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Exposure to Fine Particulate Matter and Ovarian Reserve among Women from a Fertility Clinic

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Abstract

Background.—An increasing number of studies have linked air pollution to decreased fertility. Whether this is due to an effect on ovarian reserve is unknown.

Method.—Our study included 632 women attending the Massachusetts General Hospital Fertility Center (2004–2015) who had a measured antral follicle count. Validated spatiotemporal models estimated daily particulate matter <2.5 μg/m^3 ($PM_{2.5}$) (based on residential address) for the 3 months prior to the antral follicle count. We analyzed associations with Poisson regression.

Results.—Every 2 μg/m^3 increase in estimated $PM_{2.5}$ exposure was associated with a −7.2% (95% CI −10.4%, −3.8%) lower antral follicle count adjusting for age, BMI, smoking status, and year and season of the count. The association of $PM_{2.5}$ with antral follicle count was stronger among women with female factor infertility (−16.3% per 2 μg/m^3).

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Data are not publicly available to protect human subjects' confidentiality. Code for the statistical analysis is available from the authors by request.

Conclusion.—Among women from an infertility clinic, higher $PM_{2.5}$ exposure was associated with lower ovarian reserve, raising concern that air pollution may accelerate reproductive aging.

Keywords

air pollution; ovarian reserve; fertility; fecundity

Introduction

Air pollution, specifically exposure to fine particulate matter ($PM_{2.5}$), is a substantial global health concern,[1] responsible for a growing number of adverse health effects such as cardiovascular disease,[2] stroke,[3] and cancer.[4] In the past decade, there have also been an increasing number of reports linking air pollution to diminished fertility.[5,6] Specifically, live birth rates were lower among women residing in census tracts with higher exposure to $PM_{2.5}$ and other traffic-related air pollutants[7] and women with higher $PM_{2.5}$ exposure had slightly longer time to pregnancy.[8] Adverse effects of $PM_{2.5}$ on fertility may be due to perturbations in semen quality[9] and reproductive hormones[10] among men; however, mechanisms underlying the potential effects of $PM_{2.5}$ on markers of female fertility have been understudied. Animal studies suggest that increased exposure to $PM_{2.5}$ may compromise female reproductive potential by accelerating reproductive aging.[11–13] Therefore, to address this question in women, we investigated the association between estimated residential exposure to $PM_{2.5}$ and antral follicle counts, the gold standard measure of ovarian reserve,[14] among women presenting to an infertility clinic.

Methods

Study participants were women (18 to 45 years) presenting to the Massachusetts General Hospital (MGH) Fertility Center for infertility treatment who enrolled in the Environment and Reproductive Health (EARTH) Study.[15] Approximately 60% of eligible women contacted by the research nurses enrolled. Of the initial 806 women (954 antral follicle scans) available for analysis, we excluded incomplete scans, those done while the woman was on Lupron, those done on women with polycystic ovaries, repeated scans, and scans lacking complete exposure data (eFigure 1). This resulted in a final sample size of 632 women who contributed one unstimulated antral follicle count between 2004 and 2015. The EARTH study was approved by the Human Studies Institutional Review Boards of MGH and the Harvard T.H. Chan School of Public Health.

Upon enrollment, all participants provided their residential address and this was geocoded using ArcGIS. We estimated daily residential $PM_{2.5}$ exposures starting from three months prior to the antral follicle count date to correspond with the proposed window of antral follicle development (~2–4 months).[14] As a negative control window, we also estimated daily $PM_{2.5}$ exposures in the 3 months after the antral follicle count. $PM_{2.5}$ exposures were estimated with a validated hybrid model of satellite–derived aerosol optical depth measurements and land-use terms.[16] These daily 1 km^2 spatial resolution values were then averaged to obtain the woman's 3-month average $PM_{2.5}$ exposure preceding the scan. Ovarian antral follicle count was measured using transvaginal ultrasonography by one of the

MGH reproductive endocrinologists on the 3rd day of an unstimulated menstrual cycle or progesterone withdrawal bleed. All follicles above 2 mm were counted. No fertility medications were used in the cycle prior to the count. To reduce the influence of very high counts, we truncated the measure at 30 (15 women, 2% of population). Date of birth was collected at entry, trained study staff measured weight and height to calculate body mass index (BMI) (kg/m^2). A detailed take-home questionnaire contained questions on lifestyle factors, reproductive health, and medical history. We defined regular menstrual cycles as being predictable within 10 days, and assessed time spent in leisure time physical and sedentary activities using a validated questionnaire.[17] We abstracted infertility diagnosis from electronic medical records.

