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Supplemental Material

Time-Varying Exposure to Air Pollution and Outcomes of *in Vitro* Fertilization among Couples from a Fertility Clinic

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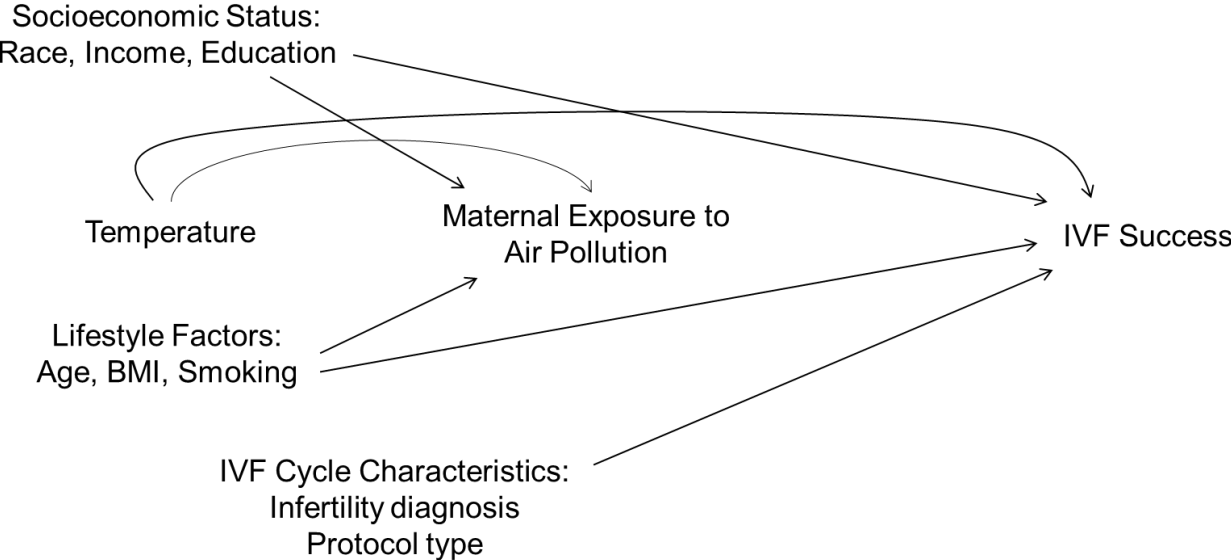
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Figure S1. Overview of the directed acyclic graph used to identify confounding based on a priori knowledge (Panel A) and descriptive statistics from our cohort (Panel B).

A.



B.

