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Environmental phthalate exposure and preterm birth

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Abstract

IMPORTANCE—Preterm birth is a leading cause of neonatal mortality with a variety of contributing causes and risk factors. Environmental exposures represent a group of understudied but potentially important factors. Phthalate diesters are used extensively in a variety of consumer products worldwide. Consequently, exposure in pregnant women is highly prevalent

OBJECTIVE—To assess the relationship between phthalate exposure during pregnancy and preterm birth.

DESIGN—Nested case-control study.

SETTING—Brigham and Women's Hospital, Boston, MA, USA.

PARTICIPANTS—Women were recruited for a prospective observational cohort study from 2006–2008. Each provided demographic data, biological samples, and information about birth outcomes. Within this group we selected 130 cases of preterm birth and 352 randomly assigned controls, and analyzed urine samples from up to three time points during pregnancy for levels of phthalate metabolites.

MAIN OUTCOME MEASURES—We examined associations between average levels of phthalate exposure during pregnancy and preterm birth, defined as <37 weeks completed gestation, as well as spontaneous preterm birth, defined as preterm preceded by spontaneous preterm labor or preterm premature rupture of the membranes (N=57).

RESULTS—Geometric means of the di-2-ethylhexyl phthalate (DEHP) metabolites mono-(2-ethyl)-hexyl phthalate (MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), as well as mono-*n*-butyl phthalate (MBP) were significantly higher in cases compared to controls. In

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CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

adjusted models, MEHP, MECPP, and DEHP metabolites were associated with significantly increased odds of preterm birth. When spontaneous preterm births were examined alone, MEHP, mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), MECPP, DEHP, MBP, and mono-(3-carboxypropyl) phthalate (MCP) metabolite levels were all associated with significantly elevated odds of prematurity.

CONCLUSIONS AND RELEVANCE—Women exposed to phthalates during pregnancy have significantly increased odds of delivering preterm. Steps should be taken to decrease maternal exposure to phthalates during pregnancy.

INTRODUCTION

Prematurity is a leading cause of neonatal mortality and can lead to an array of adverse health effects in the lives of those who survive. The contribution of environmental exposures to preterm birth is understudied; however, identification of potential contributing factors offers significant hope for combating preterm birth for several reasons: (1) Pregnant women are unintentionally exposed to many chemicals throughout gestation, some of which have demonstrated reproductive toxicities;¹ (2) Increased exposure to some chemicals over past decades correlates strongly with increased rates of preterm birth, which may be the result of various confounders but may also indicate a real association; and (3) Exposure to environmental contaminants may be largely modifiable, opportune for interventions at the individual, clinical and population levels.

Phthalates are a class of chemicals used in innumerable products worldwide, and exposure in humans and more specifically pregnant women is ubiquitous in many countries.^{2–5} Di-(2-ethylhexyl) phthalate (DEHP) exposure occurs primarily from the consumption of contaminated food and water, while exposure to other phthalates, including benzylbutyl phthalate (BzBP), dibutyl phthalate (DBP), and diethyl phthalate (DEP), occurs commonly through contact with personal care products, such as lotions, perfumes, and deodorants. Exposure in women has been linked to disrupted thyroid hormone levels, increased systemic levels of oxidative stress and inflammation, and adverse health endpoints such as endometriosis and breast cancer.^{6–9} Previous epidemiologic studies of the relationship between phthalate exposure and gestation length or preterm birth have been limited by sample size and exposure assessment methods, and results have been suggestive but not fully conclusive.^{10–14} The present study utilized a powerful nested case-control design to assess the relationship between gestational phthalate exposure and preterm birth.

Additionally, we took advantage of the large number of cases in our study to investigate the link between phthalate exposure and spontaneous preterm birth. Delineating preterm births by obstetric presentation may help to elucidate specific mechanistic pathways.¹⁵ Previously, McElrath and colleagues hypothesized that preterm births resulting from spontaneous preterm labor or preterm premature rupture of the membranes (pPROM) are likely to be the consequence of intrauterine inflammation, whereas medically indicated preterm births, typically subsequent to preeclampsia or intrauterine growth restriction, may result from aberrant placentation.¹⁵ Toxicological studies suggest a role for phthalates in the inflammatory cascade leading up to preterm parturition. Hence, we additionally examined in

this study the effects of phthalates on preterm birth in mothers who experienced spontaneous preterm birth.

