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Exploring Associations Between Postural Balance and Levels of Urinary Organophosphorus Pesticide Metabolites

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Abstract

Objective—Apply a data-driven approach to explore associations between postural balance and pesticide exposure among Latino farmworkers and non-farmworkers.

Methods—Lasso-regularized, generalized linear models were used to examine associations between postural control measures in four experimental conditions (2 visual $\times$ 2 cognitive difficulty) and dialkylphosphate (DAP) urinary metabolite levels.

Results—Obtained models generally performed poorly at explaining postural control measures. However, when both visual and cognitive conditions were altered – the most challenging balance condition – models for some postural balance measures contained several DAP metabolites and had relatively better fits.

Conclusions—The current results were equivocal regarding associations between postural control measures and DAP metabolite concentrations. However, farmworker status appears to be an important variable in understanding this association. Future work should use a posturally- and cognitively-challenging test condition to reveal any potential associations.

Keywords

Occupational exposure; Pesticides; Postural balance; Farming

INTRODUCTION

Organophosphorus pesticides (OPs) are synthetic compounds that are widely used to control pests in agriculture. OPs are neurotoxicants, and exposures are associated with neurological

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problems that include decrements in cognitive/neurological function and neurobehavioral performance ^{1,2} as well as increased risks of respiratory and reproductive problems ^{3,4}. In addition, acute exposures can cause immediate toxicological symptoms such as dizziness, muscle ache, and nausea ^{5,6}. The potential health consequences of chronic (i.e., occupational) exposures at low doses, however, are poorly understood and an important topic of debate ⁷⁻⁹. Recently, Ross et al. ¹⁰ discussed neurotoxic exposures at work (e.g., in farming) and their potential long-term health effects, and highlighted a relative dearth and need for studies on such health effects.

OPs are non-bioaccumulative; most are metabolized to at least one of six possible dialkylphosphates (DAPs) urinary metabolites that are excreted in urine within 24–48 hours ¹¹. These DAP metabolites are: dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP). Though these metabolites are not pesticide specific ¹², they have been used as biomarkers of OP exposure in occupational and environmental studies ¹³, providing information on recent pesticide exposure (1–3 days) or possibly longer-term exposure (3 months) ¹⁴.

The functional ability of the neuromuscular and musculoskeletal systems may be collectively characterized by postural balance. A number of studies have demonstrated that postural balance performance is associated with diverse factors, including personal characteristics (e.g., age, gender) and pathological conditions (e.g., peripheral neuropathy, stroke) ^{15,16}. Specific to pesticide exposure, a few studies have indicated that pesticide-exposed groups (vs. control) exhibited altered postural control, based on measures derived from static posturography ¹⁷⁻²⁰. These studies mainly focused on identifying group-level differences in metabolite levels and/or postural balance performance, with some consideration of job duration or self-reported lifetime exposure levels. To our knowledge, however, no studies have explored potential associations between postural balance performance and OP metabolites (i.e., biomarkers), with the latter considered of importance as a more direct measure of pesticide exposure.

The current study examined potential associations between recent pesticide exposure and postural balance. Urinary DAP metabolite and postural balance data were obtained from two populations of Latino immigrant men (migrant farmworkers vs. non-farmworker urban residents) as part of a larger effort to address the health of Latino farmworkers in eastern North Carolina (NC). Using static posturography, postural balance was assessed under several conditions designed to highlight select aspects of the postural control system. We used a data-driven approach here (i.e., automatic variable selection) to explore associations between postural balance performance and OP metabolite concentration levels, while considering self-reported lifetime exposure levels. Given that the majority of research has identified adverse neurological outcomes from occupational OP exposures, we hypothesized that greater levels of urinary pesticide metabolites, indicative of higher recent pesticide exposure, would be associated with decrements in postural balance.

