Association between exposure to organophosphates and carbamates and refractive error (myopia and astigmatism): NHANES 1999-2004

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Presenter Disclosures

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Myopia & Astigmatism

- Myopia (nearsightedness)
  - Prevalence risen in the U.S. (Vitale et al. 2009)
  - Causal/risk factors
    - Near work
    - High SES
    - Genetic
- Astigmatism
  - Causal/risk factors
    - Less clear than myopia
    - Genetic
- Often occur together
  - Astigmatism also co-occurs with hyperopia

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Organophosphates (OPs) & Vision

- "Saku disease"
  - Myopia and astigmatisms among Japanese adults and children in rural area in 1950-60s
  - Some experimental and epidemiological investigations
  - Organophosphates suspected causal agent
- Rediscovered in early 1990s by US EPA
- No recent epidemiological investigations
- Increased use of biomarkers of OP exposure

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Organophosphates & Carbamates

- Inhibit neuronal cholinesterase
- Insecticides
- Human exposure through:
  - Diet
    - Residue from agricultural use
  - Indoor use
    - Chlorpyrifos & diazinon have been phased out

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Study Aim & Design

- Aim
  - To investigate association between urinary biomarkers of exposure to cholinesterase inhibitors and refractive error (myopia and astigmatisms)
- Design
  - Cross-sectional survey
  - National Health and Nutrition Examination Survey (NHANES) 1999-2004
    - 3 survey period: 99-00, 01-02, 03-04
  - Nationally representative sample of non-institutionalized individuals
  - Vision data for age >= 12 (Vitale et al. 2008)
  - Urinary metabolite data for age >= 6 (sub-sample)
    - Not all measured for 3 survey periods, some missing measurements

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Variables

- Outcome—based on objective refraction
  - **Myopia**, hyperopia (vs. neither)
    - ≤ −1 diopter, ≥ 3 diopter (vs. in-between)
  - **Astigmatism**
    - ≥ 1 diopter cylinder
- Exposure—log-transformed urinary metabolites
  - Unspecific metabolites
    - Six phosphate metabolites
  - Specific metabolites
    - Include metabolites of malathion, chlorpyrifos, & parathion
- Confounders/covariates
  - Log urine creatinine, fasting time, family income, measure of walking difficulty (correlate of time spent indoor/near work)

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Unspecific OP Metabolites

Unspecific Metabolites	Parent Organophosphates																										
	Azinphos methyl	Chlorethoxyphos	Chlorpyrifos	Chlorpyrifos methyl	Coumaphos	Dichlorvos (DDVP)	Diazinon	Dicrotophos	Dimethoate	Disulfoton	Ethion	Fenitrothion	Fenthion	Isazaphos-methyl	Malathion	Methidathion	Methyl parathion	Naled	Oxydemeton-methyl	Parathion	Phorate	Phosmet	Pirimiphos-methyl	Sulfotepp	Temephos	Terbufos	Tetrachlorvinphos
Dimethyl-phosphate	•			•		•		•	•			•	•	•	•	•	•	•	•			•	•		•		•
Dimethyl-thiophosphate	•			•					•			•	•	•	•	•	•		•			•	•		•		
Dimethyl-dithiophosphate	•								•						•	•						•					
Diethyl-phosphate		•	•		•		•			•	•									•	•			•		•	
Diethyl-thiophosphate		•	•		•		•			•	•									•	•			•		•	
Diethyl-dithiophosphate										•	•										•					•	

Adapted from http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf

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Statistical Analysis

- Stata 12 svy suite for complex survey data
  - Proper weighting & variance estimation
- Myopia analysis
  - Multinomial regression
    - 3 outcome status: myopia, hyperopia, neither (ref)
- Astigmatism analysis
  - Logistic regression: astigmatism vs. normal
  - (Linear regression: spherical error)

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Proportion of measurements under detection limit (%):
Data with under detection rate < 90% used

Metabolite	1999-2000	2001-2002	2003-2004
Dimethylphosphate	51.2	52.4	51.3
Dimethylthiophosphate	38.3	50.1	24.3
Dimethyldithiophosphate	53.7	68.5	62.2
Diethylphosphate	32.2	51.0	51.7
Diethylthiophosphate	50.3	29.9	50.8
Diethyldithiophosphate	48.1	81.1	91.8
Dimethyl alkylphosphate	18.5	30.3	16.2
Diethyl alkylphosphate	25.1	22.5	28.7
Total dialkyl phosphate	8.7	11.1	7.8
Chlorpyrifos metabolite	9.1	27.4	.
Carbofuran metabolite	89.2	99.7	99.7
Coumaphos metabolite	.	96.8	.
Diazinon metabolite	69.2	95.6	.
Malathion metabolite	47.4	.	
Parathion metabolite	80.3	52.4	.
Propoxur	98.8	99.7	100.0
Acephate	.	.	97.9
Methamidaphos	.	.	99.7
Dimethoate	.	.	99.2
O-Methoate	.	.	100.0