METHODS

From 2006–2008 women from the Boston area who planned to deliver at the Brigham and Women's Hospital were recruited for participation in a large prospective cohort study designed to identify predictors of preeclampsia. In the first trimester (median ten weeks gestation) subjects completed demographic questionnaires providing information on Race/Ethnicity, tobacco and alcohol use, etc., and supplied urine and blood samples for biomarker analysis. First trimester ultrasound was used to validate and establish gestational age. During the three subsequent study visits, additional biological samples were collected in tandem with clinically relevant pregnancy characteristics. Delivery complications and neonate anthropomorphic measurements were recorded at birth. All specimens were stored at -80°C . In 2011 we selected from this population the 130 mothers who delivered prior to 37 weeks gestation and 352 randomly selected mothers who delivered at or after 37 weeks. Multiple births were excluded from our study. Within the group of mothers who delivered preterm, we also examined a subset who delivered with clinical presentation by either spontaneous preterm labor and/or PPROM ($N=57$). These were considered spontaneous preterm births for our analysis.

Urinary phthalate metabolites

Urine samples were collected from up to four visits per subject during pregnancy. For visit 1 (median=9.71 weeks gestation), 479 samples were available ($N=129$ for cases, $N=350$ for controls). For visit 2 (median=17.9 weeks gestation), 422 samples were available ($N=118$ for cases, $N=304$ for controls). For visit 3 (median=26.0 weeks gestation), 412 samples were available ($N=111$ for cases, $N=301$ for controls). For visit 4 (median=35.1 weeks gestation), 380 samples were available ($N=66$ for cases, $N=314$ for controls). By the time of visit 4, many cases had already delivered, causing a disproportionately small number of samples for cases at that visit. Hence, levels measured in visit 4 samples were excluded for this analysis.

Nine phthalate metabolites were measured in each urine sample by NSF International (Ann Arbor, MI, USA) using the CDC method described elsewhere.¹⁶ Briefly, this entails enzymatic deconjugation of glucuronidated metabolites, solid-phase extraction, separation via high performance liquid chromatography, and detection by tandem mass spectrometry. Levels below the limit of detection (LOD) were kept as is if a numerical value was reported and otherwise were replaced with the LOD divided by the square root of two.¹⁷ Because concentration can vary with urine dilution, levels were corrected for urinary specific gravity (SG) using the following formula: $P_c = P [(1.015 - 1)] / [SG - 1]$, where P_c represents the specific gravity-corrected phthalate concentration (micrograms per liter), P represents the measured concentration in urine, 1.015 is the median SG of all samples measured, and SG represents the specific gravity of the individual sample.¹¹ Both unadjusted and adjusted metabolite levels were log-normally distributed and were ln-transformed for statistical analysis.

Phthalate metabolite levels may fluctuate over time as their half-lives are short and sources of exposure are variable. Hence, we used the geometric mean of levels from visit 1–3 to estimate each woman's average exposure throughout pregnancy. In addition to examining associations with individual phthalate metabolite averages, we also examined the average of molar sums of DEHP metabolites (DEHP; nanomoles per milliliter) for each woman across pregnancy.

Statistical analysis

Population characteristics were tabulated for demographic and pregnancy-related variables of interest, including maternal age, Race/Ethnicity, education, health insurance provider, body mass index (BMI) measured at the first study visit, smoking status, alcohol use, parity, use of assisted reproductive technology (ART), and gender of infant. Each of these was considered a potential covariate for multivariate logistic regression models.