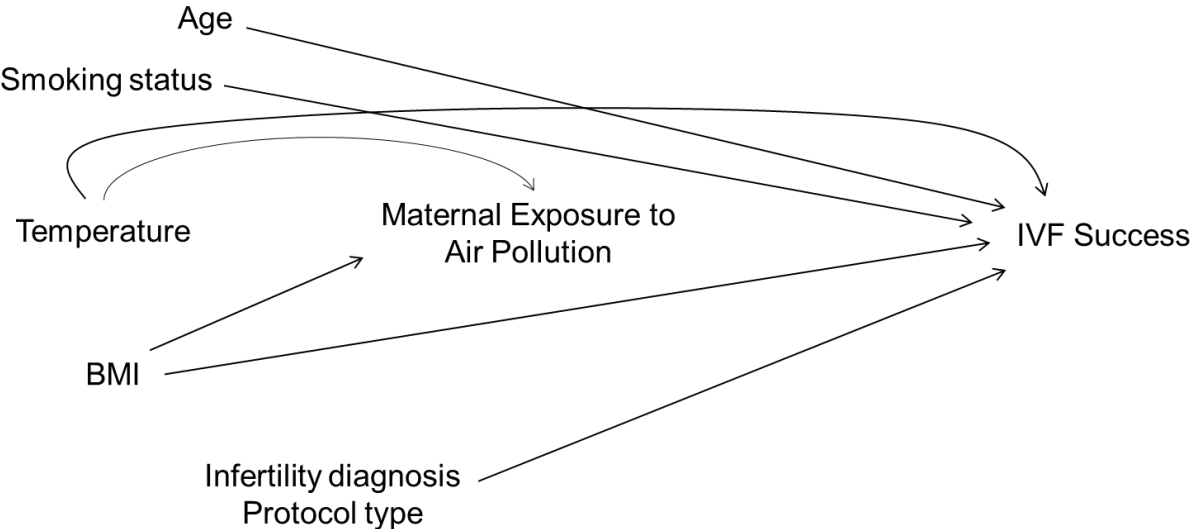
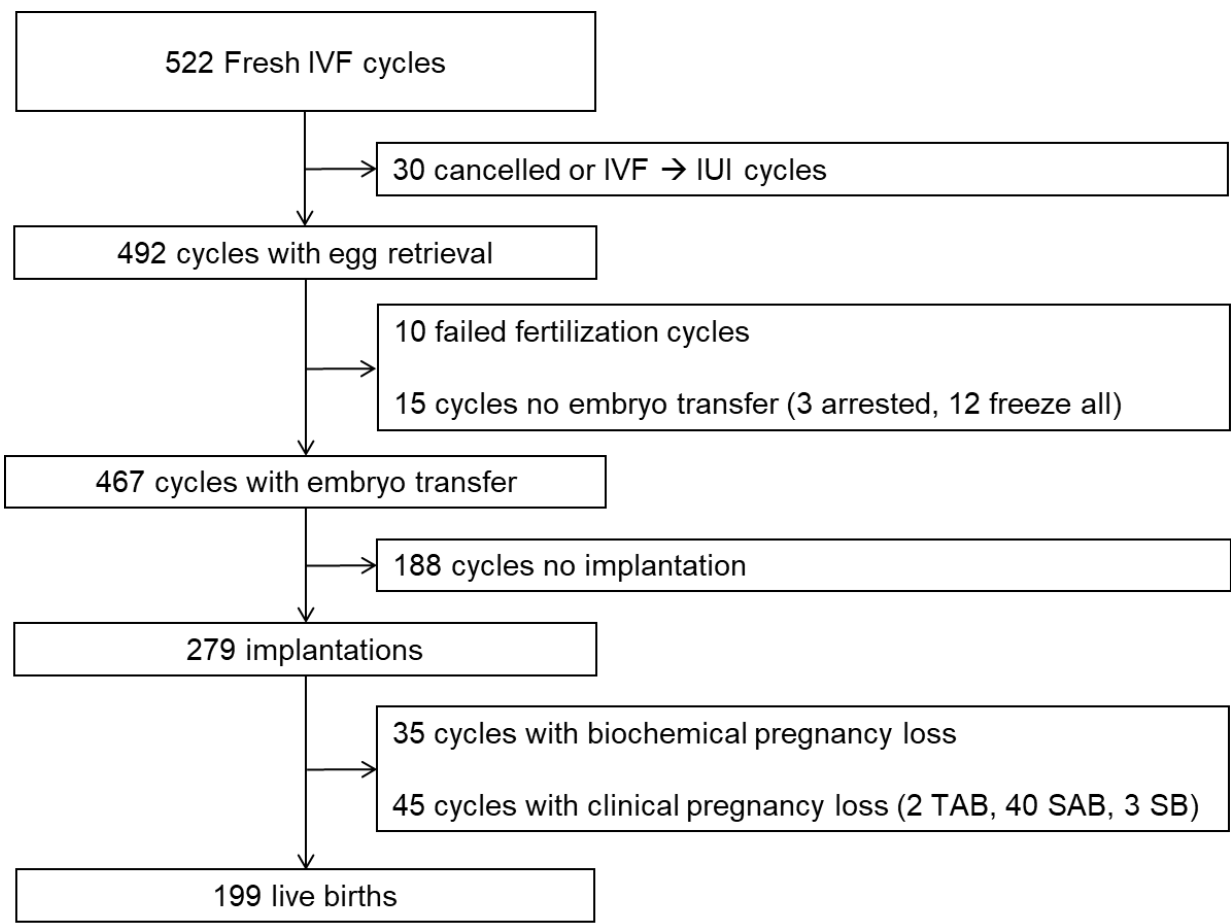


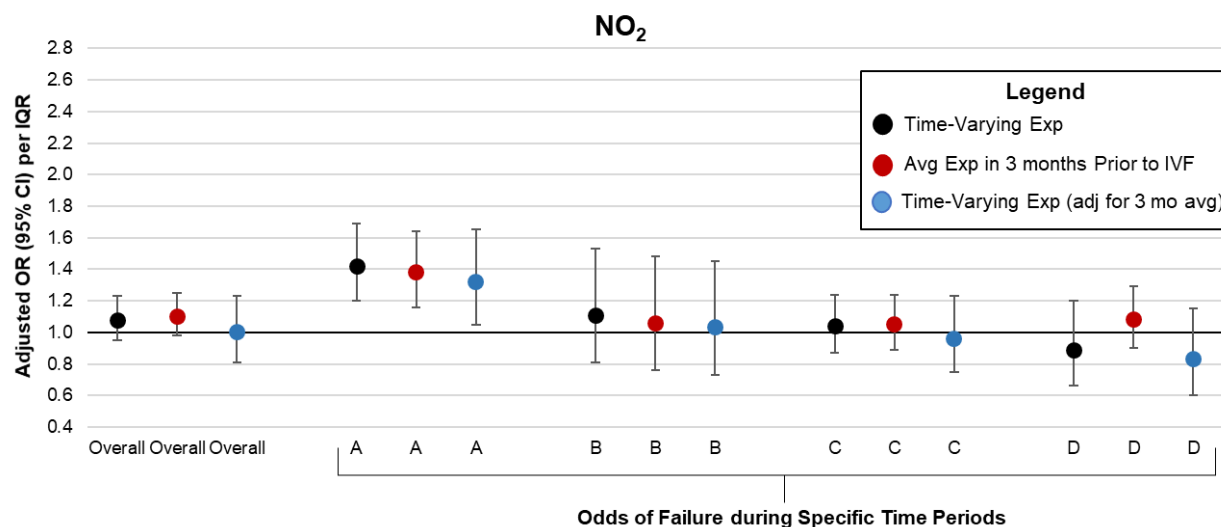
Figure S2. Overview of the outcomes of the 522 fresh in vitro fertilization cycles in the Environmental and Reproductive Health (EARTH) Study.