METHODS

Overview

Data were obtained from the Preventing Agricultural Chemical Exposure 4 (PACE4) project (see ref 21 for more details), a community-based participatory research collaboration between the NC Farmworkers Project (Benson, NC), El Buen Pastor Latino Community Services (Winston-Salem, NC), and Wake Forest School of Medicine (Winston-Salem, NC). Farmworkers were recruited from three agricultural counties in east-central NC (Harnett, Johnston, Sampson), and non-farmworkers were recruited from an urban area in central NC (Winston-Salem, Forsyth County). The study protocol was reviewed and approved by both the Wake Forest School of Medicine and the Virginia Tech IRBs, and all participants provided signed informed consent. PACE4 data collection spanned three years (2012–2014). The current study uses pesticide urinary metabolite and postural balance data obtained as part of the 2013 data collection.

Participants

Participants were aged 30 to 70 years and did not have a diagnosis of diabetes. All were males and self-identified as Latino or Hispanic. Participants were recruited with the assistance of the community partner organizations. For inclusion, farmworkers had to be employed currently in agriculture and have had worked in this sector for at least three consecutive years. Non-farmworkers could not have been employed for the past three years in jobs that expose workers to pesticides, including farm work, forestry, landscaping, grounds keeping, lawn maintenance, and pest control. Table 1 presents a summary of farmworker and non-farmworker participant characteristics.

Both postural balance and DAP metabolites data were obtained from a total of 77 farmworkers and 56 non-farmworkers. After being entered in the study cohort, each participant completed at least two data collection follow-ups in 2013. At each of the follow-ups, participants provided a spot urine sample; the volume of each urine sample was recorded, a 10-ml aliquot was prepared, and the aliquot was frozen at -80°C until it could be delivered to the laboratory for analysis. However, participants completed postural balance assessment tests in one of the follow-ups.

Urinary sample analysis

We measured six DAP metabolites in all urine samples: three dimethyl (DM) phosphate metabolites – DMP, DMTP, and DMDTP; and three diethyl (DE) phosphates – DEP, DETP, and DEDTP. Laboratory methods and quality control procedures are fully described in Arcury et al.²². Briefly, for each participant, a composite sample was prepared based upon overall volume such that the resulting composite sample would reflect the average measurement of individually tested samples across the data collection period. Each sample was extracted with acetonitrile and diethyl ether, and analyzed using gas chromatography mass-spectrometry in the single-ion monitoring mode. Analytes were quantified using isotope dilution calibration. Calibrants, blanks and quality control materials were analyzed consecutively with randomized participant samples to ensure quality measurements. Limits

of quantification (LOQs) were 0.3 µg/L for DMP, 0.2 µg/L for DMTP, 0.1 µg/L for DMDTP, 0.2 µg/L for DEP, 0.1 µg/L for DETP, and 0.1 µg/L for DEDTP.

The majority (~97%) of participants had DEDTP values below the LOQ²², so this metabolite was not considered further. To understand the overall DAP exposures, we imputed any metabolite values below the respective LOQ, using maximum likelihood estimates (MLE) obtained from 10 different bootstrap samples. This imputation was performed separately for farmworker and non-farmworker participants, and details on this procedure were reported in Arcury et al.²².

Postural balance analysis

To characterize balance ability, we derived a set of the measures of postural control from center-of-pressure (COP) time series obtained during trials of 60-s of quiet, upright stance on a force platform (AccuGait, AMTITM, Watertown, MA) in a quiet room. Detailed experimental procedures, data processing, and derived balance measures were described earlier²⁰. Participants completed two trials of quiet, upright stance under each of four experimental conditions (2 visual x 2 cognitive conditions). The visual conditions were eyes-closed (EC) and eyes-open (EO). The cognitive conditions were with and without a concurrent cognitive task – counting backward from a randomly selected three-digit number²³ in the preferred language. For each trial, the derived postural control measures included: mean COP velocity (MV) in the anteroposterior (AP) and mediolateral (ML) directions, 95% prediction ellipse area (PEA), and complexity index (CI) in the AP and ML directions using a multiscale entropy (MSE) algorithm²⁴. CI is obtained by integrating entropy values over predefined time scales, and the algorithm is fully described elsewhere²⁴. Note that postural control measures were fully reported elsewhere²⁰. Major results were that in the eyes-open condition without a concurrent cognitive task condition (i.e., baseline condition), both occupational groups exhibited comparable postural control performance in terms of MV_{AP}, MV_{ML}, and PEA, while sway complexity was significantly different between the occupational groups.