We calculated descriptive statistics and compared them across quartiles of estimated average $PM_{2.5}$ exposure. Differences in demographic and reproductive characteristics were evaluated using Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables (or Fisher's exact test where appropriate). We used Poisson regression models to estimate the association of estimated average $PM_{2.5}$ exposure with antral follicle count. Non-linearity was assessed non-parametrically with restricted cubic splines, which used the likelihood ratio test comparing the model with the linear term to the model with the linear and the cubic spline terms.[18] Results are presented as either adjusted % change in antral follicle count per 2 $\mu g/m^3$ increase in estimated $PM_{2.5}$ exposure (the interquartile range) or population marginal means. We assessed confounding based on biological relevance and descriptive statistics from our study population. Final models were adjusted for age, BMI, smoking status, year of antral follicle count (as a quadratic function), and season of count. We tested effect modification of the relationship between estimated average $PM_{2.5}$ exposure and AFC by age, BMI, smoking status, infertility diagnosis, and menstrual cycle characteristics, all well-known predictors of ovarian reserve, by adding a cross-product term to the final multivariable model.

Results

The 632 women had a mean (standard deviation) age of 35.3 (4.2) years and BMI of 24.4 (4.7) kg/m^2. The majority of women were never smokers (73%) and of Caucasian race (84%) with a college degree or higher (93%). The most common infertility diagnosis at enrollment was unexplained (41%). Women in our cohort resided in Massachusetts (96%), New Hampshire (2%), and Rhode Island (1%), as well as Maine and a few states outside of New England (<1%). The median antral follicle count in our study was 12 (range=1 to 30) (eFigure 2). During the study period (2005–2015), the average estimated $PM_{2.5}$ concentration in our population was 9.0 $\mu g/m^3$ (range=5.4 to 16.4 $\mu g/m^3$), which was similar to the average $PM_{2.5}$ concentration across the US (mean=10.2 $\mu g/m^3$) (eFigure 2).[19] Our $PM_{2.5}$ concentrations also tended to decrease over time, mirroring national trends.[19] Women in the highest quartile of estimated exposure to $PM_{2.5}$ were, on average, heavier and their antral follicle counts tended to be measured during the earlier years of the study and during the summer months compared to women in the lowest quartile (Table 1). All other characteristics were similar.

A 2 μg/m^3 increase in estimated average residential exposure to $PM_{2.5}$ in the 3 months prior to the antral follicle count was associated with a −7.2% (95% CI −10.4%, −3.8%) lower count adjusting for age, BMI, smoking status, and year and season of count (Table 2). This translated into approximately 1.1 fewer antral follicles for every 2 μg/m^3 increase in estimated average exposure to $PM_{2.5}$ (Figure. 1). There was no evidence of a departure from linearity. For comparison, a 2-year increase in age was associated with a −8.0% (95% CI −8.9%, −7.0%) lower antral follicle count. In contrast, a 2 μg/m^3 increase in estimated average residential exposure to $PM_{2.5}$ in the 3 months after antral follicle count was associated with an imprecisely measured −1.4% (95% CI −5.0%, 2.2%) lower count after multivariable adjustment.