Urinary phthalate metabolite distributions were examined for all subjects combined and by case status. Differences in phthalate concentrations in preterm cases compared to controls were investigated with T-tests of ln-transformed and SG-corrected phthalate metabolite means. Next, using multivariate logistic regression we examined odds of preterm birth in association with phthalate metabolite concentrations in crude models adjusting for urinary specific gravity only and in full models, adjusting for *a priori* covariates, including maternal age, race/ethnicity, and education level (an indicator of socioeconomic status). Additional covariates were added to models in a forward stepwise procedure and were finally included if they altered the association between phthalate metabolite and preterm birth by greater than 10%. Similar regression models were created examining the subset of preterm births with clinical presentation of preterm labor or pPROM to explore relationships within spontaneous preterm births.

To examine effects of exposure at higher levels, and the potential for non-linear relationships, we divided average phthalate metabolite concentrations into quartiles using non-standardized values from the entire population. Adjusted odds ratios were calculated for each of the top three quartiles in comparison to the lowest quartile of exposure in models adjusting for the same sets of covariates used in models with continuous exposure. Tests for trend were conducted by modeling quartiles as a single ordinal variable, again using the same covariates. Quartile analysis and tests for trend were performed for the subset of spontaneous preterm births as well. All analysis was performed using R version 2.13.1.

RESULTS

Distributions of categorical covariates are presented in Table 1 for the population overall and by preterm status. Overall the women enrolled in this study were predominantly white, well-educated, non-smokers. Few consumed alcohol during pregnancy and nearly half were nulliparous. Approximately 10% of the population utilized ART and 44% of infants were male, and proportions of these variables were equal among cases and controls. Consistent with previous US studies, elevated levels of mono-benzyl phthalate (MBzP), mono-*n*-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), and mono-ethyl phthalate (MEP) were observed in African American compared to Caucasian mothers (data not shown).

Each phthalate metabolite was detected in at least 95% of urine samples. As expected, distributions were log-normally distributed and levels were ln-transformed for statistical analysis. Spearman correlation coefficients between average phthalate levels in the overall population were modest to strong (eTable 1). Geometric means and 25th and 75th percentiles of SG-adjusted exposures overall and in cases and controls separately are presented in Table 2. Significantly ($p<0.05$) elevated levels of mono-(2-ethyl)-hexyl phthalate (MEHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), DEHP and MBP were observed in preterm cases compared to controls. Suggestively ($p<0.10$) elevated levels of mono-(3-carboxypropyl) phthalate (MCP) were also noted.

Stepwise addition to incorporate covariates into logistic regression models demonstrated two sets of covariates. Full models for DEHP metabolites included SG, age, Race/Ethnicity, and education level as covariates. For other metabolites insurance provider was also included in full models, as addition of this variable altered effect estimates by greater than 10%. Odds ratios and 95% confidence intervals are presented in Table 3. We observed significantly elevated odds of preterm birth with ln-unit increases in MEHP, MECPP, and DEHP, and suggestively elevated odds for MBP. Interestingly, odds ratios for all associations were greater in magnitude for the subset of spontaneous preterm births and were statistically significant despite the much smaller sample size. Results were similar in crude models, adjusting only for urinary specific gravity (eTable 2).

Assessment of urinary phthalate metabolite quartiles showed dose-related relationships with odds of preterm birth. Significant positive trends were observed for MEHP, MECPP, DEHP, and MBP (Figure 1). When quartiles of exposure were examined within spontaneous preterm births alone, trends became stronger for all phthalate metabolites, and odds ratios associated with the top quartile of exposure were markedly increased (Figure 2).

DISCUSSION

Our results demonstrate a robust increase in the odds of preterm birth in association with urinary phthalate metabolite concentrations during pregnancy. Specifically, maternal levels of DEHP metabolites, including MEHP (the putative toxic metabolite of DEHP), MECPP (the most stable marker of DEHP exposure), and summed DEHP metabolites showed the strongest and most clearly dose-dependent relationships with odds of birth before 37 weeks gestation. Additional suggestive relationships were observed for MBP. When spontaneous preterm births, those with clinical presentation of spontaneous preterm labor or pPROM, were examined alone, odds ratios became greater for all phthalate metabolites, and significant relationships emerged for mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), MBzP, MBP, and MCP.

