (1)	2.44	6,525	3.23	8,635	5.02	13,395	267,775
University <3 years (2)	1.97	8,128	2.79	11,541	4.66	19,288	414,529
University ≥3 years or Graduate (3)	1.83	5,649	2.58	7,945	4.26	13,154	309,072
Working at the beginning of pregnancy							
Full-time	2.21	14,295	3.03	19,574	4.86	31,437	648,050
Part-time	1.77	6,150	2.51	8,698	4.21	14,607	347,793
Absence from work							
<50 days	2.36	12,209	3.57	18,458	5.73	29,613	518,275
≥50 days and < 120 days	1.87	5,164	2.00	5,511	3.13	8,642	276,789
≥120 days	1.53	3,072	2.15	4,303	3.89	7,789	200,779
Occupational noise							
Unexposed	2.02	16,686	2.82	23,216	4.57	37,671	826,422
Exposed	2.23	3,759	2.99	5,056	4.95	8,373	169,421
Nationality							
Swedish	1.97	17,469	2.77	24,508	4.61	40,863	887,847
EU15 and Nordic countries (except Sweden)	2.35	632	2.95	794	4.43	1,194	27,029
Outside Europe (EU15)	2.91	2,339	3.68	2,963	4.93	3,973	80,711
Parity							
First child	2.91	13,379	3.79	17,449	5.87	27,007	461,203
Second child	1.29	4,640	1.92	6,915	3.42	12,315	360,660
Third child or more	1.40	2,426	2.25	3,908	3.87	6,722	173,980
Missing							0%

a. *Restricted to single births between 1994 and 2012 among mothers who worked full-time or part-time.*
b. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
c. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*
d. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*
e. *There was no missing, except for smoking (1%).*
All the confounders have been tested with chi2, and show a statistically significant difference, p-value <0.05.

Baseline characteristics are presented in table 1 above. The risk for births with adverse outcome varied with the mother’s age and seemed to be higher for younger (younger than 25 years) and older (35 years of age or older) mothers. Smokers had a higher percentage of adverse outcomes than non-smokers, and higher education was correlated with a lower prevalence of adverse birth outcomes. There also seemed to be a difference in percentage between nationalities, with a higher prevalence of cases in the group of mothers born outside Europe.

Table 2. Maternal occupational exposure [d] to inorganic particles and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work[e]				**Working full or part-time with moderate absence from work[f]**				**Working full or part-time with high absence from work[g]**			
	Crude		Adjusted[h]		Crude		Adjusted[h]		Crude		Adjusted[h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,736	1	8,551	1	8,010	1	7,828	1	2,927	1	2,853
Low Exposure	.83 (.71–.97)	156	.88 (.75–1.03)	154	.75 (.58–.99)	54	.89 (.68–1.16)	54	.85 (.60–1.21)	32	1.02 (.72–1.46)	32
High Exposure	1.35 (1.17–1.55)	207	1.20 (1.04–1.39)	203	1.21 (1.05–1.39)	210	1.06 (.92–1.22)	204	1.19 (.98–1.44)	113	.97 (.80–1.17)	112
LBW												
No Exposure	1	13,085	1	12,838	1	9,975	1	9,742	1	4,119	1	3,999
Low Exposure	.84 (.73–.95)	236	.90 (.79–1.03)	230	.98 (.79–1.21)	87	1.11 (.89–1.38)	85	.73 (.53–1.01)	39	.84 (.61–1.16)	39
High Exposure	1.52 (1.36–1.70)	346	1.32 (1.18–1.48)	341	1.11 (.98–1.26)	240	1.02 (.90–1.17)	235	1.08 (.91–1.28)	145	.93 (.78–1.11)	141
PTB												
No Exposure	1	21,003	1	20,630	1	15,904	1	15,551	1	7,469	1	7,272
Low Exposure	.83 (.75–.92)	377	.89 (.80–.99)	366	.89 (.75–1.07)	127	.98 (.82–1.17)	125	.75 (.60–.95)	73	.82 (.65–1.04)	72
High Exposure	1.38 (1.26–1.51)	502	1.18 (1.07–1.30)	491	.99 (.89–1.10)	342	.93 (.83–1.04)	334	1.01 (.89–1.16)	247	.93 (.81–1.06)	243

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m^3.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).*

g. *All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.*

h. *Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.*

Table 3. Maternal occupational exposure [d] to welding fumes and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work[e]				Working full or part-time with moderate absence from work[f]				Working full or part-time with high absence from work[g]			
	Crude		Adjusted[h]		Crude		Adjusted[h]		Crude		Adjusted[h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,916	1	8,729	1	8,097	1	7,913	1	2,982	1	2,908
Low Exposure	1.63 (1.34–1.99)	106	1.45 (1.19–1.78)	103	1.29 (1.05–1.59)	94	1.14 (.92–1.40)	92	1.21 (.90–1.64)	44	1.03 (.76–1.40)	44
High Exposure	1.14 (.91–1.43)	77	1.05 (.83–1.32)	76	1.18 (.95–1.47)	83	1.07 (.86–1.34)	81	1.15 (.85–1.54)	46	.94 (.69–1.26)	45
LBW												
No Exposure	1	13,362	1	13,109	1	10,104	1	9,867	1	4,188	1	4,068
Low Exposure	1.75 (1.49–2.05)	168	1.52 (1.30–1.79)	166	1.13 (.93–1.38)	103	1.06 (.87–1.29)	102	1.00 (.75–1.32)	51	.87 (.65–1.16)	49
High Exposure	1.37 (1.15–1.63)	137	1.22 (1.02–1.45)	134	1.08 (.88–1.33)	95	1.00 (.81–1.23)	93	1.14 (.88–1.46)	64	.99 (.76–1.27)	62
PTB												
No Exposure	1	21,451	1	21,066	1	16,109	1	15,753	1	7,586	1	7,389
Low Exposure	1.36 (1.18–1.56)	211	1.16 (1.00–1.34)	205	.98 (.82–1.16)	142	.92 (.77–1.09)	138	1.08 (.89–1.33)	100	.99 (.81–1.22)	97
High Exposure	1.38 (1.20–1.58)	220	1.24 (1.07–1.42)	216	.87 (.72–1.04)	122	.82 (.68–.98)	119	1.01 (.83–1.23)	103	.93 (.76–1.14)	101

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m^3.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).*

g. *All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.*

h. *Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.*

ORs for the association between exposure to air pollution and birth outcomes subdivided by absence from work are presented in table 2 and 3 above. An elevated risk of small for gestational age, low birth weight, and preterm birth were indicated after exposure to inorganic particles during pregnancy (table 2). In the highest exposed group of mothers working full-time with low absence from work < 50 days, a statistically significantly increased risk in all outcomes was shown, including small for gestational age (OR = 1.20; 95% CI: 1.04–1.39), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), and preterm birth (OR = 1.18; 95% CI: 1.07–1.30). An increased risk of adverse birth outcomes was not visible among mothers that had an exposed occupation, but were absent from work during pregnancy. Full-time working women who were exposed to high levels of welding fumes during pregnancy had a significantly increased risk of low birth weight (adjusted OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (adjusted OR = 1.24; 95% CI: 1.07–1.42) compared to the unexposed (table 3). Mothers with low exposures had a statistically significant increased risk of having children born small for gestational age (adjusted OR = 1.45; 95% CI: 1.19–1.78), but no dose-response was shown. Among exposed mothers with moderate or high absence from work, no increased risk for negative birth outcomes was shown.