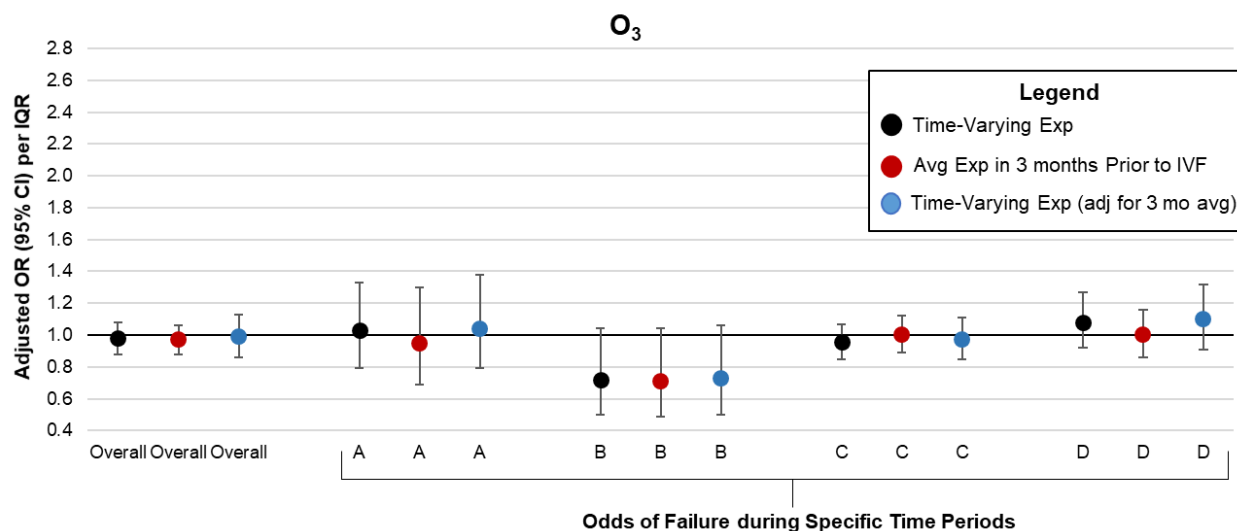
Note: IUI, intrauterine insemination; IVF, in vitro fertilization; SAB, spontaneous abortion; SB, stillbirth; TAB, therapeutic abortion;

Figure S3. Sensitivity analyses assessing whether the effects of nitrogen dioxide (NO₂) (Panel A), ozone (O₃) (Panel B), particulate matter <2.5 μm (PM_{2.5}) (Panel C), and black carbon (Panel D) on the odds of failing at IVF are specific to the IVF time windows (as opposed to characteristic of baseline exposure 3 months prior to IVF) and if short-term variations in air pollutants (above a woman's average exposure concentrations) are more important than absolute exposure levels.

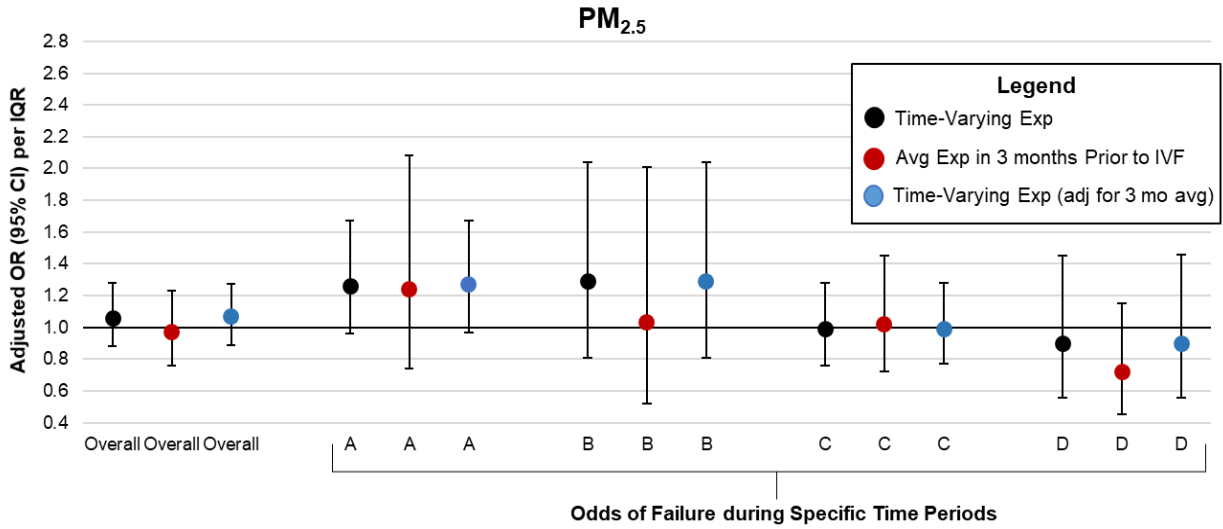
A.