Associations observed in the present study are consistent with results from previous studies of preterm birth or gestation length. Early prospective cohort studies found that exposure to DEHP metabolites was associated with decreased gestational age at delivery.^{13,18} Latini and colleagues reported that infants who had detectable levels of MEHP in cord blood had significantly shorter gestational length compared to those who did not ($N=84$, preterm=11).¹⁸ In another study where metabolites were measured during the third trimester

maternal urine, gestational age similarly decreased with increasing DEHP metabolite exposure (N=311, preterm=10).¹³ More recently, a small nested case-control study in Mexico City revealed significantly increased odds of preterm birth in association with third trimester levels of MECPP, MBP, and MCP in models adjusted for urinary specific gravity and maternal factors (N=60, preterm=30).¹¹

Other authors, however, have reported contrary or null results. Adibi and colleagues found that odds of preterm birth were decreased with increasing exposure to the DEHP metabolites MEHP, MEOHP, and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) measured in maternal urine during the third trimester (N=283, preterm=14).¹⁰ Likewise, a 2008 study noted a positive association between third trimester low-molecular-weight phthalate (e.g., MEP) exposure and gestational age at delivery (N=404).¹⁴ Finally, in a study of women in Tokyo, Japan, Suzuki and colleagues were unable to detect an association between gestational length and any of nine urinary phthalate metabolites taken any time between the 9th and 40th weeks of gestation (N=149, preterm=2).¹²

Limitations in previous studies of phthalate exposure and prematurity potentially account for the differences in these findings, and highlight the advantages in our analysis. First, exposure assessment in prior studies utilized a single spot urine phthalate metabolite concentration from the third trimester. This is problematic since a single measurement, particularly late in pregnancy, is only loosely correlated with long-term exposure.¹⁹ Second, prior work used self-recalled and reported dates of last menstrual period to calculate gestational age at delivery. Finally, sample size, either overall or in proportion of preterm births, lacked power to detect real associations. The present study is the first to use multiple urine samples collected longitudinally across gestation in order to more accurately integrate overall exposure. Additionally, the present work utilizes clinically and first trimester ultrasound validated gestational dates. These aspects greatly reduced the potential for exposure and outcome misclassification. This power was heightened by the case-control design and large sample size. Lastly, the sample size in the present study afforded more than adequate power.

We further leveraged the parent cohort study's strengths by examining the relationship between gestational phthalate exposure and spontaneous preterm birth. Relationships within this subset have not been previously explored, likely because of already limited numbers of preterm births in earlier studies. However, the results from this analysis both strengthened the overall findings and highlighted a potential mechanism for the connection between phthalate exposure and prematurity. As mentioned previously, McElrath and colleagues suggested that spontaneous preterm birth is associated with intrauterine inflammation. The strong link observed between phthalate exposure and spontaneous preterm births found in the present study suggests phthalate exposure is associated with increased intrauterine inflammation. This is consistent with both *in vitro* data that have demonstrated the pro-inflammatory activity of phthalates, and limited cross-sectional human studies, which have shown that phthalate exposure is associated with increased systemic markers of inflammation.^{7,20}

Reducing rates of preterm birth is unlikely to occur by identification of one or two obvious causes; rather, detailed investigation of many component contributors is necessary. A recent study predicted that current interventions to prevent preterm birth will decrease rates by only 5% or less by 2015, making identification of preventable exposures crucial.²¹ In our study women with average gestational MEHP exposure in the top quartile had 4 times the odds of preterm birth compared to women in the bottom quartile. As over two thirds of preterm births every year are spontaneous, the subset of the population susceptible to these effects may be quite large.²²

Also, importantly, phthalate exposure may be preventable with behavioral modification. A recent dietary intervention study demonstrated that when subjects altered their diets to consume only “fresh foods” that were not packaged in cans or plastic, urinary levels of DEHP metabolites decreased markedly.²³ However, another recent study with a similar dietary intervention did not observe the same effects.²⁴ Low-molecular weight phthalates, including DBP and DEP, are used frequently as solvents in cosmetic products such as fragrances, hair spray, nail polish, deodorants, and body lotions. Women who refrain from using such products may have lower levels of exposure.^{25–27}

While we cannot rule out the role of unmeasured confounders in our study (e.g. dietary patterns that may be associated with both phthalate exposure and preterm birth), we did examine the potential for confounding among known predictors of preterm birth in our analysis. Another potential limitation in our study may be the measurement of phthalate metabolites in excreted urine. Although this is the best method to measure cumulative exposure to phthalates to date, differences in individual metabolism and excretion patterns may affect urinary phthalate metabolite concentrations. However, these individual patterns would likely contribute non-differential measurement error which would shift measured associations toward the null.