Statistical analysis

Differences in metabolite detection frequencies between farmworker and non-farmworker participants were compared using unpaired Fisher's exact tests. To explore potential associations between COP-based balance measures and DAP metabolites concentration levels, we used regression models in the following form:

$$y \sim \text{Farmworker status} + \text{Years of exposure} + \text{all DAP concentration level} + \text{urinary creatinine level} + \text{Body mass} + \text{Stature} + 1^{st} \text{ order interaction terms}.$$

where y was a specific postural control measure. We applied a lasso-regularized, generalized linear model to select variables. Note that the lasso approach is a shrinkage method that imposes constraints on regression coefficients to be zero, enabling automated variable selection^{25,26}, and is often used to handle high-dimensional data in other disciplines (e.g., bioinformatics, manufacturing). In these models, there were a large number of potential

predictors (including main and 1st order interaction terms), and thus the lasso approach was considered particularly relevant.

Two sets of models of the noted form were used. In the first set, y was a postural control measure obtained from the baseline condition (i.e., EO and without concurrent cognitive task). In the second set, y was a *normalized* postural control measure obtained in one of the conditions that including additional challenges (i.e., EC and/or concurrent cognitive task). Normalized measures were obtained as: [(measure – baseline condition value) / baseline condition value]. This second set was similar to Romberg's quotient ²⁷, and was employed here to explore whether exposure effects might be isolated to specific central nervous systems function such as vision or executive function after adjusting for baseline condition values. In all models, Farmworker status was included as a categorical variable (non-farmworker = 0 and farmworker = 1), and Years of exposure was included as self-reported years of occupational pesticide exposure. Body mass and Stature were in kg and meter, respectively. As suggested by Barr et al. ²⁸, individual urinary creatinine level (in $\mu\text{g/L}$) was included as a covariate, rather than adjusting DAP metabolite concentration levels to urinary creatinine levels. Models were first fit separately for each of the postural control measures from the baseline condition, and then fit separately for each of the five normalized measures in each of the remaining conditions.

We used the *EBglmnet* package ²⁹ for lasso implementation in R statistical software, and the tuning parameter for the lasso method was selected using 10-fold cross validation. This analysis was replicated with each of the 10 imputed metabolite datasets, and regression coefficients from the 10 imputed datasets were combined using the *mi* package ³⁰. As measures of model fits, the mean of r^2 , adjusted r^2 , and root mean square error (RMSE) were obtained.

RESULTS

While farmworkers reported a longer duration of occupational exposure (Table 1), and non-farmworkers were not employed in jobs that expose workers to pesticides, detection frequencies and concentration levels of urinary DAP metabolites were comparable between these two groups (Table 2). Though not statistically significant, DETP detection frequency was higher for farmworkers (41.6%) than non-farmworkers (25%).

Table 3 summarizes the associations between COP-based postural control measures and DAP metabolites concentration levels obtained using the lasso method. Detailed model fit outcomes are provided in online Supplemental Digital Content 1. Among the postural control measures at baseline condition, resulting models for sway complexity index had a relatively better fit (e.g., $r^2 = 0.21\text{--}0.22$) than was obtained for the remaining postural control measures ($r^2 = 0.00\text{--}0.10$). Only CI_{ML} had a positive association with a DAP metabolite, specifically DEP, with a corresponding coefficient = 0.013 (95% confidence interval: $-0.002, 0.029$). When visual information was removed and/or a cognitive task was present, resulting models for normalized postural control measures included some DAP metabolite concentration levels as variables, though the models performed poorly in general. Models for MV_{ML} and CI_{ML} from the most challenging condition (EC + concurrent

cognitive task condition), however, showed a relatively better fit (e.g., $r^2 = 0.14\text{--}0.16$) and the associated coefficients are shown in Figure 1.