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Urinary metabolite Summary

Metabolite	N	Below detection limit (%)	Urinary metabolite concentration, nmol/L: Geometric Mean	Interquartile range
Dimethylphosphate	5171	(51.7)	8.9	2.8-27.0
Dimethylthiophosphate	5171	(37.2)	11.3	2.0-44.5
Dimethyldithiophosphate	5140	(62.1)	1.5	0.4-5.6
Diethylphosphate	5138	(46.1)	4.3	0.9-22.9
Diethylthiophosphate	5117	(43.2)	1.7	0.7-4.9
Diethyldithiophosphate	3240	(66.8)	0.6	0.4-0.4
Dimethyl alkylphosphate	5138	(21.8)	31.9	7.8-89.3
Diethyl alkylphosphate	5080	(25.5)	9.2	1.6-28.8
Total dialkyl phosphate	5046	(9.2)	52.1	18.3-130.9
Carbofuran metabolite	1447	(89.1)	1.0	0.9-1.7
Chlorpyrifos metabolite	3271	(19.4)	8.3	3.6-21.7
Diazinon metabolite	1334	(68.5)	4.3	3.2-3.9
Malathion metabolite	1404	(47.4)	0.8	0.3-2.2
Parathion metabolite	3245	(64.7)	2.6	0.5-7.9

- Interquartile range ≅ 10-fold
- Positively correlated with each other

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Prevalence by age

Sample with	Age groups: 12-19	20-39	40-59	>= 60
Vision data (entire sample)				
Myopia	32.3%	36.2%	37.6%	20.7%
Hyperopia	1.3%	1.0%	2.4%	9.9%
Astigmatism	23.3%	33.0%	41.2%	66.0%
Vision + unspecific metabolite (dimethyl-phosphate)				
Myopia	32.4%	36.2%	37.0%	20.9%
Hyperopia	1.0%	0.7%	2.8%	6.1%
Astigmatism	21.6%	34.5%	41.6%	67.8%
Vision + malathion (1999-2000)				
Myopia	30.0%	32.7%	36.0%	100.0%*
Hyperopia	1.9%	1.7%	3.3%	-
Astigmatism	23.1%	32.6%	38.7%	100.0%*

* Only one individual of age >=60

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Myopia Results: Unadjusted and adjusted associations

- Unadjusted models
  - Each w/ one metabolite as single predictor
- Partially-adjusted models
  - Each w/ one metabolite and all other covariates
- Fully-adjusted model
  - All metabolites and covariate in a single model

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Myopia Results

Metabolite	Unadjusted N	Unadjusted OR*	Unadjusted p	Partially-adjusted for covariates** N	Partially-adjusted for covariates** OR	Partially-adjusted for covariates** p	Fully-adjusted for covariates** & metabolites (N = 1220) OR	Fully-adjusted for covariates** & metabolites (N = 1220) p
Dimethylphosphate	5171	0.96	0.50	5075	1.01	0.93	0.79	0.14
Dimethylthiophosphate	5171	1.06	0.27	5075	1.11	0.04	1.16	0.16
Dimethyldithiophosphate	5140	1.17	0.008	5045	1.19	0.002	1.33	0.06
Diethylphosphate	5138	0.92	0.10	5042	0.93	0.21	0.79	0.70
Diethylthiophosphate	5117	1.02	0.85	5023	1.06	0.51	0.84	0.53
Diethyldithiophosphate	3240	0.98	0.87	3160	0.95	0.70	1.24	0.25
Dimethyl alkylphosphate	5138	1.06	0.43	5043	1.13	0.11	0.63	0.21
Diethyl alkylphosphate	5080	0.90	0.20	4986	0.94	0.42	1.36	0.72
Total dialkyl phosphate	5046	1.03	0.75	4953	1.11	0.22	1.08	0.82
Carbofuran metabolite	1447	1.17	0.72	1405	1.19	0.65	1.28	0.60
Chlorpyrifos metabolite	3271	0.81	0.001	3187	0.89	0.14	0.57	0.01
Diazinon metabolite	1334	0.86	0.52	1297	0.78	0.31	0.85	0.55
Malathion metabolite	1404	1.33	0.01	1367	1.44	0.003	1.45	0.01
Parathion metabolite	3245	0.81	0.01	3162	0.89	0.17	0.94	0.81

* Odds ratio for per 10-fold increase in urine metabolite concentration
** Age-sex strata, race, fasting time, family income, log creatinine, & walking difficulty

Myopia Results: Parsimonious model

Metabolite	Reduced Model OR*	Reduced Model p	Parsimonious Model OR	Parsimonious Model p
Dimethylthiophosphate	0.95	0.50	-	-
Dimethyldithiophosphate	1.15	0.15	-	-
Chlorpyrifos	0.58	0.002	0.58	0.001
Malathion	1.52	0.001	1.54	0.001
Parathion	0.91	0.56	-	-

* Odds ratio for per 10-fold increase in urine metabolite concentration
Covariates adjusted: age-sex strata, race, fasting time, log creatinine, family income, and walking difficulty