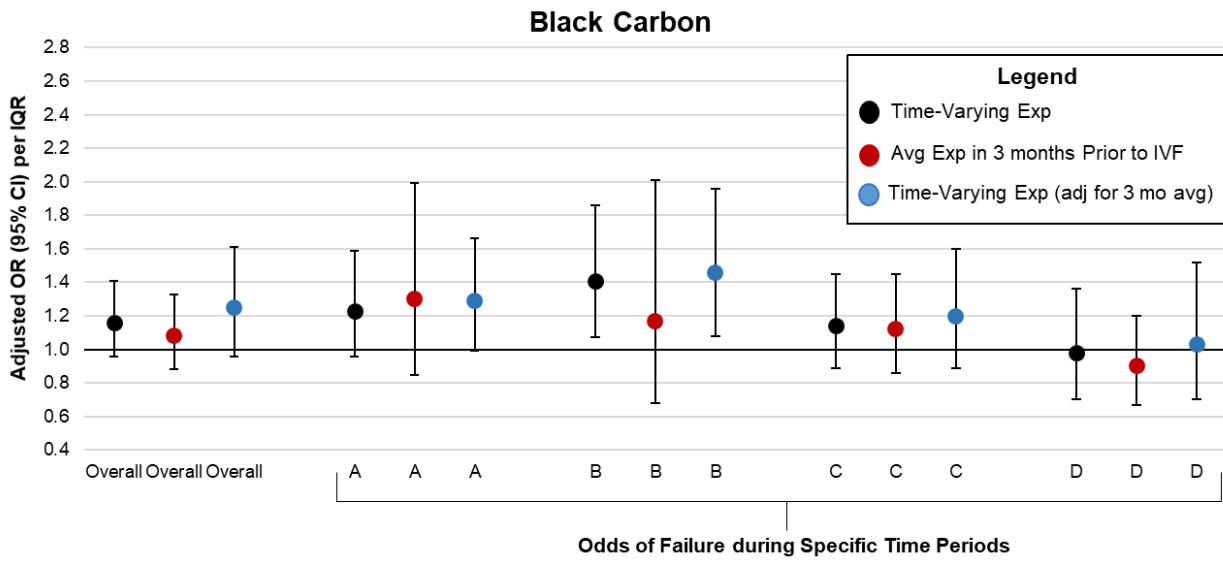
B.



C.



D.



Odds ratios were estimated using a discrete time Cox proportional hazards models. A robust sandwich covariance estimate was used to account for the multiple cycles per woman. The ORs estimate the odds of failing the IVF cycle at any point, conditional on not failing at an earlier moment during the same cycle. Women were considered at risk of failing IVF for the duration of their initiated cycle until their specific point of failure. Adjusted for age, BMI, smoking status (ever, never), infertility diagnosis (female, male, unexplained), protocol (luteal, antagonist/flare), and mean temperature. An IQR increase was 2 $\sqrt{\text{ppb}}$ for NO₂, 1.3 $\sqrt{\text{ppb}}$ for O₃, 3 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, and 0.2 $\mu\text{g}/\text{m}^3$ for BC. Period A: time between initiation of controlled ovarian stimulation and oocyte retrieval, Period B: time between oocyte retrieval and embryo transfer, Period C: time between embryo transfer and first human chorionic gonadotropin (hCG) pregnancy test (i.e. implantation), Period D: time between a positive hCG test and live birth.

Table S1. Average nitrogen dioxide (NO₂), ozone (O₃), particulate matter <2.5 μm (PM_{2.5}) and black carbon (BC) concentrations for each of the IVF windows of exposure among the 345 women in Environment and Reproductive Health (EARTH) Study (2004-2015).

Pollutant	Number of cycles	Minimum	Q1	Median	Q3	Maximum
NO₂ (ppb)						
Period A	522	0.63	11.7	21.5	34.1	380.3
Period B	492	0.73	12.2	21.0	34.2	341.1
Period C	467	0.67	11.9	21.1	31.6	351.7
Period D	279	0.66	13.2	21.8	32.4	279.8
O₃ (ppb)						
Period A	522	0.0	25.5	33.8	43.3	200.0
Period B	492	0.0	25.1	34.2	43.8	200.0
Period C	467	0.0	26.7	35.3	43.8	200.0
Period D	279	0.0	29.4	35.2	41.3	200.0
PM_{2.5} (μg/m³)						
Period A	522	3.0	7.2	8.5	10.4	19.1
Period B	492	2.6	6.7	8.4	10.7	29.2
Period C	467	2.0	7.1	8.6	10.2	19.8
Period D	279	3.3	7.9	8.8	9.7	15.4
BC (μg/m³)						
Period A	512	0.22	0.40	0.50	0.63	1.18
Period B	482	0.20	0.40	0.50	0.64	2.66
Period C	458	0.22	0.41	0.49	0.61	1.32
Period D	273	0.17	0.42	0.50	0.60	1.23

Note: BC, black carbon; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 μm; Q1, 25th percentile; Q3, 75th percentile. Period A: time between initiation of controlled ovarian stimulation and oocyte retrieval, Period B: time between oocyte retrieval and embryo transfer, Period C: time between embryo transfer and first human chorionic gonadotropin (hCG) pregnancy test (i.e. implantation), Period D: time between a positive hCG test and live birth.