The association between estimated $PM_{2.5}$ exposure and antral follicle count was similar across age (<35 vs. ≥35 yrs), BMI (<25 vs. ≥25 kg/m^2), and smoking status (never vs. ever) groups; however, the estimated effect of $PM_{2.5}$ exposure on antral follicle count was stronger among women whose primary infertility diagnosis was attributable to a female cause (% change= −16.3% 95% CI −21.5, −10.7%) compared to women with an unexplained or male factor diagnosis (% change= −2.8% 95% CI −6.9, 1.6%) (p-for-interaction=<0.001) (Table 3). Moreover, this effect was consistently negative across all diagnostic categories of female factor infertility (e.g. diminished ovarian reserve, endometriosis, ovulation disorders, tubal, and uterine). The association between estimated $PM_{2.5}$ exposure and antral follicle count was also more pronounced among women with non-regular menstrual cycles (p-for-interaction=<0.001) and those with short (<24 days) or long (>38 days) cycles (p-for-interaction=0.01) compared to women with regular and normal length menstrual cycles, respectively. While the association between estimated $PM_{2.5}$ and antral follicle count was slightly stronger between years 2005–2009 (% change= −7.6% 95% CI −12.7%, −2.4%) versus 2010–2015 (% change= −5.0% 95% CI −9.8%, 0.1%); the difference was imprecise. Results for the main analysis were also consistent after excluding women who resided outside of Massachusetts (% change= −6.8% 95% CI −10.2, −3.3%).

Discussion

In our prospective study of women seeking infertility treatment, we found that higher residential exposure to $PM_{2.5}$ was inversely associated with antral follicle count, a well-accepted marker of ovarian reserve. Moreover, the magnitude of this association was approximately equivalent to a 2-year increase in female age. Our results also suggest that the effects of $PM_{2.5}$ on antral follicle count may be more pronounced among women with a female factor infertility diagnosis and abnormal menstrual cycles, whose counts are generally lower than those of women presenting with other diagnoses or regular menstrual cycles. To our knowledge, this is the first study in humans to investigate a link between air pollution exposure and a biomarker of ovarian aging.

In the laboratory setting, three previous studies have examined the association between air pollution exposure and ovarian reserve in mice. In the first study, mice exposed to nonfiltered ambient air sampled close to a highly trafficked street (average $PM_{2.5}$ of 27.5 μg/m^3 per day) prior to and during pregnancy had reduced numbers of antral follicles compared to mice who only received filtered air.[13] In the second study, there was a reduction

in the proportional area occupied by primordial follicles in mice exposed to diesel exhaust (average $PM_{2.5}$ of 21.5 μg/m^3 per day) during pregnancy, postnatally, or both periods compared to mice exposed to only clean air.[12] In the third study, mice treated with a $PM_{2.5}$ suspension (10 mg/kg), every 2 days, for 22 days had serum anti-Müllerian hormone levels that were decreased by more than half compared to the control group.[11] Furthermore, IL-6 and TNF-α concentrations and the number of apoptotic cells were increased in ovarian tissue and ovarian histologic structures showed evidence of hemorrhage and vascular congestion in mice exposed to $PM_{2.5}$ compared to the control group.[11] Taken together with our findings, these data suggest that exposure to $PM_{2.5}$ throughout adult life may enhance follicular atresia through effects on ovarian inflammation, oxidative stress, and apoptosis, even at exposure levels within the World Health Organization guidelines (e.g. <25 μg/m^3 24-hour mean).

Limitations of our study are worth noting. Due to the sole inclusion of women undergoing infertility treatment, it may not be possible to generalize our findings to all women of reproductive age. However, previous work has shown that infertile women <40 years have similar antral follicle counts compared with women of the same age with no history of infertility.[20] We also used residence-based $PM_{2.5}$ exposure as a proxy for personal exposure, potentially leading to exposure misclassification particularly due to lack of information on the women's work addresses or their time–activity patterns. However, the spatio-temporal models we used are validated and the use of outdoor ambient exposures can be valuable because regulation typically focuses on these concentrations. We also lacked information on other spatial variables such as noise or light pollution, which tend to correlate with $PM_{2.5}$ exposure and may still confound our association between $PM_{2.5}$ and antral follicle counts. Strengths of our study include its prospective design, large sample size, gold-standard assessment of ovarian reserve,[14] and our comprehensive adjustment for other reproductive and lifestyle factors that enhanced our ability to adjust for confounding. The null results we observed in our sensitivity analysis using the average estimated $PM_{2.5}$ concentrations in the 3 months after antral follicle assessment (our negative control window) also further strengthen our argument for a causal association between $PM_{2.5}$ in the 3 months prior to antral follicle count and assessment of ovarian reserve.