Table 4. Maternal occupational exposure [d] to inorganic particles, subdivided into iron particles, stone and concrete particles, and other inorganic particles, and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c].

	Working full-time with low amount of absence from work [e]			
	Crude		Adjusted [f]	
	OR (95% CI)	n/cases	OR (95% CI)	n/cases
Iron particles				
SGA				
Unexposed	1	361,282/8,916	1	354,903/8,729
Exposed	1.38 (1.19–1.61)	5,361/183	1.25 (1.07–1.46)	5,253/179
LBW				
Unexposed	1	356,889/13,362	1	350,574/13,109
Exposed	1.55 (1.38–1.75)	5,239/305	1.37 (1.22–1.54)	5,132/300
PTB				
Unexposed	1	348,989/21,451	1	342,797/21,066
Exposed	1.37 (1.24–1.51)	5,119/431	1.20 (1.08–1.33)	5,016/421
Stone and concrete particles				
SGA				
Unexposed	1	358,427/8,924	1	352,060/8,735
Exposed	.86 (.74–1.00)	8,216/175	.89 (.76–1.04)	8,096/173
LBW				
Unexposed	1	354,007/13,396	1	347,700/13,145
Exposed	.88 (.78–1.00)	8,121/271	.92 (.81–1.04)	8,006/264
PTB				
Unexposed	1	346,142/21,450	1	339,957/21,068
Exposed	.88 (.79–.97)	7,966/432	.91 (.82–1.00)	7,856/419
Other inorganic particles				
SGA				
Unexposed	1	366,317/9,089	1	359,836/8,898
Exposed	1.24 (.66–2.32)	326/10	1.07 (.57–2.02)	320/10
LBW				
Unexposed	1	361,804/13,655	1	355,388/13,397
Exposed	.98 (.55–1.75)	324/12	.77 (.43–1.37)	318/12
PTB				
Unexposed	1	353,796/21,858	1	347,507/21,463
Exposed	1.25 (.82–1.89)	312/24	.94 (.62–1.43)	306/24

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*
c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*
d. *Exposure divided into unexposed and exposed.*
e. *Full-time workers who stated that they were working full-time at the interview in week 10 and who had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*
f. *Odds Ratio (OR) adjusted for the confounders of the mothers' age, education, smoking habits, nationality, occupational exposure to noise, and the children's parity.*

In table 4, exposure to iron particles showed statistically significantly increased risks of small for gestational age (OR = 1.25; 95% CI: 1.07–1.46), low birth weight (OR = 1.37; 95% CI: 1.22–1.54), and preterm birth (OR = 1.20; 95% CI: 1.08–1.33) in the exposed group that had been working full-time. There was no association between welding fumes and adverse birth outcomes among mothers who had high absence from work. Overall, the trend was that exposed mothers with less absence had higher risk of adverse birth outcomes. Examples of common occupations in the group exposed to iron particles were welders, car builders, flight engineers, metal workers, and plumbers. For stone and concrete and other inorganic dust, there was no statistically significant increase in the risk for any of the outcomes.

Discussion

Among the full-time working mothers with low absence from work and high exposure to inorganic particles during pregnancy, statistically significantly increased risks for small for gestational age, low birth weight, and preterm birth were observed. No previous studies have been found on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcome [25]. A statistically significant increased risk for low birth weight and preterm birth was also found in children to mothers who were exposed to welding fumes during pregnancy and with a low absence from work. This was in line with the only previous study made on maternal occupational exposure to welding fumes, metal dust, and adverse birth outcome [17]. In addition, polycyclic aromatic hydrocarbons that are prevalent in welding fumes have been associated with adverse pregnancy outcomes [26].

As was mentioned in the introduction the mechanism is not yet fully understood, but oxidative stress is seen as a putative pathway. Oxidative stress occurs when the capacity of the antioxidant system cannot keep up with the generated reactive oxygen species (ROS). Both chronic oxidative stress as well as acute exposure to high levels of ROS can be harmful and can damage proteins, lipids, and DNA [27] as detected through biomarkers in blood and urine. This is a process that might be reinforced by different exposures, and in high quality studies, exposures to particles and welding fumes have been associated with oxidative DNA damage [28, 29]. Graczyk et al. found an association between welding and the biomarker 8-OHdG in plasma and urine, and there was an exposure response with the number of fine particles but not when particles were measured gravimetrically [30]. Associations between welding fumes and indications of ROS, increased oxidative stress, and lipid peroxidation have also been seen [30, 29].

The size distribution of the particles and the toxicity of the substances are important to know in order to interpret the results. Inorganic particles (such as iron, concrete, plaster, and insulation material) mostly contain coarse particles and are therefore likely to deposit in the nasopharyngeal region [31], even if there is also a smaller fraction with finer particles that might deposit farther down in the tracheobronchial and alveolar regions of the lung. Particle size can explain the distribution and where in the respiratory system the particles deposit, but not the toxicity to lung tissue among different substances [32, 33]. Welding fumes are difficult to define because they contain both small and large particles as well as many different compounds [34]. However, among the three subgroups of inorganic particles, only iron particles showed an increased risk of adverse outcomes.

Measured gravimetrically, most of the iron particles are coarse and deposit mainly in the upper airways and thus can be transported out of the airways. Measurements of blood markers for cardiovascular disease and inflammation indications in subway platform workers – who are exposed to high levels of iron particles in the underground system – showed only slightly increased levels [35]. Even so, measured in numbers there could also be a large amount of fine particles, especially if the iron particles are derived from welding. The translocation of carbon particles from the lung to the systemic circulation in humans has been shown to be low [36, 37], but inhalation of iron particles in rats has been shown to lead to oxidative stress [38].

It is also interesting that a synergistic interaction between soot and iron particles regarding oxidative stress has been shown in rats [39]. All of the occupations in the group exposed to iron particles listed above have one or more other exposures in addition to iron particles, and thus the observed effect cannot with certainty be attributed solely to iron.

This register-based cohort study has several strengths, and it is in many ways unique in a global perspective. First, it contained a vast amount of information on all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers. The variables from the Medical Birth Register and the Longitudinal integration database for health insurance and labour market studies are of high quality with few missing observations (see table 1). The free text data on occupations from the Medical Birth Register have been manually coded (blinded), which ensures accuracy, and even if some misclassification cannot be ruled out, these are most likely non-differential misclassifications. The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known. The information about the exposure was assessed from the job-exposure matrix objectively and blinded from the outcome.