Table S2. Spearman correlation between the average nitrogen dioxide (NO₂), ozone (O₃), particulate matter <2.5 μm (PM_{2.5}), and black carbon (BC) levels in the 3 months prior to IVF among 345 women in Environment and Reproductive Health (EARTH) Study (2004-2015).

	NO ₂	O ₃	PM _{2.5}	BC
NO ₂	1	-0.22	0.14	0.40
O ₃		1	0.05	-0.27
PM _{2.5}			1	0.30
BC				1

Table S3. Spearman correlation of air pollutants over time during different time windows of IVF within the 345 women in Environment and Reproductive Health (EARTH) Study (2004-2015).

A. Nitrogen dioxide (NO₂)

	3 months prior	A	B	C	D
3 months prior	1	0.90	0.86	0.87	0.71
A		1	0.92	0.96	0.75
B			1	0.94	0.75
C				1	0.79
D					1

B. Ozone (O₃)

	3 months prior	A	B	C	D
3 months prior	1	0.69	0.61	0.59	0.39
A		1	0.87	0.90	0.52
B			1	0.88	0.56
C				1	0.60
D					1

C. Particulate matter <2.5 μm (PM_{2.5})

	3 months prior	A	B	C	D
3 months prior	1	0.28	0.23	0.21	0.35
A		1	0.48	0.58	0.31
B			1	0.45	0.33
C				1	0.48
D					1

D. Black carbon (BC)

	3 months prior	A	B	C	D
3 months prior	1	0.73	0.63	0.67	0.55
A		1	0.73	0.83	0.72
B			1	0.72	0.63
C				1	0.82
D					1

Period A: time between initiation of controlled ovarian stimulation and oocyte retrieval, Period B: time between oocyte retrieval and embryo transfer, Period C: time between embryo transfer and first human chorionic gonadotropin (hCG) pregnancy test (i.e. implantation), Period D: time between a positive hCG test and live birth.

Table S4. Baseline characteristics of 345 women in Environment and Reproductive Health (EARTH) Study (2004-2015) according to quartiles of air pollution exposure in the 3 months prior to their first IVF cycle.

	NO ₂		O ₃		PM _{2.5}		Black Carbon	
	Q1 86	Q4 86	Q1 86	Q4 86	Q1 86	Q4 86	Q1 84	Q4 85
Personal Characteristics								
Age, years	34.9 ± 4.0	34.7 ± 3.8	34.9 ± 3.8	34.9 ± 3.9	34.9 ± 4.0	35.1 ± 3.5	34.7 ± 4.2	35.1 ± 4.2
BMI, kg/m ²	25.2 ± 5.1	23.9 ± 4.0	23.4 ± 4.1	24.3 ± 4.3*	23.6 ± 4.2	23.6 ± 4.0	25.0 ± 4.3	23.8 ± 3.8
Smoking Status, n (%)								
Never smoker	63 (73.3)	62 (72.1)	64 (74.4)	62 (72.1)	62 (72.1)	61 (70.9)	64 (76.2)	65 (76.5)
Ever smoker	23 (26.7)	24 (27.9)	22 (25.6)	24 (27.9)	24 (27.9)	25 (29.1)	20 (23.8)	20 (23.5)
Race, n (%)								
White/Caucasian	76 (88.4)	73 (84.9)	67 (77.9)	78 (90.7)	74 (86.1)	76 (88.4)	73 (86.9)	71 (83.5)
Other	10 (11.6)	13 (15.1)	19 (22.1)	8 (9.3)	12 (14.0)	10 (11.5)	11 (13.1)	14 (16.5)
Education level, n (%)								
Less than college	8 (9.3)	5 (5.8)	9 (10.5)	5 (5.8)	7 (8.1)	7 (8.1)	10 (11.9)	9 (10.6)
College degree	35 (40.7)	21 (24.4)	20 (23.3)	32 (37.2)	23 (26.7)	33 (38.4)	27 (32.1)	22 (25.9)
Graduate degree	43 (50.0)	60 (69.8)	57 (66.3)	49 (57.0)	56 (65.1)	46 (53.5)	47 (56.0)	54 (63.5)
Census tract median income, \$	107,947 ± 36,181	98,301 ± 45,431	97,827 ± 46,729	113,696 ± 45,288*	103,290 ± 39,163	104,712 ± 44,191	110,520 ± 41,094	105,080 ± 56,302
Employment Status, n (%)								
Currently working	82 (95.4)	82 (95.4)	84 (97.7)	83 (96.5)	85 (98.8)	82 (95.4)	82 (97.6)	81 (95.3)
Currently not working	4 (4.7)	4 (4.7)	2 (2.3)	3 (3.5)	1 (1.2)	4 (4.7)	2 (2.4)	4 (4.7)
Distance to major roadway, m								
	364.5 ± 467.5	100.5 ± 90.4*	108.3 ± 104.4	224.6 ± 392.2	259.7 ± 440.6	130.3 ± 139.4	299.2 ± 365.0	71.0 ± 98.7*
Average temperature in 3 months prior to IVF, C°								
	11.9 ± 8.4	9.2 ± 7.9	6.2 ± 6.6	13.7 ± 7.4*	7.4 ± 6.2	12.3 ± 10.1*	11.1 ± 6.9	8.6 ± 8.5*
Cycle Characteristics								
Gravidity, n (%)								
0	54 (62.8)	57 (66.3)	53 (61.6)	55 (64.0)	53 (61.6)	53 (61.6)	50 (59.5)	50 (58.8)
≥1	32 (37.2)	29 (33.7)	33 (38.4)	31 (36.1)	33 (38.4)	33 (38.4)	34 (40.5)	35 (41.2)
Parity, n (%)								
0	72 (83.7)	77 (89.5)	71 (82.6)	70 (81.4)	73 (84.9)	78 (90.7)	68 (81.0)	75 (88.2)
≥1	14 (16.3)	9 (10.5)	15 (17.4)	16 (18.6)	13 (15.1)	8 (9.3)	16 (19.1)	10 (11.8)
Infertility diagnosis, n (%)								