In conclusion, our study's findings are consistent with the hypothesis that exposure to relatively low concentrations of $PM_{2.5}$ may decrease human fertility by accelerating ovarian aging. Moreover, this association may be particularly pronounced among women with an existing female-specific cause of infertility and women with abnormal menstrual cycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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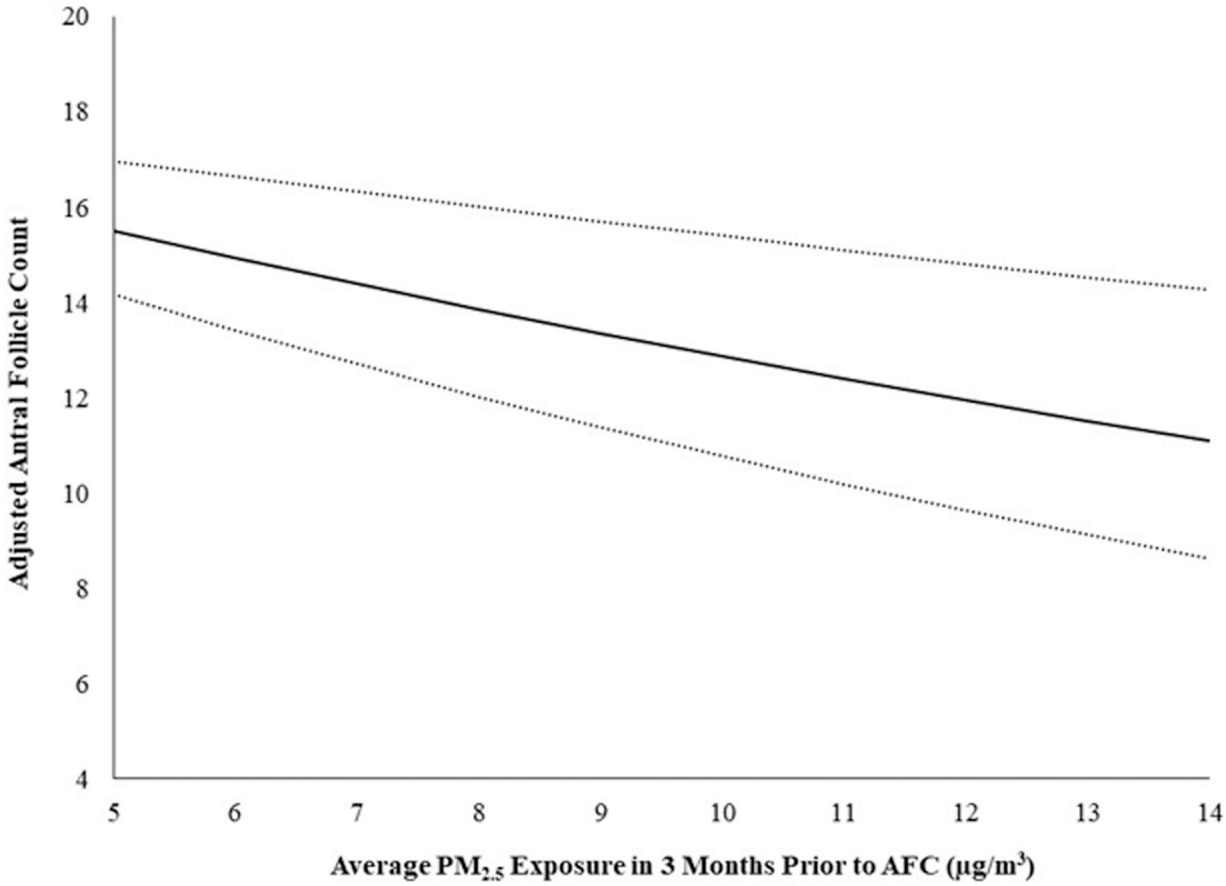

Figure. 1. Association between ambient exposure to particulate matter <2.5 µm in diameter ($PM_{2.5}$) and antral follicle counts (AFC) among 632 women in the EARTH Study.

The solid line shows the predicted mean antral follicle counts for the average woman in our cohort (mean age 35 years, BMI of 23.3 kg/m^2, never smoker, and AFC scan performed in 2010 during Oct to Dec) from the 1^{st} to 99^{th} percentile of $PM_{2.5}$ exposure levels. The dotted lines are the 95% confidence intervals.

