

Can atmospheric pollutants influence menstrual cycle function? Supplementary material

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Can Atmospheric Pollutants Influence Menstrual Cycle Function?

Supplementary Material

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Estimation of exposure to atmospheric pollution

A fine spatial exposure model for NO_2 and PM_{10} with 1x1 km spatial resolution and daily temporal resolution was developed by INERIS (French national institute for industrial environment and risks), covering the whole country for years 2009-2010. The model was developed by kriging daily data from the CHIMERE chemistry-transport model and using as drift daily data from air quality monitors and -for NO_2- NO_X emission inventory (Benmerad et al, 2017).

As the urine samples were collected between October 2007 and January 2008 and as we were interested in the exposures in the 30 days before the start of the cycle and the 90 days before the end of the cycle, we retrieved data from all the air quality monitoring stations of the country from ADEME (French Environment and Energy Management Agency) between January 2002 and July 2009. Each home address was linked to the nearest point of grid and to the nearest monitoring station at less than 100 km from home. To back-extrapolate the exposures from the model to the study period, we assumed that the spatial contrast at the country scale were similar in 2009 than during the other years of the study period (2007-2008). We estimated the ratio of the model's estimate at the home address during the 30 days of 2009 corresponding to the days and months of the exposure window divided by the model's estimate at the nearest station for the same 30 days period and used this spatial ratio to correct the average during the true exposure window of the daily concentrations at the nearest station. For each exposure window, we considered as missing exposure variables of women for whom less than 75% of the daily averages during the relevant time window of the station used for back-extrapolation were available.

Going more in details, to explicit this assumption of stability of the spatial contrasts in air pollution across the years of the study period, we assumed that if during a time period in the year 2009 (dt_{2009}) the exposure level at a location (X_1,Y_1) corresponded to a proportion x of the whole country average during dt_{2009}, then for the same time period (defined in calendar days and months) during another year A (dt_A, with A being another year in the study period), exposure at the same location (X_1,Y_1) would also correspond to the same proportion x of the exposure in the whole country during dt_A, i.e.:

$$\frac{model_{dt_{2009}}(X_1,Y_1)}{model_{2009}(France)} = \frac{model_{dt_A}(X_1,Y_1)}{model_{dt_A}(France)} = x(X_1,Y_1) \qquad (1)$$

For any pair of locations $(X_1,Y_1)_i$ (the point on the grid closest from the home address of woman i) and $(X_2,Y_2)_i$ (the point on the grid closest to the monitoring station closest of the home address of woman i) we can deduce from equation (1) that:

$$\begin{aligned} model_{dt_A}(France) &= \frac{model_{dt_A}(X_1,Y_1)_i}{model_{dt_{2009}}(X_1,Y_1)_i} model_{dt_{2009}}(France) \\ &= \frac{model_{dt_A}(X_2,Y_2)_i}{model_{dt_{2009}}(X_2,Y_2)_i} model_{dt_{2009}}(France) \end{aligned}$$

$$\Leftrightarrow model_{dt_A}(X_1,Y_1)_i = \frac{model_{dt_{2009}}(X_1,Y_1)_i}{model_{dt_{2009}}(X_2,Y_2)_i} model_{dt_A}(X_2,Y_2)_i \qquad (2)$$

For each woman, from the model defined on a 1x1 km grid, we estimated $model_{dt_{2009}}(X_1,Y_1)_i$ (i.e. the exposure estimated at home address of woman i during the exposure window dt moved in 2009) and $model_{dt_{2009}}(X_2,Y_2)_i$ (i.e. the exposure estimated at the location of nearest station from home address of woman i during the exposure window dt moved in 2009). To estimate our target exposure $model_{dt}(X_1,Y_1)_i$ (i.e. the exposure estimated at the home address of woman i during the exposure window dt_i corresponding to 30 days before the index cycle of woman i), we applied equation (2). According to (2), $model_{dt}(X_1,Y_1)_i$ was estimated as the exposure estimated at the location of the nearest station from home address of woman i during the 30 days (dt) before her index cycle (i.e. $model_{dt}(X_2,Y_2)_i$) multiplied by a corrective factor defined during the 30 days of 2009 corresponding to the days and months of the exposure window (dt_{2009}).

We need to approximate the term $model_{dt}(X_2,Y_2)_i$ of expression (2), which we approximated from the values measured at the station located in (X_2,Y_2). We averaged the daily data from the nearest station of home address of woman i during dt (this average was called $station_{\mathrm{dt}}(X_2,Y_2)_i$). Then, we estimated the exposure of woman i at her home address during the exposure window dt (called $exposure_{\mathrm{dt}}(X_1,Y_1)_i$) by applying the corrective factor to the exposure estimated during dt_i with the nearest station for home address of woman i:

$$exposure_{dt}(X_1,Y_1)_i = \frac{model_{dt_{2009}}(X_1,Y_1)_i}{model_{dt_{2009}}(X_2,Y_2)_i} station_{\mathrm{dt}}(X_2,Y_2)_i \qquad (3)$$

Supplementary Table 1: Comparison of the study population with all women recruited in Obseff study.