There are also some weaknesses in this kind of study design. Job-exposure matrices were used, which can introduce non-differential misclassification [40]. The job-exposure matrices were based on measurements among workers in different occupations, and based on those measurements a mean value for the occupational group was calculated. This way of classifying exposure is valid, but is not equal to individual measurements throughout the pregnancy for each participant. Therefore it could introduce a misclassification, but the misclassification would not likely be differential and would therefore only push the risk towards null in the middle and high-exposure groups [20]. The risks might therefore in reality be higher than we found in the present study.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. To manage this issue, information on absence can be used. If the exposed groups (according to job title) have high amounts of absence, they would not have been exposed and thus should not have an increased risk of adverse outcome. In this study, there were no statistically significantly increased risks among the exposed women with high absence from work, which indicates no or little residual confounding regarding socioeconomic factors related to the occupational title among the study participants.

In addition, there was no information in the present study on relocation or change of work task within the workplace in order to avoid exposure during pregnancy; therefore, some of the women might have been misclassified regarding exposure, and this might be the reason for the OR being lower than expected in the group of working women with low absence from work and high exposure to welding fumes. Another limitation is that information on absence from work does not include short-term sick leave of less than 14 days, which might lead to non-differential misclassification and underestimate the risk.

In this study multiple analysis have been performed that increase the risk of chance findings, but the analyses have followed a priori hypothesis and the pattern of results (including consideration taken to absence, which shows low residual confounding) does not point to chance findings.

Conclusion

Maternal exposure to air pollution from iron particles and welding fumes in the work environment during pregnancy was associated with negative health effects in the children. No increased risk was found in association with exposure to stone and concrete or other inorganic dust. The results emphasise that women should not be exposed to high levels of iron particles and welding fumes during pregnancy. However, since so few studies have been made in this area, these results need confirmation in future studies.

Compliance with Ethical Standards

Source of Funding: The results reported herein correspond to specific aims of grant no 2013-1438 from Swedish Research Council for Health, Working life and Welfare.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. The study was approved by the regional ethics committee in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

Contributorship statement

J. S., P. G., M. A., L. R. and P. W. conceived of the presented idea. F. N. performed the analysis under supervision of J. S., P. G., M. A., L. R. and P. W. P. W. and N. P. supported in the occupational exposure assessment and M. W. supported in the definition and interpretation of the outcome variables. All supervised the findings of this work. All authors discussed the results and contributed to and approved the final version of the manuscript. Acknowledgement: We thank Annika Gustavsson for her valuable contribution to the data management.

Data sharing statement

Data can be obtained thru acquisition from Swedish registers. The data collection process is described in the method section of this paper. Data code for analysis in STATA can be obtained from the corresponding author on request.

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Research checklist STROBE statement

1) Title and abstract
   a) The study design is indicated with the term “cohort” in the title (title page)
   b) An informative and balanced abstract is provided (page 1)
2) Introduction with an explanation of the scientific background (page 2)
3) State specific objectives: the objective of this cohort study was to investigate the relationship between the mothers’ exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes: small for gestational age, low birth weight, and preterm birth. (page 3)
4) The key elements of study design is presented at first in the abstract (page 1)with the statement “This cohort study included all single births from 1994 to 2012 by occupationally active mothers in Sweden” and then with further description of the study design and the data sources in the beginning and the following sections of the method-section (page 3).
5) The setting, locations and relevant dates are described (including periods of recruitment, exposure, and data collection) in the method-section (page 3-5).
6) Details regarding selection of participants are described (page 3-5)
7) The method section includes description of variables (page 3-5)
8) The data source of each variable has been described and also details of methods regarding exposure assessment and the occupational free text variable (page 3-5 and figure 1).
9) We have tried to explain and assess the impact of different biases on the results in the method section, table 1 and in the discussion (page 3-5, table 1 and page 12-14).
10) The study size was restricted on occupational status and single births in combination with the availability of crucial data. This is further explained in the text in the method section as well as in figure 1 (page 3-5 and figure 1).
11) The mean value for exposure according to the job exposure matrix was divided into the following exposure groups based on percentiles: unexposed (0), low exposure (0 to 50th percentile), and high exposure (equal to or over the 50th percentile). When the study participants were few, the exposure was dichotomized into unexposed or exposed. Confounders were divided as follow; the mother´s age (five categories; <20 years, ≥20, <25 years, ≥25, <30 years, ≥30, <35 years and ≥35 years) according to common practice, current smoking habits divided according to Medical birth register (three categories: non-smokers, smokers of 1–9 cigarettes per day, and smokers of 10 cigarettes per day or more), highest completed educational level was divided close to common practice and with regards to the amount of participants in each category (three categories: high school 2 years or less, high school more than 2 years or university less than 3 years, and university 3 years or more or graduated), working at the beginning of pregnancy (three categories: full-time, part-time, and not at all) according to the Medical birth register, occupational exposure to noise was divided as common practice and with regards to the amount of participants in each category (two categories: <75dB and ≥75dB), nationality measured as country of origin (three categories: Swedish, EU15/Nordic countries except Sweden, and outside Europe (outside EU 15)) and parity was divided close to common practice and with regards to the amount of participants in each category (three categories: first child, second child, and third child

or more). Working at beginning of pregnancy followed the grouping of the medical birth registry. Leave of absence was divided by the median level (50th percentile) and the 75th percentile. The variables are described in table 1.

12) Analyses were done with logistic regression. By reading previous literature and by testing the variables with the regression model, potential confounders were identified (p. 4-5). All the confounders listed in table 1 have been tested with chi-square, and show a statistically significant difference, p-value <0.05. In the analysis the participants with missing data used in the model were excluded. Logistic regression was also used for sub group analyses.
13) This is described in in the first method section (page 3).
14) This is described in table 1.
15) Outcome measures over time: Outcome was measured at every individual child's birth.
16) See the text in method section (page 3-5) and table 2 and 3.
17) Described in the result section of the paper (page 5-12).
18) Described in the discussion part of the paper (page 12-14).
19) Described in the discussion part of the paper (page 12-14).
20) Described in the discussion part of the paper (page 12-14).
21) In the conclusion part of the manuscript (page 14), the conclusions we have drawn from the results of the study are presented. The aim of this study was to investigate the relationship between the mothers' exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes. The composition of occupational particle exposure and other effect modifiers might differ between populations and thereby also the results, but the biological mechanism of this association is still valid in other populations.
22) The study was funded by FORTE (The Swedish Research Council for Health, Working Life and Welfare). The authors have complete scientific independence from the sponsor.

Occupational exposure to inorganic particles during pregnancy and birth outcomes – a nationwide cohort study in Sweden

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Original Research Article for the BMJ Open.

Occupational exposure to inorganic particles during pregnancy and birth outcomes – a nationwide cohort study in Sweden

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Abstract

Objectives The aim of this study was to investigate if occupational exposure to inorganic particles or welding fumes during pregnancy is associated with negative birth outcomes.

Design A prospective national cohort study.