Table 1.

Baseline demographic and reproductive characteristics by quartiles of ambient exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$) among 632 women in the EARTH Study.

	$PM_{2.5}$ Exposure in the 3 Months Prior to AFC			
Quartile (Range, μg/m^3)	**Q1 (5.4–7.6)**	**Q2 (7.7–8.6)**	**Q3 (8.7–9.9)**	**Q4 (10.0–16.4)**
Number of Women	**158**	**158**	**158**	**158**
Demographic characteristics[b]				
Age (years), mean (SD)	35.0 (4.4)	35.1 (4.1)	35.5 (4.3)	35.4 (4.3)
Body Mass Index (kg/m^2), mean (SD)	23.9 (4.6)	24.0 (4.3)	25.2 (5.0)	24.7 (4.8)
Total physical activity (hr/week), mean (SD)	8.0 (11.2)	6.9 (9.7)	5.8 (7.0)	6.0 (6.8)
Race/Ethnic group, n (%)				
White/Caucasian	130 (82.3)	134 (84.8)	131 (82.9)	133 (84.2)
Black	6 (3.8)	3 (1.9)	8 (5.1)	2 (1.3)
Asian	13 (8.2)	15 (9.5)	13 (8.2)	14 (8.9)
Other	9 (5.7)	6 (3.8)	6 (3.8)	9 (5.7)
Smoking status, n (%)				
Never smoked	112 (70.9)	115 (72.8)	117 (74.1)	118 (74.7)
Ever smoked	46 (29.1)	43 (27.2)	41 (26.0)	40 (25.3)
Education, n (%)				
< College	11 (7.0)	9 (5.7)	12 (7.6)	14 (8.9)
College graduate	73 (46.2)	72 (45.6)	64 (40.5)	59 (37.3)
Graduate degree	74 (46.8)	77 (48.7)	82 (51.9)	85 (53.8)
Reproductive characteristics				
Usual menstrual cycle length (days), mean (SD)	30.5 (9.3)	30.9 (12.8)	31.6 (13.7)	30.7 (13.7)
Year of AFC, mean (SD)	2012.6 (2.3)	2011.1 (2.6)	2010.0 (2.3)	2008.1 (1.9)
Regular menstrual cycles, n (%)	135 (85.4)	135 (85.4)	144 (91.1)	144 (91.1)
History of being pregnant, n (%)	74 (46.8)	75 (47.5)	67 (42.4)	69 (43.7)
Previous infertility exam, n (%)	132 (83.5)	130 (82.3)	121 (76.6)	128 (81.0)
Previous infertility treatment, n (%)	80 (50.6)	86 (54.4)	72 (45.6)	82 (51.9)
Initial infertility diagnosis[a], n (%)				
Male factor	32 (20.3)	44 (27.9)	43 (27.2)	44 (27.9)
Female factor	53 (33.5)	46 (29.1)	60 (38.0)	50 (31.7)
DOR	19 (12.0)	19 (12.0)	21 (13.3)	15 (9.5)
Endometriosis	5 (3.2)	9 (5.7)	10 (6.3)	11 (7.0)
Ovulation Disorders	18 (11.4)	9 (5.7)	16 (10.1)	14 (8.9)
Tubal	8 (5.1)	6 (3.8)	11 (7.0)	9 (5.7)
Uterine	3 (1.9)	3 (1.9)	2 (1.3)	1 (0.6)
Unexplained	73 (46.2)	66 (41.8)	54 (34.2)	64 (40.5)
Season of AFC, n (%)				
Jan-Mar	22 (13.9)	55 (34.8)	46 (29.1)	51 (32.3)
Apr-Jun	54 (34.2)	47 (29.8)	30 (19.0)	19 (12.0)

	$PM_{2.5}$ Exposure in the 3 Months Prior to AFC			
Quartile (Range, μg/m^3)	**Q1 (5.4–7.6)**	**Q2 (7.7–8.6)**	**Q3 (8.7–9.9)**	**Q4 (10.0–16.4)**
Number of Women	**158**	**158**	**158**	**158**
Jul-Sept	15 (9.5)	19 (12.0)	28 (17.7)	63 (39.9)
Oct-Dec	67 (42.4)	37 (23.4)	54 (34.2)	25 (15.8)

Abbreviations: AFC, antral follicle count; DOR, diminished ovarian reserve;

[a]Numbers may not add up to the total due to missing values (i.e. 3 women missing infertility diagnosis).