Our results indicate a significant association between exposure to phthalates during pregnancy and preterm birth, which solidifies prior laboratory and epidemiologic evidence. Furthermore, as exposure to phthalates is widespread, and because the prevalence of preterm birth among women in our study cohort was similar to that in the general population, our results are generalizable to women in the US and elsewhere. These data provide strong support for taking action in the prevention or reduction of phthalate exposure during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank Kurtis Kneen, Scott Clipper, Gerry Pace, David Weller, and Jennifer Bell of NSF International in Ann Arbor, MI, USA for urine phthalate analysis, and Dr. Russ Hauser of Harvard School of Public Health for guidance on study design. Funding was provided by the National Institute of Environmental Health Sciences, National Institutes of Health (R01ES018872, P42ES017198, and P30ES017885).

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Figure 1.

Odds of preterm birth and 95% confidence levels by quartile of average phthalate metabolite level measured during pregnancy.

Figure 2.

Odds of spontaneous preterm birth and 95% confidence levels by quartile of average phthalate metabolite level measured during pregnancy.

Table 1Distribution of population characteristics by cases status: N (%) or median (25th, 75th percentiles).

Demographic characteristics		Overall (N=482)	Cases (N=130)	Controls (N=352)
Maternal age (years)		32.7 (29.0, 35.7)	32.8 (29.3, 35.8)	32.7 (28.7, 35.7)
Race/Ethnicity	Caucasian	282 (58.5)	75 (57.7)	207 (58.8)
	African-American	77 (16.0)	22 (16.9)	55 (15.6)
	Other	123 (25.5)	33 (25.4)	90 (25.6)
Education	High school	68 (14.1)	21 (16.2)	47 (13.4)
	Technical school	77 (16.0)	25 (19.2)	52 (14.8)
	Junior college or some college	139 (28.8)	38 (29.2)	101 (28.7)
	College graduate	187 (38.8)	45 (34.6)	142 (40.3)
	Missing	11 (2.30)	1 (0.80)	10 (2.80)
Health insurance	Private insurance/HMO/Self-pay	385 (79.9)	108 (83.1)	277 (78.7)
	Medicaid/SSI/MassHealth	85 (17.6)	20 (15.4)	65 (18.5)
	Missing	12 (2.50)	2 (1.50)	10 (2.80)
Body mass index (BMI)	Less than 25 kg/m ² (underweight to normal weight)	250 (51.9)	62 (47.7)	188 (53.4)
	25 to less than 30 kg/m ² (overweight)	126 (26.1)	32 (24.6)	94 (26.7)
	Greater than 30 kg/m ² (obese to morbidly obese)	102 (21.2)	36 (27.7)	66 (18.8)
	Missing	4 (0.80)	0 (0)	4 (1.10)
Tobacco use	Smoked during pregnancy	31 (6.40)	11 (8.50)	20 (5.7)
	No smoking during pregnancy	445 (92.3)	119 (91.5)	326 (92.6)
	Missing	6 (1.20)	0 (0)	6 (1.70)
Alcohol use	Alcohol use during pregnancy	20 (4.10)	1 (0.80)	19 (5.40)
	No alcohol use during pregnancy	452 (93.8)	126 (96.9)	326 (92.6)
	Missing	10 (2.10)	3 (2.30)	7 (2.00)
Parity	Nulliparous	215 (44.6)	55 (42.3)	160 (45.5)
	Non-nulliparous	267 (55.4)	75 (57.7)	192 (54.5)

Table 2

Average phthalate levels across gestation in overall population and in cases compared to controls.