Setting All single births from 1994 to 2012 in Sweden. Information on birth weight, preterm birth, small for gestational age, smoking habits, nationality, age, occupation, absence from work, and education was obtained from nation-wide registers. Exposure to inorganic particles (mg/m^3) was assessed from a job exposure matrix.

Participants This study included all single births by occupationally active mothers (995,843).

Outcome measures Associations between occupational exposures and negative birth outcomes in form of low birth weight, preterm birth, and small for gestational age.

Results Mothers who had high exposure to inorganic particles and had less than 50 days (median) of absence from work during pregnancy showed an increased risk of preterm birth (OR = 1.18; 95% CI: 1.07– 1.30), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), as well as small for gestational age (OR = 1.20; 95% CI: 1.04– 1.39). The increased risks were driven by exposure to iron particles. No increased risks were found in association with exposure to stone and concrete particles. High exposure to welding fumes was associated with an increased risk of low birth weight (OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (OR = 1.24; 95% CI: 1.07–1.42).

Conclusions The results indicate that pregnant women should not be exposed to high levels of iron particles or welding fumes.

Strengths and limitations of this study:

This register-based cohort study contains a vast amount of information with few missing observations about all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers, which make it possible to assess maternal occupational exposure to inorganic particle or welding fumes and adverse pregnancy outcome.

The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known.

The information about the exposure was assessed from the job-exposure matrix which can introduce non-differential misclassification even though it is assessed objectively and blinded from the outcome.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. In this study this issue was managed by the use of information on absence.

Introduction

Many studies have shown associations between exposure to traffic-related residential air pollution during pregnancy (including the combustion products SO_2, NO_X, and CO and particles ($PM_{2.5}$ and PM_{10})) and low birth weight, preterm birth, and small for gestational age [1, 2]. However, few studies have assessed the association between occupational exposure to particles and adverse pregnancy outcomes, even though the levels of pollutants can be substantially higher at work than in the general outdoor environment.

A majority of Swedish women are in the active work force, 64% of women in ages 20-64 are employed or self-employed. In a Swedish survey from 2009, 23% of occupationally active women in the age group 16 to 29 years and 16% in the age group 30 to 49 years reported exposure to air pollution at the workplace for at least a quarter of the working day [3]. Most women continue to work during pregnancy. Women in physically very demanding work can apply for pregnancy benefit during the last 60 days of pregnancy. A few occupations/exposures are not allowed for pregnant women: lead exposure, diving, fire-fighting with smoke helmet, underground mining work, and work involving exposure to certain microbiological agents [4]. Women exposed to substances or physical conditions that may affect pregnancy negatively can apply for pregnancy benefit during the whole pregnancy, but this is rare. Thus, a large number of Swedish women keep working during pregnancy.

Adverse birth effects, such as low birth weight (<2,500 g), small for gestational age (birth weight less than two standard deviations below the mean for gestational length), and preterm birth (<37 full weeks) are relatively common conditions among new-born's. About 2.7%–4.4% of the children born in 1998–2007 in Sweden were born small for gestational age, and about 3.7%–5.1% were born with low birth weight [5]. The proportion of premature births has been quite constant in recent decades, and in 2013 about 5% of all single births were premature [6]. Low birth weight has been associated with an increased risk of asthma and respiratory problems [7] as well as increased risk of cardiovascular disease [8]. In addition, children with low birth weight have a higher mortality than children with normal birth weight [9], and low birth weight and preterm birth both might result in cognitive deficits later in life [10, 11]. The mechanism behind the association between exposure to air pollution during pregnancy and foetal health effects is not yet fully understood [2]. Several plausible pathways have been suggested [12], where oxidative stress is one putative mechanism [13]. Low birth weight could possibly be caused by cardiovascular mechanisms related to oxidative stress, inflammation, coagulation, disturbed endothelial function, and hemodynamic responses [12]. Preterm delivery and intrauterine growth retardation could by themselves or together be the underlying cause of low birth weight. Adverse effects in the development of the foetus during pregnancy, such as intrauterine growth restriction [14, 15], have previously been associated with low birth weight, and stress during pregnancy has been shown to lead to preterm birth [16].

One epidemiological study has assessed the association between occupational particle exposure in form of welding fumes and metal dust during pregnancy and foetal effects [17]. The Finnish cross-sectional study showed a 78% non-significant increased risk of small for gestational age in relation to welding fumes and threefold significant increased risk of small for gestational age in relation to a combination of welding fumes and metal dust [17]. However, the study was retrospective which gives an increased risk of recall bias. No previous study has been found on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcomes. There is therefore a strong need for a prospective cohort study in this area of research.

The aim of this cohort study was to investigate the relationship between the mothers' exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes: small for gestational age, low birth weight, and preterm birth.

Methods

Study setting and dataset

The study population was selected among mother and child pairs with children born from January 1, 1994 to December 31, 2012. Only single births were included in the study (1,826,743 observations). Additional inclusion criteria were that the mother should have an occupation during pregnancy that could be coded into Arbetsmarknadsstyrelsens yrkesklassificering (AMSYK) or Nordisk yrkesklassificering 1983 (NYK 83) (1,148,312 observations) and that they also reported working full-time or part-time at the beginning of pregnancy (995,843 observations).

The study was based on data from three Swedish registers – the Medical Birth Register at the National Board of Health and Welfare, the Longitudinal integration database for health insurance and labour market studies at Statistics Sweden, and the Register of sick leave and parental leave from the Swedish Social Insurance Agency.

The Medical Birth Register includes information about the mother's occupation in free-text (un-coded) and if the mother was working full-time, part-time, or not at all, which is reported during the registration interview at prenatal care facilities around week 10 of the pregnancy. It also includes important information about the outcome variables and potential confounders. The register includes in total about 98%–99% of all children born in Sweden [18].

To increase the specificity of the information on occupational exposures, information about absence from work for pregnancies between 1994 and 2012 was collected from the register of sick leave and parental leave and matched by birth date and gestational length, in order to assess the number of days of absence from the workplace during each pregnancy. Citizens report sick leave and parental leave in order to get social insurance benefits. The register does not cover short-term sick leave of less than 14 days (when the employer is responsible for the benefit), but it covers long-term sick leave, parental leave, and special sick leave related to the pregnancy from day 1.

The Longitudinal integration database for health insurance and labour market studies contains all persons in Sweden aged 16 and older who are registered in Sweden as of the 31st of December every year [19]. The information about the mother's highest level of education from the register was used to adjust for socioeconomic status.

Exposure

Information on the mothers’ occupation obtained during the registration interview was coded manually by occupational hygienists according to AMSYK/Standard för svensk yrkesklassificering (SSYK), the Swedish version of ISCO-88 (International Labour Office (ILO) 1990). A detailed description of the coding procedure has been published earlier by Selander et al. 2016 [20]. Exposure to air pollution at work was assessed by matching of the mother’s occupational title during pregnancy to a job-exposure matrix, based on Finnish Information System on Occupational Exposure (FINJEM) and adopted to Swedish conditions by the research group [21]. The matrix included estimations for fourteen different types of particles for about one hundred different occupational groups and two time periods.