DISCUSSION

This study explored potential associations between postural control measures and urinary DAP metabolite concentration levels, using an automatic variable selection method. Postural sway complexity in the ML direction (CI_{ML}), obtained under the baseline condition (EO and no concurrent cognitive task), was positively associated with farmworker status, anthropometry (Body mass $\times$ Stature), and DEP. Models derived from the variable selection method generally performed poorly, though, at explaining/predicting (normalized) postural control measures obtained from the experimental conditions involving visual information removal and/or a concurrent cognitive task. However, when both visual and cognitive conditions were altered – the most challenging condition – it was notable that the resulting models for MV_{ML} and CI_{ML} involved several DAP metabolites, and that model fits were superior to those for other postural control measures.

Baseline postural control measures appeared not to be associated with DAP metabolites, despite the one exception of a positive association between CI_{ML} and DEP. In this case, the coefficient was 0.013, and DEP concentration levels were on the order of 10 or less (Table 2). When fitting CI_{ML} with and without DEP, the r^2 and RMS difference between fitted CI_{ML} values were 0.91 and 0.22, respectively, suggesting that the contribution of DEP on CI_{ML} was rather small. While baseline postural elliptical sway area (i.e., PEA) was not sufficiently explained by DAP metabolite concentration levels here, Steenland et al.¹⁹ reported a significant positive association between the levels of a metabolite of Chlorpyrifos (3,5,6-trichloro-2-pyridinol; TCP) and the area of sway. This difference may be attributable to the monitoring of different metabolite levels (TCP earlier vs. DAP metabolites in the current study) as they have different biological half-lives and bioaccumulation levels and differences in postural control test procedures (i.e., 30 seconds with shoes earlier vs. 60 seconds without shoes here).

Some DAP metabolite concentration levels may, to some degree, explain/predict normalized postural control measures in the ML direction (specifically, normalized MV_{ML} and CI_{ML} , see Table 3 and Figure 1). This was evident only when these measures were obtained under the most challenging condition (i.e., eyes closed and with a concurrent cognitive task), and the resulting models for MV_{ML} and CI_{ML} included some DAP metabolites. Further, the coefficients of selected DAP metabolites (Figure 1) indicated that, under such challenging condition, farmworkers exhibited a decrease in the mean COP velocity and that sway complexity was associated positively with the DEP $\times$ Stature interaction. Though the fit of resulting models was rather weak ($r^2 = 0.14\text{--}0.16$), this is potentially interesting in that a lower value of mean COP velocity is often interpreted as indicative of better postural control^{15,31} and a higher value of sway complexity may suggest adaptive or efficient postural control^{32,33}.

Given these results, the question remains as to whether they suggest that being a farmworker or having greater DEP concentration levels might be beneficial to postural control

performance. In analyses using data from other components of the PACE4 study, we have documented that pesticide exposure is related to cholinesterase inhibition³⁴, impaired olfaction^{35,36} and aspects of neurobehavioral function³⁷. These support sub-clinical effects of OP exposure on health. OPs are cholinesterase inhibitors, affecting the cholinergic system³⁸ and the contribution of OP dose to neurological effects is obviously complicated. Patients with Alzheimer's disease (AD), which is associated with decreased acetylcholine neurotransmission, are commonly treated with cholinesterase inhibiting medications to help alleviate their cognitive symptoms^{39,40}. A growing literature also indicates that cholinesterase inhibitors actually reduce falls and improve gait in AD and Parkinson's diseases^{41–43}. It remains unclear, though, whether these effects are mediated through direct effects on balance or if they are instead the result of improved cognition. Recent work from Montero-Odasso et al.⁴² found that AD patients exhibited the most substantial gait improvements during a dual-task condition, suggesting that the cholinesterase inhibitors are improving gait through beneficial effects on executive function and reduced distraction. Our findings of an association between normalized CI_{ML} and urinary DAP metabolite levels implies that acute exposure to OPs was associated with better postural control performance. We caution that this finding should not be over interpreted at this stage. Our data-driven analysis raises this as potential hypothesis but cannot unequivocally determine beneficial versus detrimental effects of acute OP exposure on balance. It is also important to note that even if acute beneficial effects were to ultimately be identified, the long-term effects of exposure could still be detrimental. Clearly there is a need for additional research into the mechanisms by which OP exposures, both acute and chronic, affect the neurological system.