Male factor	24 (27.9)	27 (31.4)	26 (30.2)	19 (22.1)	23 (26.7)	28 (32.6)	32 (38.1)	26 (30.6)
Female factor	27 (31.4)	28 (32.6)	29 (33.7)	34 (39.5)	25 (29.1)	27 (31.4)	21 (25.0)	32 (37.7)
Unexplained	35 (40.7)	31 (36.1)	31 (36.1)	33 (38.4)	38 (44.2)	31 (36.1)	31 (36.9)	27 (31.8)
Treatment protocol, n (%)								
Luteal phase agonist	63 (73.3)	71 (82.6)	68 (79.1)	71 (82.6)	59 (68.6)	70 (81.4)	62 (73.8)	64 (75.3)
Flare or antagonist	23 (26.7)	15 (17.4)	18 (20.9)	15 (17.4)	27 (31.4)	16 (18.6)	22 (26.2)	21 (24.7)
Number of IVF cycles contributed to analysis	1.6 (0.9)	1.6 (0.9)	1.5 (1.0)	1.5 (0.7)	1.5 (0.7)	1.5 (0.8)	1.6 (0.9)	1.5 (0.7)

Note: BC, black carbon; ET, embryo transfer; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 µm; Q1, quartile 1; Q4, quartile 4. P-values for differences across quartiles was calculated using Kruskal-Wallis tests for continuous variables and Chi-Square tests for categorical variables. *Indicates a p-value<0.05 for differences across quartiles.

Table S5. Effects of nitrogen dioxide (NO₂), ozone (O₃), particulate matter <2.5 µm (PM_{2.5}), and black carbon concentrations on the odds of failing at IVF with further adjustment for other pollutants.

	Adjusted Odds Ratio ^a (95% CI) of Failing at IVF per IQR ^b increase				
	Exposure Updated Throughout Cycle	Failure During Specific Time Periods ^c			
		A	B	C	D
NO ₂	1.08 (0.95, 1.23)	1.42 (1.20, 1.69)	1.11 (0.81, 1.53)	1.04 (0.87, 1.24)	0.89 (0.66, 1.20)
Adjusted for O ₃	1.08 (0.95, 1.23)	1.42 (1.20, 1.69)	1.11 (0.81, 1.52)	1.04 (0.87, 1.24)	0.89 (0.66, 1.20)
Adjusted for PM _{2.5}	1.07 (0.94, 1.22)	1.42 (1.20, 1.69)	1.11 (0.80, 1.52)	1.04 (0.87, 1.23)	0.88 (0.65, 1.19)
Adjusted for BC	1.03 (0.90, 1.19)	1.39 (1.17, 1.66)	1.01 (0.69, 1.48)	0.99 (0.82, 1.19)	0.87 (0.64, 1.18)
O ₃	0.98 (0.88, 1.08)	1.03 (0.79, 1.33)	0.72 (0.50, 1.04)	0.96 (0.85, 1.07)	1.08 (0.92, 1.27)
Adjusted for NO ₂	0.98 (0.88, 1.08)	1.03 (0.80, 1.31)	0.73 (0.51, 1.04)	0.96 (0.85, 1.07)	1.08 (0.92, 1.26)
Adjusted for PM _{2.5}	0.97 (0.88, 1.08)	1.02 (0.79, 1.32)	0.72 (0.50, 1.03)	0.95 (0.84, 1.07)	1.08 (0.92, 1.26)
Adjusted for BC	0.96 (0.87, 1.06)	1.02 (0.81, 1.28)	0.74 (0.52, 1.05)	0.95 (0.84, 1.06)	1.06 (0.90, 1.24)
PM _{2.5}	1.06 (0.88, 1.28)	1.26 (0.96, 1.67)	1.29 (0.81, 2.04)	0.99 (0.76, 1.28)	0.90 (0.56, 1.45)
Adjusted for NO ₂	1.05 (0.87, 1.26)	1.25 (0.95, 1.65)	1.28 (0.80, 2.03)	0.98 (0.75, 1.27)	0.88 (0.54, 1.43)
Adjusted for O ₃	1.07 (0.89, 1.29)	1.27 (0.97, 1.67)	1.29 (0.81, 2.06)	1.00 (0.77, 1.30)	0.91 (0.56, 1.46)
Adjusted for BC	1.00 (0.81, 1.21)	1.18 (0.87, 1.59)	1.14 (0.71, 1.85)	0.92 (0.71, 1.23)	0.93 (0.59, 1.46)
BC	1.16 (0.96, 1.41)	1.23 (0.96, 1.59)	1.41 (1.07, 1.86)	1.14 (0.89, 1.45)	0.98 (0.70, 1.36)
Adjusted for NO ₂	1.15 (0.94, 1.40)	1.22 (0.94, 1.59)	1.40 (1.05, 1.86)	1.12 (0.87, 1.44)	0.96 (0.69, 1.34)
Adjusted for O ₃	1.17 (0.97, 1.42)	1.24 (0.96, 1.59)	1.41 (1.08, 1.83)	1.15 (0.90, 1.47)	0.99 (0.71, 1.38)
Adjusted for PM _{2.5}	1.16 (0.95, 1.42)	1.24 (0.95, 1.63)	1.42 (1.06, 1.63)	1.14 (0.89, 1.47)	0.98 (0.70, 1.36)