Characteristics	Did not participate in the ancillary study N=813		Participate in the ancillary study N=184		p-value
	N	%*	N	%*	
Age at inclusion (years)					
< 30	247	36	33	24	.06
30-34	231	30	53	30	
35-39	195	20	61	27	
>40	140	14	37	19	
Body Mass Index (kg/m^2) [b]					
< 18.5	74	11	12	9	.53
18.5-24.9	508	59	125	63	
25-29.9	139	18	31	20	
≥ 30	81	12	13	8	
Nulliparous					
No	473	57	105	54	.64
Yes	340	43	79	46	
Active smoking at inclusion					
No	550	64	135	70	.20
Yes	263	36	49	30	
Education level					
Before baccalaureate	222	43	26	26	<0.01
Baccalaureate	332	37	63	39	
After baccalaureate	259	20	95	35	
Employed					
No	221	31	41	25	.26
Yes	592	69	143	75	

* Percentages and test were corrected for possible selection bias and over-representation of urban compared with rural areas. See (Slama et al., 2012) for more details.

Supplementary Table 2: Adjusted changes in the follicular, luteal phases and menstrual cycle durations associated with atmospheric pollution levels in the 90-day period before the end of the cycle (181 women not using hormonal contraception).

	Follicular phase length				Luteal phase length [b]				Total cycle length [c]			
Pollutant and exposure window [a]	**N**	**β**	**95% CI**	**p-value**	**N**	**β**	**95% CI**	**p-value**	**N**	**β**	**95% CI**	**p-value**
NO_2, 90 days before the cycle end [d]												
Continuous [e]	*136*	*0.34*	*-0.29; 0.96*	*0.29*	*122*	*0.40*	*-0.05; 0.85*	*0.08*	*139*	*0.24*	*-0.82; 1.31*	*0.65*
Lowest tertile (6-18 µg/m^3)	33	0	reference	0.55 [f]	30	0	reference	0.24 [f]	37	0	reference	0.57 [f]
Medium tertile (18-29 µg/m^3)	44	-0.38	-2.29; 1.52		41	0.65	-0.56; 1.86		45	-2.43	-5.93; 1.08	
Highest tertile (29-55 µg/m^3)	59	0.41	-1.32; 2.13		51	0.83	-0.48; 2.15		57	0.35	-2.52; 3.21	
PM_{10}, 90 days before the cycle end [d]												
Continuous [e]	*136*	*-0.22*	*-1.83; 1.39*	*0.79*	*122*	*-0.13*	*-1.88; 1.61*	*0.88*	*140*	*-1.77*	*-5.03; 1.49*	*0.28*
Lowest tertile (13-18 µg/m^3)	35	0	reference	0.88 [f]	30	0	reference	0.89 [f]	36	0	Reference	0.33 [f]
Medium tertile (18-21 µg/m^3)	44	0.52	-1.34; 2.38		41	0.69	-0.69; 2.06		48	-0.86	-4.97; 3.24	
Highest tertile (21-30 µg/m^3)	57	0.15	-1.26; 1.56		51	0.19	-1.21; 1.60		56	-1.55	-4.78; 1.67	
Two-pollutant models, 90 days before the cycle end [d]												
NO_2	136	0.43	-0.28; 1.14	0.23	122	0.49	-0.01; 0.99	0.06	139	0.55	-0.52; 1.62	0.31
PM_{10}	136	-0.82	-2.65; 1.00	0.37	122	-0.79	-2.69; 1.11	0.41	139	-2.59	-5.78; 0.59	0.11

[a] Linear regression adjusted for woman age (<30; 30-34; 35-39; 40-45 years), body mass index (<25, ≥25 kg/m^2, 3 missing values imputed in the lowest category), age at menarche (8-12; 12-18 years, 3 missing values imputed in the higher category), parity (nulliparous/parous), alcohol consumption in the week before inclusion (yes/no), caffeine consumption in the week before inclusion (yes/no), active smoking at inclusion (yes/no), passive smoking at inclusion (yes/no), education level (3 categories) and professional activity (yes/no).

[b] Missing values for luteal phase (n=29) were imputed 1000 times using age and follicular length.

[c] Missing values for total cycle length (n=41) were imputed 1000 times using age and follicular length is the cycle was ovulatory, and using age only for anovulatory cycles.

[d] 90 days before the end of the index cycle (only available for women with observed menses at the end of the index cycle).

[e] Changes in mean duration (day) associated with an increase by 10 µg/m^3 in air pollution level.

[f] p-value for trend across exposure tertiles.

Supplementary Table 3: Odds-ratios (OR) of anovulation associated with exposure to nitrogen dioxide (NO_2) or particulate matter (PM_{10}) levels. Logistic regression considering each exposure and exposure window separately. Because of the limited number of anovulatory cycles, only age was taken into account as adjustment factor in all models.

Pollutant and exposure window	N	Number of anovulatory cycles	OR	95% CI	p-value
NO_2					
30 days before the cycle start	180	21	0.66	0.43;1.03	0.07
Days 1-10 before cycle start	180	21	0.82	0.60;1.12	0.22
Days 11-30 before cycle start	180	21	0.64	0.41;1.02	0.06
PM_{10}					
30 days before the cycle start	180	21	0.65	0.26 ;1.65	0.37
Days 1-10 before cycle start	180	21	0.93	0.62 ;1.39	0.72
Days 11-30 before cycle start	180	21	0.69	0.26;1.81	0.45

Analyses were adjusted for woman's age (continuous coding).

Reference (Supplementary Material)

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