Parent phthalate compound	Phthalate metabolite	Adjusted geometric mean (25 th , 75 th percentiles) (µg/L)		
		Overall (N=482)	Cases (N=130)	Controls (N=352)
Di-2-ethylhexyl phthalate (DEHP)	Mono-(2-ethyl)-hexyl phthalate (MEHP)	10.5 (5.51, 18.1)	12.3 (6.91, 23.7)	9.91 (5.17, 16.9) **
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	31.9 (17.2, 55.3)	32.3 (15.0, 56.6)	31.7 (17.5, 54.4)
	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	16.9 (9.33, 29.7)	18.3 (9.33, 35.5)	16.3 (9.43, 28.9)
	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	41.3 (20.6, 73.8)	52.1 (25.1, 93.4)	37.9 (19.3, 67.1) **
	Summed DEHP metabolites (DEHP)	36.5 (20.2, 63.2)	42.6 (21.3, 80.2)	34.5 (19.7, 67.1) **
Benzyl butyl phthalate (BzBP)	Mono-benzyl phthalate (MBzP)	6.47 (3.25, 11.6)	6.85 (3.21, 13.4)	6.34 (3.27, 10.9)
Dibutyl phthalate (DBP)	Mono- <i>n</i> -butyl phthalate (MBP)	16.7 (10.5, 23.2)	18.9 (10.8, 26.0)	15.9 (10.2, 22.5) **
	Mono-isobutyl phthalate (MiBP)	6.75 (4.48, 10.3)	6.85 (4.63, 10.5)	6.71 (4.42, 10.27)
Diethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)	134 (55.7, 276)	150 (64.3, 293)	129 (55.5, 273)
Di- <i>n</i> -octyl phthalate (DOP) and others	Mono-(3-carboxypropyl) phthalate (MCPP)	2.02 (1.09, 3.09)	2.27 (1.25, 3.36)	1.93 (1.07, 2.95) *

Summed DEHP levels in nanomoles/milliliter.

* Suggestively increased levels of phthalate metabolites in cases compared to controls (p<0.10).

** Statistically significant (p<0.05) increased levels of phthalate metabolites in cases compared to controls.

Table 3

Odds ratios from fully adjusted logistic models of preterm birth (<37 weeks) and spontaneous preterm birth.

Phthalate metabolite	Preterm birth		Spontaneous preterm birth	
	Odds ratio (95% confidence interval)	p value	Odds ratio (95% confidence interval)	p value
MEHP	1.34 (1.07, 1.68)**	0.012	1.65 (1.20, 2.26)**	0.002
MEHHP	1.03 (0.82, 1.30)	0.784	1.27 (0.91, 1.78)	0.154
MEOHP	1.16 (0.91, 1.47)	0.235	1.47 (1.04, 2.08)**	0.030
MECPP	1.40 (1.13, 1.74)**	0.002	1.56 (1.15, 2.13)**	0.005
DEHP	1.33 (1.04, 1.70)**	0.021	1.63 (1.15, 2.31)**	0.006
MBzP	1.09 (0.86, 1.38)	0.492	1.41 (1.02, 1.95)**	0.037
MBP	1.27 (0.99, 1.63)*	0.063	1.49 (1.08, 2.06)**	0.014
MiBP	0.98 (0.72, 1.34)	0.906	1.52 (0.97, 2.38)*	0.066
MEP	1.11 (0.93, 1.32)	0.247	1.22 (0.96, 1.56)	0.101
MCPP	1.19 (0.95, 1.49)	0.127	1.36 (1.02, 1.81)**	0.038

Models for MEHP, MEHHP, MEOHP, MECPP, and DEHP adjusted for average specific gravity, maternal age at first visit, race/ethnicity, and education. Models for other metabolites additionally adjusted for insurance provider. Spontaneous preterm births limited to those with presentation of spontaneous preterm labor or pPROM.

* Suggestively increased OR of preterm birth in association with ln-unit increase in phthalate level ($p < 0.10$).

** Statistically significant ($p < 0.05$) increase.