Note: BC, black carbon; IQR, interquartile range; IVF, in vitro fertilization; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 µm.

^aOdds ratios were estimated using a multivariable discrete time Cox proportional hazards models adjusted for age, BMI, smoking status, infertility diagnosis, protocol, and mean temperature. A robust sandwich covariance estimate was used to account for the multiple cycles per woman. The ORs estimate the odds of failing the IVF cycle at any point, conditional on not failing at an earlier moment during the same cycle. Women were considered at risk of failing IVF for the duration of their initiated cycle until their specific point of failure.

^bAn IQR increase was 2 √ppb for NO₂, 1.3 √ppb for O₃, 3 µg/m³ for PM_{2.5}, and 0.2 µg/m³ for BC.

^cPeriod A: time between initiation of controlled ovarian stimulation and oocyte retrieval, Period B: time between oocyte retrieval and embryo transfer, Period C: time between embryo transfer and first human chorionic gonadotropin (hCG) pregnancy test (i.e. implantation), Period D: time between a positive hCG test and live birth.

Table S6. Effects of nitrogen dioxide (NO₂), ozone (O₃), particulate matter <2.5 μm (PM_{2.5}), and black carbon concentrations on the odds of failing at IVF after accounting for spatial autocorrelation of model residuals.

	Adjusted Odds Ratio ^a (95% CI) of Failing at IVF per IQR ^b increase				
	Exposure Updated Throughout Cycle	Failure During Specific Time Periods ^c			
		A	B	C	D
NO₂					
Original Model	1.08 (0.95, 1.23)	1.42 (1.20, 1.69)	1.11 (0.81, 1.53)	1.04 (0.87, 1.24)	0.89 (0.66, 1.20)
Random Effect for Zipcode	1.11 (0.97, 1.27)	1.50 (1.19, 1.89)	1.16 (0.82, 1.65)	1.07 (0.89, 1.28)	0.87 (0.65, 1.18)
O₃					
Original Model	0.98 (0.88, 1.08)	1.03 (0.79, 1.33)	0.72 (0.50, 1.04)	0.96 (0.85, 1.07)	1.08 (0.92, 1.27)
Random Effect for Zipcode	0.99 (0.91, 1.07)	1.05 (0.85, 1.30)	0.72 (0.55, 0.94)	0.97 (0.87, 1.07)	1.10 (0.96, 1.26)
PM_{2.5}					
Original Model	1.06 (0.88, 1.28)	1.26 (0.96, 1.67)	1.29 (0.81, 2.04)	0.99 (0.76, 1.28)	0.90 (0.56, 1.45)
Random Effect for Zipcode	1.08 (0.91, 1.28)	1.28 (0.90, 1.81)	1.30 (0.90, 1.88)	1.00 (0.79, 1.26)	0.92 (0.61, 1.37)
BC					
Original Model	1.16 (0.96, 1.41)	1.23 (0.96, 1.59)	1.41 (1.07, 1.86)	1.14 (0.89, 1.45)	0.98 (0.70, 1.36)
Random Effect for Zipcode	1.25 (1.07, 1.46)	1.31 (0.96, 1.78)	1.48 (1.12, 1.95)	1.22 (0.99, 1.51)	1.03 (0.74, 1.43)

Note: BC, black carbon; IQR, interquartile range; IVF, in vitro fertilization; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 μm.

^aOdds ratios from the original model were estimated using a multivariable discrete time Cox proportional hazards models adjusted for age, BMI, smoking status, infertility diagnosis, protocol, and mean temperature. A robust sandwich covariance estimate was used to account for the multiple cycles per woman. The odds ratios from the models with a random effect for zipcode were estimated using a multivariable discrete time Cox proportional hazards model with a random intercept for zipcode adjusted for age, BMI, smoking status, infertility diagnosis, protocol, and mean temperature.