The mean value for exposure was divided into the following exposure groups based on percentiles: unexposed (0), low exposure (0 to 50th percentile), and high exposure (equal to or over the 50th percentile). The cut off value between low exposure and high exposure (50th percentile) was 0.09 mg/m^3 for both inorganic particles and welding fumes, with a range of 0.01 to 1.60 mg/m^3 for inorganic particles and 0.01 to 3.20 mg/m^3 for welding fumes. When the study participants were few, the exposure was dichotomized into unexposed or exposed.

The occupational exposures were further divided into three subgroups. The subgroup of iron dust included occupational exposure to iron dust or fumes from welding, smelting, grinding, or other processing of steel and other materials containing iron. The subgroup of concrete dust included dust from stone and concrete material, and the subgroup of other inorganic dust included dust from plaster and insulation.

The presence of the pregnant mother at the workplace was divided into three categories – i) working full-time with low absence from work (reported full-time work and with fewer than 50 days of absence from work (<50th percentile) during pregnancy), ii) working full-time or part-time with moderate absence from work (reported part-time work or with 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy), and iii) working full-time or part-time with high absence from work (reported full-time or part-time work and with 112 or more days of absence from work (≥75th percentile) during pregnancy).

Confounders

Potential confounders were identified through a review of previous studies on small for gestational age, preterm birth, and low birth weight in association with exposure to residential or occupational air pollution [22, 23] and included the mother´s age (five categories: <20 years, ≥20-<25 years, ≥25-<30 years, ≥30-<35, ≥35 years), current smoking habits (three categories: non-smokers, smokers of 1–9 cigarettes per day, and smokers of 10 cigarettes per day or more), highest completed educational level (three categories: high school 2 years or less, high school more than 2 years or university less than 3 years, and university 3 years or more or graduated), working at the beginning of pregnancy (three categories: full-time, part-time, and not at all), occupational exposure to noise (two categories: <75dB and ≥75dB), nationality measured as country of origin (three categories: Swedish, EU15/Nordic countries except Sweden, and outside Europe (EU15)) and parity (three categories: first child, second child, and third child or more).

The selection of variables for confounding adjustment was based on the effect each potential confounder had on the association between occupational exposure and outcome. The inclusion criterion for the final model was a deviation >5% in the point estimate with the confounder in the model compared to the model without the confounder. The mother´s BMI, physical strenuous work and psychosocial stress, family structure and the children's gender and birth year were also tested, but since they affected the point estimate of the crude analysis 5 % or less, they were excluded from the final model.

Outcome

Outcome variables available through the Medical Birth Registry were small for gestational age (a calculated growth curve of weight and gestational age estimated by the National Board of Health and Welfare), birth weight, and gestational length. Preterm birth was defined by dichotomizing gestational length at gestational week 37, and low birth weight was defined by dichotomizing birth weight at 2,500 g. Small for gestational age was defined as birth weight below two standard deviations of the mean[24].

Statistical analysis

Analyses were done with logistic regression in STATA SE 13.1 (StataCorp LLC, Texas, USA) generating odds ratios (ORs) and 95% confidence intervals (CIs). All the confounders listed in table 1 have been tested with chi-square, and show a statistically significant difference, p-value <0.05. The study was approved by the Regional Ethical Review Board in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

Patient and Public Involvement

The research question and outcome measures have been developed through questions by occupational active women to Karolinska Institutet and Stockholm county council about risks with exposure during pregnancy, as well as a review of previous studies and literature. Formal consent is not obligated in this register based cohort study; therefore, neither patients/study participants nor the public were involved in the recruitment to or conduct of the study. The study participants have been interviewed in about week 10 and the information has been added to the Medical birth register. All the registries involved have done a confidentiality control on the behalf of the study participants. The study does not include publication of results on or to individual study participants. The results will be published through this paper and maybe alter the recommendations to pregnant women at antenatal clinics in Sweden.

Results

In total, the population included 1,826,743 single births. After restriction that the mother had to have an occupation during pregnancy that could be coded into AMSYK or NYK 83 the sample decreased to 1,148,312 observations. Out of these, 995,843 had complete data on mother's occupation (including information on full-time or part-time work) and were selected as the final study population. The study included 20,445 cases of small for gestational age, 28,272 cases of low birth weight, and 46,044 cases of pre-term birth.

Table 1. Baseline characteristics of the study participants [a] (995,843) in per cent (%) and number (n) of cases in relation to the adverse outcomes of small for gestational age (SGA) [b], low birth weight (LBW) [c], and preterm birth (PTB) [d].

	SGA		LBW		PTB		All births
Per cent (%) and number (n) of cases.	%	n	%	n	%	n	n[e]
Mother´s age							
<20 years	3.42	111	4.41	143	6.37	207	3,259
≥20, <25 years	2.20	2,370	3.12	3,355	5.28	5,680	107,792
≥25, <30 years	1.96	6,433	2.73	8,936	4.69	15,398	328,776
≥30, <35	1.95	7,064	2.65	9,593	4.27	15,456	362,597
≥35 years	2.32	4,467	3.24	6,245	4.82	9,303	193,419
Smoking							
Non-smokers	1.86	16,679	2.66	23,912	4.52	40,605	900,154
Smokers, ≥1, ≤9 cig per day	3.91	2,331	4.39	2,620	5.45	3,252	59,874
Smokers, ≥10 cig per day	5.15	1,125	5.82	1,272	6.57	1,437	21,945
Highest completed educational level							
High school ≤2 years (1)	2.44	6,525	3.23	8,635	5.02	13,395	267,775
University <3 years (2)	1.97	8,128	2.79	11,541	4.66	19,288	414,529
University ≥3 years or Graduate (3)	1.83	5,649	2.58	7,945	4.26	13,154	309,072
Working at the beginning of pregnancy							
Full-time	2.21	14,295	3.03	19,574	4.86	31,437	648,050
Part-time	1.77	6,150	2.51	8,698	4.21	14,607	347,793
Absence from work							
<50 days	2.36	12,209	3.57	18,458	5.73	29,613	518,275
≥50 days and < 120 days	1.87	5,164	2.00	5,511	3.13	8,642	276,789
≥120 days	1.53	3,072	2.15	4,303	3.89	7,789	200,779
Occupational noise							
Unexposed	2.02	16,686	2.82	23,216	4.57	37,671	826,422
Exposed	2.23	3,759	2.99	5,056	4.95	8,373	169,421
Nationality							
Swedish	1.97	17,469	2.77	24,508	4.61	40,863	887,847
EU15 and Nordic countries (except Sweden)	2.35	632	2.95	794	4.43	1,194	27,029
Outside Europe (EU15)	2.91	2,339	3.68	2,963	4.93	3,973	80,711
Parity							
First child	2.91	13,379	3.79	17,449	5.87	27,007	461,203
Second child	1.29	4,640	1.92	6,915	3.42	12,315	360,660
Third child or more	1.40	2,426	2.25	3,908	3.87	6,722	173,980
Missing							0%

a. *Restricted to single births between 1994 and 2012 among mothers who worked full-time or part-time.*
b. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
c. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*
d. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*
e. *There was no missing, except for smoking (1%).*
All the confounders have been tested with chi2, and show a statistically significant difference, p-value <0.05 in relation to the outcome of small for gestational age, low birth weight or preterm birth.