A few limitations of the current study should be acknowledged. First, all participants were male and were recruited from locations in a single state. The number of participants included in this analysis was also small in the context of the models fitted in this work. Second, a limited number of pesticide urinary metabolites and no other biomarkers were included in the analysis. Not all OPs were reflected in the DAPs; for example, acephate, which is widely used in tobacco production, does not metabolize to a DAP. Other neurotoxicant insecticides to which participants may have been exposed, including the carbamates and pyrethroids, were also not considered in this analysis. In the PACE4 Study, Quandt et al.³⁴ reported that farmworkers (vs. non-farmworkers) exhibited more suppressed cholinesterase activities during agricultural seasons (July and/or August). Potential differences in these biomarkers may be collectively reflected in farmworker status. Third, while urine samples were collected up to four times at one-month intervals, postural control measures were obtained at one of these times. Urine samples were combined into one proportionate composite sample (proportionate to the total volume of urine provided for each sample), and this composite sample was analyzed. Thus, while this approach provides information on exposure and dose across a four-month period, it may not reflect the specific metabolites to which participants were exposed, closest to when data on postural control were collected. Finally, the determination of pesticide detections and concentrations was limited by the current state of laboratory procedures.

CONCLUSIONS

A data-driven approach was used to examine potential associations between recent pesticide exposure and postural balance. Though our results did not support our initial hypothesis – of a negative association between postural control performance and urinary DAP metabolite levels – we suggest caution before rejecting this hypothesis without further investigation into the mechanics of neurological OP exposure outcomes. Baseline values of sway complexity were associated to a greater degree with farmworker status and body measurements than with urinary DAP metabolite concentration levels. When visual information was removed and a concurrent cognitive task was present (i.e., the most challenging balance condition), a relatively strong, positive association between CI_{ML} and $DEP \times Stature$ was revealed. Overall, though farmworkers and non-farmworkers exhibited comparable concentration levels of DAP metabolites, farmworker status may be an important variable to understand potential associations between pesticide exposure and postural balance. Further, using a posturally and cognitively challenging test condition should be considered in future work to reveal any potential associations between pesticide exposure and postural balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Coefficients selected by the lasso method for normalized MV_{ML} (Top) and CI_{ML} (Bottom) obtained from the most challenging condition (eyes-closed and with a concurrent cognitive task). Note that error bars are 95% confidence intervals, CR is urinary creatinine level, and FW is farmworker status.

Table 1

Summary [mean (min., max.)] of farmworker and non-farmworker characteristics.

	Farmworkers (n = 77)	Non-farmworkers (n = 56)	<i>p</i> value
Age (years)	38.9 (30, 57)	40.3 (30, 70)	0.34
Body mass (kg)	84.1 (53.8, 140.7)	80.7 (58.2, 155.1)	0.21
Stature (m)	1.69 (1.5, 1.79)	1.66 (1.51, 1.90)	0.06
BMI (kg/m ²)	29.6 (20.9, 49.0)	29.1 (19.4, 52.9)	0.59
Years of occupational pesticide exposure (years) ^I	15.2 (3, 35)	4.1 (0, 17)	<0.0001

Note that comparisons between occupational groups were done using two sample *t* tests, and that significant differences between groups are highlighted with bold text.

^IData on years of occupational pesticide exposure are from Arcury et al.²¹.

Table 2

Dialkylphosphate (DAP) urinary metabolite levels (µg/L) and detections (%) for farmworkers and non-farmworkers.