^bAn IQR increase was 2 √ppb for NO₂, 1.3 √ppb for O₃, 3 μg/m³ for PM_{2.5}, and 0.2 μg/m³ for BC.

Table S7. Sensitivity analysis for the association between black carbon concentrations 3 months prior to IVF and during ovarian stimulation on controlled ovarian stimulation outcomes of IVF.

	Adjusted Beta Coefficients (95% CI) ^a per IQR ^b		Adjusted Percent Change (95% CI) per IQR		
	Estradiol Levels at hCG Trigger, pmol/L	Endometrial Thickness, mm	Total Oocyte Yield, N	Mature Oocyte Yield, N	Normally Fertilized Oocytes, N
Original Analysis (n=326 women, 482 cycles)					
3 Months Prior to IVF ^c	122.2 (24.8, 219.5)	0.01 (-0.26, 0.28)	2.7 (-2.5, 8.1)	4.8 (-0.8, 10.5)	7.0 (0.5, 13.8)
During Ovarian Stimulation ^d	149.7 (63.7, 235.6)	0.04 (-0.19, 0.27)	6.8 (2.1, 11.8)	9.0 (4.0, 14.2)	8.8 (3.0, 14.9)
Excluding Hyper-Responders ^e (n=299 women, 422 cycles)					
3 Months Prior to IVF ^c	53.6 (-22.4, 129.6)	0.07 (-0.21, 0.36)	3.4 (-2.2, 9.4)	4.5 (-1.2, 10.7)	5.2 (-1.7, 12.5)
During Ovarian Stimulation ^d	64.9 (-3.2, 132.9)	0.06 (-0.19, 0.31)	7.2 (2.1, 12.6)	8.5 (3.2, 14.1)	6.8 (0.6, 13.4)

Note: CI, confidence interval; ET, embryo transfer; hCG, human chorionic gonadotropin; IQR, interquartile range.

^aModels are adjusted for age, BMI, smoking status (ever, never), infertility diagnosis (female, male, unexplained), protocol (luteal, antagonist/flare), and mean temperature. All outcomes are run with inverse probability weights to control for potential selection bias introduced by restricting the analysis to women who had a successful oocyte retrieval (n=492 cycles). Weights comprised factors associated with the probability of oocyte retrieval, including age, BMI, smoking status (ever, never), infertility diagnosis (female, male, unexplained), protocol (luteal, antagonist/flare), and NO₂ and PM_{2.5} concentrations.

^bAn IQR increase was 0.2 µg/m³ for BC.

^cExposure of interest was the average air pollutant concentrations in the 3 months prior to starting IVF.

^dExposure of interest was the average air pollutant concentrations between initiation of controlled ovarian stimulation and oocyte retrieval.

^eHyper-responders were defined as cycles which resulted in freeze-all embryos and cycles with peak estradiol levels >3000 pmol/L.

Table 8. Association between nitrogen dioxide (NO₂), ozone (O₃), particulate matter <2.5 µm (PM_{2.5}) and black carbon (BC) concentrations during controlled ovarian stimulation on day 3 embryo quality outcomes of IVF (n=312 women, 436 IVF cycles with an embryo transfer on day 3 or 5).

	Adjusted Odds Ratio (95% CI) ^a per IQR ^b			
	% Poor quality embryos	% High quality embryos	% Slow embryo cleavage	% Accelerated embryo cleavage
During Controlled Ovarian Stimulation ^c				
NO ₂	1.06 (0.95, 1.20)	1.01 (0.92, 1.11)	1.02 (0.91, 1.13)	0.96 (0.81, 1.15)
O ₃	0.95 (0.88, 1.03)	1.05 (0.99, 1.11)	0.99 (0.93, 1.06)	0.90 (0.81, 0.99)*
PM _{2.5}	1.14 (0.99, 1.32)	0.97 (0.87, 1.07)	1.17 (1.03, 1.32)*	0.84 (0.70, 1.00)
BC	1.02 (0.87, 1.21)	1.01 (0.90, 1.13)	0.95 (0.83, 1.10)	1.08 (0.89, 1.31)

Note: BC, black carbon; ET, embryo transfer; IQR, interquartile range; IVF, in vitro fertilization; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 µm.

^aModels are adjusted for age, BMI, smoking status (ever, never), infertility diagnosis (female, male, unexplained), protocol (luteal, antagonist/flare), and mean temperature. All outcomes except are run with inverse probability weights to control for potential selection bias introduced by restricting the analysis to women who had an embryo transfer on day 3 or day 5 (n=436 cycles). Weights comprised factors associated with the probability of having a transfer on day 3 or 5, including age, BMI, smoking status (ever, never), infertility diagnosis (female, male, unexplained), protocol (luteal, antagonist/flare), and NO₂ and PM_{2.5} concentrations.

^bAn IQR increase was 2 √ppb for NO₂, 1.3 √ppb for O₃, 3 µg/m³ for PM_{2.5}, and 0.2 µg/m³ for BC.

^cExposure of interest was the average air pollutant concentrations between initiation of controlled ovarian stimulation and oocyte retrieval

*P-value <0.05