Baseline characteristics are presented in table 1 above. The risk for births with adverse outcome varied with the mother’s age and seemed to be higher for younger (younger than 25 years) and older (35 years of age or older) mothers. Smokers had a higher percentage of adverse outcomes than non-smokers, and higher education was correlated with a lower prevalence of adverse birth outcomes. There also seemed to be a difference in percentage between nationalities, with a higher prevalence of cases in the group of mothers born outside Europe.

Table 2. Maternal occupational exposure [d] to inorganic particles and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work[e]				**Working full or part-time with moderate absence from work[f]**				**Working full or part-time with high absence from work[g]**			
	Crude		Adjusted[h]		Crude		Adjusted[h]		Crude		Adjusted[h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,736	1	8,551	1	8,010	1	7,828	1	2,927	1	2,853
Low Exposure	.83 (.71–.97)	156	.88 (.75–1.03)	154	.75 (.58–.99)	54	.89 (.68–1.16)	54	.85 (.60–1.21)	32	1.02 (.72–1.46)	32
High Exposure	1.35 (1.17–1.55)	207	1.20 (1.04–1.39)	203	1.21 (1.05–1.39)	210	1.06 (.92–1.22)	204	1.19 (.98–1.44)	113	.97 (.80–1.17)	112
LBW												
No Exposure	1	13,085	1	12,838	1	9,975	1	9,742	1	4,119	1	3,999
Low Exposure	.84 (.73–.95)	236	.90 (.79–1.03)	230	.98 (.79–1.21)	87	1.11 (.89–1.38)	85	.73 (.53–1.01)	39	.84 (.61–1.16)	39
High Exposure	1.52 (1.36–1.70)	346	1.32 (1.18–1.48)	341	1.11 (.98–1.26)	240	1.02 (.90–1.17)	235	1.08 (.91–1.28)	145	.93 (.78–1.11)	141
PTB												
No Exposure	1	21,003	1	20,630	1	15,904	1	15,551	1	7,469	1	7,272
Low Exposure	.83 (.75–.92)	377	.89 (.80–.99)	366	.89 (.75–1.07)	127	.98 (.82–1.17)	125	.75 (.60–.95)	73	.82 (.65–1.04)	72
High Exposure	1.38 (1.26–1.51)	502	1.18 (1.07–1.30)	491	.99 (.89–1.10)	342	.93 (.83–1.04)	334	1.01 (.89–1.16)	247	.93 (.81–1.06)	243

a. *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*

b. *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*

c. *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*

d. *Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m³.*

e. *Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*

f. *Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).*

g. *All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.*

h. *Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.*

Table 3. Maternal occupational exposure [d] to welding fumes and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c] subdivided by work participation during pregnancy.

	Working full-time with low absence from work[e]				Working full or part-time with moderate absence from work[f]				Working full or part-time with high absence from work[g]			
	Crude		Adjusted[h]		Crude		Adjusted[h]		Crude		Adjusted[h]	
	(n=376,831)		(n=370,126)		(n=418,233)		(n=410,370)		(n=200,779)		(n=196,878)	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
No Exposure	1	8,916	1	8,729	1	8,097	1	7,913	1	2,982	1	2,908
Low Exposure	1.63 (1.34–1.99)	106	1.45 (1.19–1.78)	103	1.29 (1.05–1.59)	94	1.14 (.92–1.40)	92	1.21 (.90–1.64)	44	1.03 (.76–1.40)	44
High Exposure	1.14 (.91–1.43)	77	1.05 (.83–1.32)	76	1.18 (.95–1.47)	83	1.07 (.86–1.34)	81	1.15 (.85–1.54)	46	.94 (.69–1.26)	45
LBW												
No Exposure	1	13,362	1	13,109	1	10,104	1	9,867	1	4,188	1	4,068
Low Exposure	1.75 (1.49–2.05)	168	1.52 (1.30–1.79)	166	1.13 (.93–1.38)	103	1.06 (.87–1.29)	102	1.00 (.75–1.32)	51	.87 (.65–1.16)	49
High Exposure	1.37 (1.15–1.63)	137	1.22 (1.02–1.45)	134	1.08 (.88–1.33)	95	1.00 (.81–1.23)	93	1.14 (.88–1.46)	64	.99 (.76–1.27)	62
PTB												
No Exposure	1	21,451	1	21,066	1	16,109	1	15,753	1	7,586	1	7,389
Low Exposure	1.36 (1.18–1.56)	211	1.16 (1.00–1.34)	205	.98 (.82–1.16)	142	.92 (.77–1.09)	138	1.08 (.89–1.33)	100	.99 (.81–1.22)	97
High Exposure	1.38 (1.20–1.58)	220	1.24 (1.07–1.42)	216	.87 (.72–1.04)	122	.82 (.68–.98)	119	1.01 (.83–1.23)	103	.93 (.76–1.14)	101

a. Small for gestational age, estimated by a calculated growth curve of weight and gestational age.

b. Low birth weight, dichotomized as <2,500 g and ≥2,500 g.

c. Preterm birth, dichotomized as <37 weeks and ≥37 weeks.

d. Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m³.

e. Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).

f. Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).

g. All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.

h. Odds Ratio (OR) adjusted for mothers´ age, education, smoking habits, nationality, occupational exposure to noise, and parity.

ORs for the association between exposure to air pollution and birth outcomes subdivided by absence from work are presented in table 2 and 3 above. An elevated risk of small for gestational age, low birth weight, and preterm birth were indicated after exposure to inorganic particles during pregnancy (table 2). In the highest exposed group of mothers working full-time with low absence from work < 50 days, a statistically significantly increased risk in all outcomes was shown, including small for gestational age (OR = 1.20; 95% CI: 1.04–1.39), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), and preterm birth (OR = 1.18; 95% CI: 1.07–1.30). An increased risk of adverse birth outcomes was not visible among mothers that had an exposed occupation, but were absent from work during pregnancy. Full-time working women who were exposed to high levels of welding fumes during pregnancy had a significantly increased risk of low birth weight (adjusted OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (adjusted OR = 1.24; 95% CI: 1.07–1.42) compared to the unexposed (table 3). Mothers with low exposures had a statistically significant increased risk of having children born small for gestational age (adjusted OR = 1.45; 95% CI: 1.19–1.78), but no dose-response was shown. Among exposed mothers with moderate or high absence from work, no increased risk for negative birth outcomes was shown.

Table 4. Maternal occupational exposure [d] to inorganic particles, subdivided into iron particles, stone and concrete particles, and other inorganic particles, and small for gestational age (SGA) [a], low birth weight (LBW) [b], and preterm birth (PTB) [c].