Table 2.

Association between ambient exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$) and antral follicle counts (AFC) among 632 women in the EARTH Study.

	Unadjusted % Change in AFC	Adjusted % Change in AFC[a]
3 Months Prior to AFC		
Per 2 μg/m^3 increase in $PM_{2.5}$	−7.2 (−9.4, −5.0)	−7.2 (−10.4, −3.8)
Quartiles of $PM_{2.5}$		
Q1 (5.4–7.6 μg/m^3)	REF	REF
Q2 (7.7–8.6 μg/m^3)	−4.0 (−9.5, 1.8)	−2.2 (−8.1, 4.2)
Q3 (8.7–9.9 μg/m^3)	−8.8 (−14.1, −3.2)	−5.5 (−11.8, 1.1)
Q4 (10.0–16.4 μg/m^3)	−13.6 (−18.7, −8.2)	−9.0 (−16.3, −1.1)
3 Months After the AFC[b]		
Per 2 μg/m^3 increase in $PM_{2.5}$	−4.8 (−7.1, −2.4)	−1.4 (−5.0, 2.2)
Quartiles of $PM_{2.5}$		
Q1 (3.9–7.6 μg/m^3)	REF	REF
Q2 (7.7–8.5 μg/m^3)	−9.2 (−14.6, −3.5)	−5.5 (−11.4, 0.9)
Q3 (8.6–9.9 μg/m^3)	−4.6 (−10.2, 1.3)	−0.7 (−7.3, 6.3)
Q4 (10.0–16.8 μg/m^3)	−12.3 (−17.5, −6.7)	−4.4 (−12.2, 4.0)
Per 2 year increase in age	−8.1 (−9.1, −7.2)	−8.0 (−8.9, −7.0)

We obtained effect estimates using Poisson regression.

[a] Adjusted models account for age (continuous), BMI (continuous), smoking status (ever, never), year of AFC (quadratic), season of AFC (Jan-Mar, Apr-Jun, Jul-Sept, Oct-Dec).

[b] 615 women were included in this analysis (17 women who had their AFC performed in late 2015 were excluded because they were missing more than 7 days of PM data).

Table 3.

Effect modification of the association between ambient exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$) and antral follicle counts (AFC) among 632 women in the EARTH Study.

	n	Adjusted % Change in AFC per 2 μg/m^3 increase in $PM_{2.5}$ [a]
Age		
<35 years	330	−7.5 (−11.8, −3.0)
≥35 years	302	−6.8 (−11.9, −1.4)
P for interaction [b]		0.79
BMI		
<25 kg/m^2	413	−8.7 (−12.6, −4.7)
≥25 kg/m^2	219	−4.1 (−10.1, 2.3)
P for interaction		0.35
Smoking Status		
Never smoker	462	−7.8 (−11.5, −3.9)
Ever smoker	170	−8.1 (−14.8, −0.9)
P for interaction		0.33
Infertility Diagnosis		
Female	209	−16.3 (−21.5, −10.7)
Male & Unexplained	423	−2.8 (−6.9, 1.6)
P for interaction		<0.001
Year of AFC		
2005–2009	263	−7.6 (−12.7, −2.4)
2010–2015	369	−5.0 (−9.8, 0.1)
P for interaction		0.06
Regular Menstrual Cycles		
Yes	558	−3.0 (−6.8, 0.9)
No	74	−19.0 (−26.3, −10.9)
P for interaction		<0.001
Menstrual Cycle Length		
24–38 days	571	−5.0 (−8.5, −1.2)
<24 or >38 days	61	−17.8 (−26.8, −7.7)
P for interaction		0.01

[a] Effect estimates were obtained using Poisson regression adjusted for age (continuous), BMI (continuous), smoking status (ever, never), year of AFC (quadratic), season of AFC (Jan-Mar, Apr-Jun, Jul-Sept, Oct-Dec).

[b] P for interaction was calculated by adding a cross product term to the final multivariable model.