- Association stronger w/ adjustment for each other
- Independent association for chlorpyrifos & malathion in the **opposite** direction
- Animal experiment report on suppression of myopia by chlorpyrifos (Geller et al. 1998)

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Astigmatism Results

Metabolite	Unadjusted N	Unadjusted OR*	Unadjusted p	Partially-adjusted for covariates** N	Partially-adjusted for covariates** OR	Partially-adjusted for covariates** p	Fully-adjusted for covariates** & metabolites (N = 1219) OR	Fully-adjusted for covariates** & metabolites (N = 1219) p
Dimethylphosphate	5171	1.11	0.17	5075	1.09	0.27	0.89	0.56
Dimethylthiophosphate	5171	1.08	0.11	5075	1.05	0.33	0.81	0.29
Dimethyldithiophosphate	5140	1.14	0.02	5045	1.10	0.07	1.10	0.30
Diethylphosphate	5138	1.00	0.93	5042	0.99	0.88	1.52	0.41
Diethylthiophosphate	5117	1.06	0.37	5023	1.02	0.79	0.79	0.27
Diethyldithiophosphate	3240	1.05	0.70	3160	1.03	0.78	1.81	0.02
Dimethyl alkylphosphate	5138	1.11	0.11	5043	1.10	0.18	0.87	0.84
Diethyl alkylphosphate	5080	1.03	0.70	4986	1.00	0.95	0.55	0.34
Total dialkyl phosphate	5046	1.13	0.10	4953	1.13	0.14	1.46	0.56
Carbofuran metabolite	1447	1.02	0.95	1405	1.03	0.91	1.13	0.65
Chlorpyrifos metabolite	3271	0.87	0.24	3187	0.95	0.63	0.66	0.20
Diazinon metabolite	1334	1.15	0.52	1297	1.10	0.64	1.21	0.42
Malathion metabolite	1404	1.16	0.25	1367	1.21	0.12	1.47	0.04
Parathion metabolite	3245	1.02	0.84	3162	1.03	0.73	1.09	0.64

* Odds ratio for per 10-fold increase in urine metabolite concentration
** Age-sex strata, race, fasting time, family income, log creatinine, & walking difficulty

Astigmatism Results: Parsimonious model

Metabolite	Reduced Model OR*	Reduced Model p	Parsimonious Model OR	Parsimonious Model p
Diethyldithiophosphate	1.20	0.30	-	-
Chlorpyrifos	0.62	0.03	0.64	0.04
Malathion	1.27	0.04	1.28	0.04

* Odds ratio for per 10-fold increase in urine metabolite concentration
Covariates adjusted: age-sex strata, race, fasting time, family income, and walking difficulty

- Independent association for chlorpyrifos & malathion in the **opposite** direction
- Similar results from linear regression of spherical error (continuous measure of astigmatisms)

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Observed Associations

- Myopia & Astigmatism
  - Higher prevalence with higher urinary malathion metabolite
  - Lower prevalence with higher urinary chlorpyrifos metabolite

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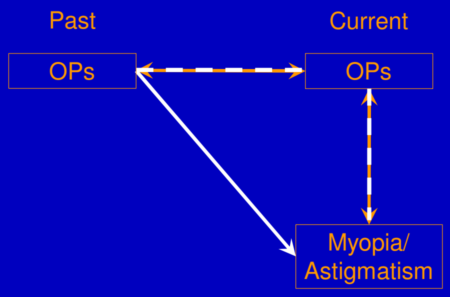
Interpretation: Past OP exposure → Current Myopia



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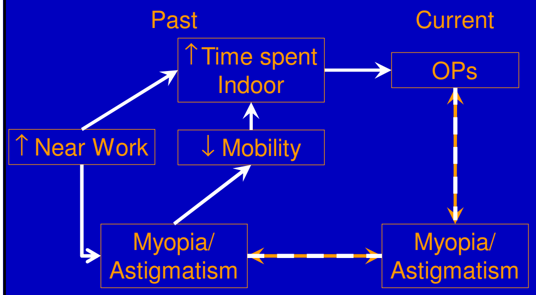
Reverse Causality Interpretation: Past Myopia (its cause) → Current OP exposure



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Counter argument for reverse causality

- Negative association w/ chlorpyrifos unexplainable
- Indoor OP exposure < dietary OP exposure
  - No registered indoor use of malathion
- Malathion-myopia association persists after adjustment for walking difficulty

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Discussions

- Cross-sectional design
  - Temporality ambiguous (yet reverse causality unlikely)
  - Common cause for both OP & refractive errors possible
- Colinearity
  - Other urinary metabolite(s) may be true culprit
    - Threshold for effects may be < limit of detection
- Beneficial diet (fruits & veg's ~ OP exposure) unadjusted
- If causal, mechanism likely non-cholinergic

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Conclusion

- Malathion urinary metabolite positively associated with current myopia & astigmatisms
- Chlorpyrifos negatively associated with them
  - Concordance with experiment evidence
- Confirmation with longitudinal study needed
- Add evidence for adverse effects on low level exposure to organophosphates
- Caution for additional OP uses, e.g.
  - Indoor use for bed bug control petitioned for malathion

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