	Detections (>LOQ)								<i>p</i> -value
	Farmworkers				Non-farmworkers				
	Arithmetic Mean (SD)	Geometric Mean (IQR)	n	%	Arithmetic Mean (SD)	Geometric Mean (IQR)	n	%	
DMP	12.05 (19.65)	2.33 (13.48)	57	74.0	6.61 (11.22)	1.06 (10.18)	37	66.1	0.341
DMTP	11.05 (15.55)	4.13 (11.61)	70	90.9	11.26 (18.59)	3.49 (12.73)	49	87.5	0.575
DMDTP	1.07 (2.75)	0.02 (1.01)	22	28.6	1.25 (3.14)	0.004 (0.08)	13	23.2	0.553
DEP	11.53 (18.89)	6.95 (6.88)	77	100	12.13 (13.73)	6.06 (14.52)	55	98.2	0.421
DETP	0.96 (1.83)	0.07 (1.39)	32	41.6	0.46 (1.01)	0.02 (0.47)	14	25	0.06

IQR = Interquartile range

LOQ = Limit of Quantification

Note that the difference in % detections between occupational groups were assessed using Fisher's exact tests (*p* values provided).

Table 3

Variables and first-order interactions selected using the lasso method, and regression fit outcomes [i.e., r^2 , adjusted r^2 , and root mean square error (RMSE)].

Experimental condition	MV _{AP}		MV _{ML}		PEA	CI _{AP}	CI _{ML}
Eyes-Open w/o Cognitive task (Baseline)	Variables selected	DMP×DMDTP(+)	DEP(-), DMTp×YE(-), DMDTP×YE(+)	DEP(+)	FW(+), BM×Stature(-)	FW(+), DEP(+), BM×Stature(-)	
	r^2	0.02		0.00	0.22	0.21	
	adj r^2	0.01	0.08	0.00	0.21	0.19	
	RMSE	2.73	3.03	32.54	16.60	16.92	
Eyes-Open w/ Cognitive task	Variables selected	FW(-), DMP(-), DEP(+), CR×DETP (+), CR×YE (+)	FW(-), DMP(-), CR×DETP (+)	DEP(-), CR×DETP(+)	DMP(+), DEP(+), YE(-), DETP×YE(-)	DETP(-), DMP×Stature(+), DMP×DEP(-), DMP×YE(-), DEP×DMDTP(+)	
	r^2	0.11	0.06	0.04	0.08	0.11	
	adj r^2	0.07	0.04	0.02	0.05	0.08	
	RMSE	3.60	3.16	6.12	0.82	0.89	
Eyes-Closed w/o Cognitive task	Variables selected	FW(-), CR(+)	DEP(+)	FW(-), DMTp(-), CR×DETP (+)	DMTP×DEP(+)	DMP×Stature(+)	
	r^2	0.05	0.01	0.06	0.04	0.02	
	adj r^2	0.03	0.00	0.04	0.04	0.01	
	RMSE	3.57	3.93	6.60	0.77	0.94	
Eyes-Closed w/ Cognitive task	Variables selected	FW(-), DMP(-), CR×YE (-)	FW(-), DEP×DETP(+), CR×DETP (-)	FW(-), DMTp(-)	DMP×DMDTP(+), DMP×DMTP(+), DMDTP×DEP(+)	DMP×DEP(-), DMP×DETP(-), DMP×Stature(+), CR×DMTP(+), CR×FW (+)	
	r^2	0.06	0.16	0.03	0.07	0.14	
	adj r^2	0.04	0.14	0.02	0.05	0.11	
	RMSE	3.57	3.60	3.57	0.70	0.87	

FW = farmworker status, YE = years of occupational pesticide exposure, CR = urinary creatinine level, and BM = body mass

MV, PEA, and CI are center-of-pressure mean velocity, 95% prediction ellipse area, and complexity index, respectively

Subscripts AP and ML indicate the anteroposterior and mediolateral directions, respectively.

Note that the symbols (+) and (-) indicate the sign of the coefficient for respective variable, and that the postural control measures for the experimental condition excluding the baseline condition are normalized as described in the text.