	Working full-time with low amount of absence from work [e]			
	Crude		Adjusted [f]	
	OR (95% CI)	n/cases	OR (95% CI)	n/cases
Iron particles				
SGA				
Unexposed	1	361,282 /8,916	1	354,903 /8,729
Exposed	1.38 (1.19–1.61)	5,361 /183	1.25 (1.07–1.46)	5,253 /179
LBW				
Unexposed	1	356,889 /13,362	1	350,574 /13,109
Exposed	1.55 (1.38–1.75)	5,239 /305	1.37 (1.22–1.54)	5,132 /300
PTB				
Unexposed	1	348,989 /21,451	1	342,797 /21,066
Exposed	1.37 (1.24–1.51)	5,119 /431	1.20 (1.08–1.33)	5,016 /421
Stone and concrete particles				
SGA				
Unexposed	1	358,427 /8,924	1	352,060 /8,735
Exposed	.86 (.74–1.00)	8,216 /175	.89 (.76–1.04)	8,096 /173
LBW				
Unexposed	1	354,007 /13,396	1	347,700 /13,145
Exposed	.88 (.78–1.00)	8,121 /271	.92 (.81–1.04)	8,006 /264
PTB				
Unexposed	1	346,142 /21,450	1	339,957 /21,068
Exposed	.88 (.79–.97)	7,966 /432	.91 (.82–1.00)	7,856 /419
Other inorganic particles				
SGA				
Unexposed	1	366,317 /9,089	1	359,836 /8,898
Exposed	1.24 (.66–2.32)	326 /10	1.07 (.57–2.02)	320 /10
LBW				
Unexposed	1	361,804 /13,655	1	355,388 /13,397
Exposed	.98 (.55–1.75)	324 /12	.77 (.43–1.37)	318 /12
PTB				
Unexposed	1	353,796 /21,858	1	347,507 /21,463
Exposed	1.25 (.82–1.89)	312 /24	.94 (.62–1.43)	306 /24

- ***a.*** *Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
- ***b.*** *Low birth weight, dichotomized as <2,500 g and ≥2,500 g.*
- ***c.*** *Preterm birth, dichotomized as <37 weeks and ≥37 weeks.*
- ***d.*** *Exposure divided into unexposed and exposed.*
- ***e.*** *Full-time workers who stated that they were working full-time at the interview in week 10 and who had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).*
- ***f.*** *Odds Ratio (OR) adjusted for the confounders of the mothers' age, education, smoking habits, nationality, occupational exposure to noise, and the children's parity.*

In table 4, exposure to iron particles showed statistically significantly increased risks of small for gestational age (OR = 1.25; 95% CI: 1.07–1.46), low birth weight (OR = 1.37; 95% CI: 1.22–1.54), and preterm birth (OR = 1.20; 95% CI: 1.08–1.33) in the exposed group that had been working full-time. There was no association between welding fumes and adverse birth outcomes among mothers who had high absence from work. Overall, the trend was that exposed mothers with less absence had higher risk of adverse birth outcomes. Examples of common occupations in the group exposed to iron particles were welders, car builders, flight engineers, metal workers, and plumbers. For stone and concrete and other inorganic dust, there was no statistically significant increase in the risk for any of the outcomes.

Discussion

Among the full-time working mothers with low absence from work and high exposure to inorganic particles during pregnancy, statistically significantly increased risks for small for gestational age, low birth weight, and preterm birth were observed. No previous studies have been found on maternal occupational exposure to inorganic particles like stone and concrete and adverse pregnancy outcome [25]. A statistically significant increased risk for low birth weight and preterm birth was also found in children to mothers who were exposed to welding fumes during pregnancy and with a low absence from work. This was in line with the only previous study made on maternal occupational exposure to welding fumes, metal dust, and adverse birth outcome [17]. In addition, polycyclic aromatic hydrocarbons that are prevalent in welding fumes have been associated with adverse pregnancy outcomes [26].

As was mentioned in the introduction the mechanism is not yet fully understood, but oxidative stress is seen as a putative pathway. Oxidative stress occurs when the capacity of the antioxidant system cannot keep up with the generated reactive oxygen species (ROS). Both chronic oxidative stress as well as acute exposure to high levels of ROS can be harmful and can damage proteins, lipids, and DNA [27] as detected through biomarkers in blood and urine. This is a process that might be reinforced by different exposures, and in high quality studies, exposures to particles and welding fumes have been associated with oxidative DNA damage [28, 29]. Graczyk et al. found an association between welding and the biomarker 8-OHdG in plasma and urine, and there was an exposure response with the number of fine particles but not when particles were measured gravimetrically [30]. Associations between welding fumes and indications of ROS, increased oxidative stress, and lipid peroxidation have also been seen [30, 29].

The size distribution of the particles and the toxicity of the substances are important to know in order to interpret the results. Inorganic particles (such as iron, concrete, plaster, and insulation material) mostly contain coarse particles and are therefore likely to deposit in the nasopharyngeal region [31], even if there is also a smaller fraction with finer particles that might deposit farther down in the tracheobronchial and alveolar regions of the lung. Particle size can explain the distribution and where in the respiratory system the particles deposit, but not the toxicity to lung tissue among different substances [32, 33]. Welding fumes are difficult to define because they contain both small and large particles as well as many different compounds [34]. However, among the three subgroups of inorganic particles, only iron particles showed an increased risk of adverse outcomes.

Measured gravimetrically, most of the iron particles are coarse and deposit mainly in the upper airways and thus can be transported out of the airways. Measurements of blood markers for cardiovascular disease and inflammation indications in subway platform workers – who are exposed to high levels of iron particles in the underground system – showed only slightly increased levels [35]. Even so, measured in numbers there could also be a large amount of fine particles, especially if the iron particles are derived from welding. The translocation of carbon particles from the lung to the systemic circulation in humans has been shown to be low [36, 37], but inhalation of iron particles in rats has been shown to lead to oxidative stress [38].

It is also interesting that a synergistic interaction between soot and iron particles regarding oxidative stress has been shown in rats [39]. All of the occupations in the group exposed to iron particles listed above have one or more other exposures in addition to iron particles, and thus the observed effect cannot with certainty be attributed solely to iron.

This register-based cohort study has several strengths, and it is in many ways unique in a global perspective. First, it contained a vast amount of information on all children born in Sweden from the beginning of 1994 to the end of 2012 and their mothers. The variables from the Medical Birth Register and the Longitudinal integration database for health insurance and labour market studies are of high quality with few missing observations (see table 1). The free text data on occupations from the Medical Birth Register have been manually coded (blinded), which ensures accuracy, and even if some misclassification cannot be ruled out, these are most likely non-differential misclassifications. The data were collected prospectively in the sense that the information about the mother and child were collected during pregnancy and information about the occupation was collected before the birth outcome was known. The information about the exposure was assessed from the job-exposure matrix objectively and blinded from the outcome.

There are also some weaknesses in this kind of study design. Job-exposure matrices were used, which can introduce non-differential misclassification [40]. The job-exposure matrices were based on measurements among workers in different occupations, and based on those measurements a mean value for the occupational group was calculated. This way of classifying exposure is valid, but is not equal to individual measurements throughout the pregnancy for each participant. Therefore it could introduce a misclassification, but the misclassification would not likely be differential and would therefore only push the risk towards null in the middle and high-exposure groups [20]. The risks might therefore in reality be higher than we found in the present study. In addition, it was not possible in this study to adjust for exposure to air pollution in the outdoor environment, away from the work place, which if it correlates with occupations can be a potential confounder.

In epidemiological studies, the risk shown might be associated with residual confounding from socioeconomic factors related to the type of work rather than the exposure. To manage this issue, information on absence can be used. If the exposed groups (according to job title) have high amounts of absence, they would not have been exposed and thus should not have an increased risk of adverse outcome. In this study, there were no statistically significantly increased risks among the exposed women with high absence from work, which indicates no or little residual confounding regarding socioeconomic factors related to the occupational title among the study participants.

In addition, there was no information in the present study on relocation or change of work task within the workplace in order to avoid exposure during pregnancy; therefore, some of the women might have been misclassified regarding exposure, and this might be the reason for the OR being lower than expected in the group of working women with low absence from work and high exposure to welding fumes. Another limitation is that information on absence from work does not include short-term sick leave of less than 14 days, which might lead to non-differential misclassification and underestimate the risk.

In this study multiple analysis have been performed that increase the risk of chance findings, but the analyses have followed a priori hypothesis and the pattern of results (including consideration taken to absence, which shows low residual confounding) does not point to chance findings.

Conclusion

Maternal exposure to air pollution from iron particles and welding fumes in the work environment during pregnancy was associated with negative health effects in the children. No increased risk was found in association with exposure to stone and concrete or other inorganic dust. The results emphasise that women should not be exposed to high levels of iron particles and welding fumes during pregnancy. However, since so few studies have been made in this area, these results need confirmation in future studies.

Compliance with Ethical Standards

Source of Funding: The results reported herein correspond to specific aims of grant no 2013-1438 from Swedish Research Council for Health, Working life and Welfare.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. The study was approved by the Regional Ethical Review Board in Stockholm on 8/14/2014 (case number; 2014/1108-31/5).

Contributorship statement

J. S., P. G., M. A., L. R. and P. W. conceived of the presented idea. F. N. performed the analysis under supervision of J. S., P. G., M. A., L. R. and P. W. P. W. and N. P. supported in the occupational exposure assessment and M. W. supported in the definition and interpretation of the outcome variables. All supervised the findings of this work. All authors discussed the results and contributed to and approved the final version of the manuscript. Acknowledgement: We thank Annika Gustavsson for her valuable contribution to the data management.

Data sharing statement

Data can be obtained thru acquisition from Swedish registers. The data collection process is described in the method section of this paper. Data code for analysis in STATA can be obtained from the corresponding author on request.

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Research checklist STROBE statement

1) Title and abstract
   a) The study design is indicated with the term “cohort” in the title (title page)
   b) An informative and balanced abstract is provided (page 1)
2) Introduction with an explanation of the scientific background (page 2)
3) State specific objectives: the objective of this cohort study was to investigate the relationship between the mothers’ exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes: small for gestational age, low birth weight, and preterm birth. (page 3)
4) The key elements of study design is presented at first in the abstract (page 1) in design, setting, participants and then with further description of the study design and the data sources in the beginning and the following sections of the method-section (page 3).
5) The setting, locations and relevant dates are described (including periods of recruitment, exposure, and data collection) in the method-section (page 3-5).
6) Details regarding selection of participants are described (page 3-5)
7) The method section includes description of variables (page 3-5)
8) The data source of each variable has been described and also details of methods regarding exposure assessment and the occupational free text variable (page 3-5 and figure 1).
9) We have tried to explain and assess the impact of different biases on the results in the method section, table 1 and in the discussion (page 3-5, table 1 and page 11-13).
10) The study size was restricted on occupational status and single births in combination with the availability of crucial data. This is further explained in the text in the method section as well as in figure 1 (page 3-5 and figure 1).
11) The mean value for exposure according to the job exposure matrix was divided into the following exposure groups based on percentiles: unexposed (0), low exposure (0 to 50th percentile), and high exposure (equal to or over the 50th percentile). When the study participants were few, the exposure was dichotomized into unexposed or exposed. Confounders were divided as follow; the mother´s age (five categories; <20 years, ≥20, <25 years, ≥25, <30 years, ≥30, <35 years and ≥35 years) according to common practice, current smoking habits divided according to Medical birth register (three categories: non-smokers, smokers of 1–9 cigarettes per day, and smokers of 10 cigarettes per day or more), highest completed educational level was divided close to common practice and with regards to the amount of participants in each category (three categories: high school 2 years or less, high school more than 2 years or university less than 3 years, and university 3 years or more or graduated), working at the beginning of pregnancy (three categories: full-time, part-time, and not at all) according to the Medical birth register, occupational exposure to noise was divided as common practice and with regards to the amount of participants in each category (two categories: <75dB and ≥75dB), nationality measured as country of origin (three categories: Swedish, EU15/Nordic countries except Sweden, and outside Europe (outside EU 15)) and parity was divided close to common practice and with regards to the amount of participants in each category (three categories: first child, second child, and third child or more). Working at beginning of pregnancy followed the grouping of the medical birth registry.

Leave of absence was divided by the median level (50th percentile) and the 75th percentile. The variables are described in table 1.

12) Analyses were done with logistic regression. By reading previous literature and by testing the variables with the regression model, potential confounders were identified (p. 4-5). All the confounders listed in table 1 have been tested with chi-square, and show a statistically significant difference, p-value <0.05 in relation to the outcome of small for gestational age, low birth weight or preterm birth. In the analysis the participants with missing data used in the model were excluded. Logistic regression was also used for sub group analyses.
13) This is described in in the first method section (page 3).
14) This is described in table 1.
15) Outcome measures over time: Outcome was measured at every individual child's birth.
16) See the text in method section (page 3-5) and table 2 and 3.
17) Described in the result section of the paper (page 5-11).
18) Described in the discussion part of the paper (page 11-13).
19) Described in the discussion part of the paper (page 11-13).
20) Described in the discussion part of the paper (page 11-13).
21) In the conclusion part of the manuscript (page 13), the conclusions we have drawn from the results of the study are presented. The aim of this study was to investigate the relationship between the mothers' exposures to inorganic particles and welding fumes in the work environment during pregnancy and the risk of the following negative birth outcomes. The composition of occupational particle exposure and other effect modifiers might differ between populations and thereby also the results, but the biological mechanism of this association is still valid in other populations.
22) The study was funded by FORTE (The Swedish Research Council for Health, Working Life and Welfare). The authors have complete scientific independence from the sponsor.