Depressive Symptoms and Environmental Toxicants

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Background

- Major Depressive Disorder (MDD) is a disorder that is accompanied by persistent feelings of disinterest, and depressed mood, among other symptoms for a period of at least two weeks.[1]
- MDD is of significant public health concern as it is estimated to effect 16.2 million adults annually in the United States alone[2]
- Environmental risk factors play a key role in the development of depression
- Environmental toxicants have been shown to play a significant role in the development of other neuronal disorders such as the development of Autism Spectrum Disorder.[3]
- Little is known about the relationship between environmental toxicants and depression

Objective

- Using method often applied to genomic data, estimate associations between environmental toxicants and depression, controlling for known risk factors of depression in the National Health and Nutrition Examination Survey (NHANES)

Methods

Study

- NHANES is a cross-sectional complex, multistage survey sample design conducted in two year cycles at selected points across the United States, allowing for a sample that is nationally-representative of all civilian non-institutionalized citizens.[4]
- Our study population is American adults 20 years and older.

Measures

- *Depression phenotype:*
  - In 1999-2004 depression phenotyping was assessed via an NHANES specific version of the Composite International Diagnostic Interview (CIDI) designed by the World Health Organization (WHO) .
  - In 2005-2014, was collected via the 9-item patient health questionnaire (PHQ-9)
- *Toxicants:*
  - Toxicant were measured in selected subsamples of the survey population. *Chemicals* that were measured in more than 10% of the sample or whose measures were above the limit of detection in at least 70% of the samples were tested using logistic regression
- *Covariates:*
  - Sex (m/f), race/ethnicity, cotinine (as proxy for smoking), marital status, education status, poverty index, BMI, urinary creatinine, and wave of NHANES

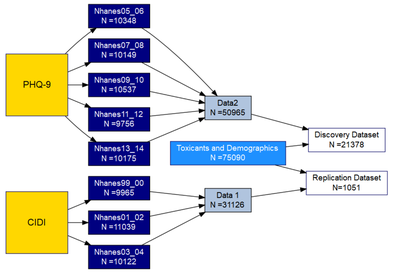


Figure 1. Discovery and replication data set composition

Statistical Methods

- We followed the methodology laid out by Patel et al to perform an Environmental-Wide Association Study (EWAS)[5]
- We performed multivariable logistic regressions for each toxicant exposure adjusting for the covariates listed above
- Discovery: waves 2005-2014
- Replication: waves 1999-2004 using a more clinical definition of depression

Results

Table 1. Sample descriptive statistics, NHANES 1999-2014, N=22,429

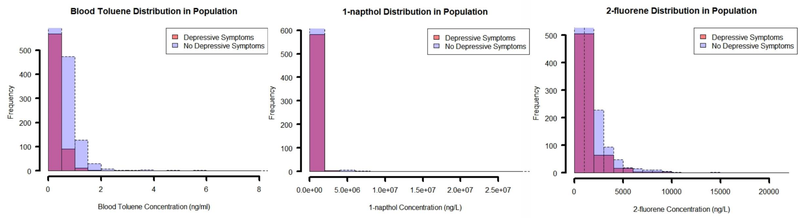
	Discovery			Replication		
	No Depressive Symptoms N = 19,428	Depressive Symptoms N = 1,950	p-value	No Depressive Symptoms N = 982	Depressive Symptoms N = 69	p-value
Sex			<0.001			0.007
Male	9830 (50.6%)	689 (35.8%)		443 (45.1%)	19 (27.5%)	
Female	9598 (49.4%)	1233 (64.2%)		539 (54.9%)	50 (72.5%)	
Race/Ethnicity			<0.001			0.523
Mexican American	2996 (15.4%)	300 (15.4%)		246 (25.1%)	12 (17.4%)	
Other Hispanic	1580 (8.13%)	226 (11.6%)		48 (4.89%)	3 (4.35%)	
Non-Hispanic White	9324 (48.0%)	876 (44.9%)		462 (47.0%)	40 (58.0%)	
Non-Hispanic African-American	3905 (20.1%)	427 (21.9%)		187 (19.0%)	12 (17.4%)	
Other (Including Multi-Racial)	1623 (8.35%)	121 (6.21%)		39 (3.97%)	2 (2.90%)	
Cotinine	55.9 (128)	99.3 (153)	<0.001	52.2 (109)	94.0 (142)	0.019
Marital Status			<0.001			0.053
Married/Living with Partner	12011 (61.8%)	909 (46.6%)		607 (61.8%)	34 (49.3%)	
Single	7417 (38.2%)	1041 (53.4%)		375 (38.2%)	35 (50.7%)	
Education Status			<0.001			0.526
≤ High School	8982 (46.2%)	1186 (60.8%)		466 (47.5%)	36 (52.2%)	
> High School	10446 (53.8%)	764 (39.2%)		516 (52.5%)	33 (47.8%)	
Poverty Index Ratio	2.64 (1.63)	1.70 (1.37)	<0.001	2.51 (1.61)	2.42 (1.68)	0.661
BMI	28.9 (6.65)	30.8 (8.27)	<0.001	27.8 (6.52)	28.2 (7.93)	0.644
Wave:			<0.001			0.566
2005-2006/1999-2000	3641 (18.7%)	269 (13.8%)		229 (23.3%)	16 (23.2%)	
2007-2008/2001-2002	4012 (20.7%)	429 (22.0%)		412 (42.0%)	25 (36.2%)	
2009-2010/2003-2004	4131 (21.3%)	453 (23.2%)		341 (34.7%)	28 (40.6%)	
2011-2012	3619 (18.6%)	366 (18.8%)				
2013-2014	4025 (20.7%)	433 (22.2%)				
Urinary Creatinine	123 (77.8)	133 (88.3)	<0.001	151 (87.8)	146 (97.7)	0.686

Table 2. Significant (p<0.001) toxicant-depression results for discovery sample with replication

		Discovery			Replication		
Toxicant	Chemical Class	OR	95% (CI)	p-value	OR	95% (CI)	p-value
Cadmium, blood (ug/L)	Metals	1.34	(1.24,1.44)	1.7E-14*	0.81	(0.55,1.18)	2.7E-01
1-napthol (ng/L)	**Polyaromatic Hydrocarbons (PAH)**	**1.20**	**(1.13,1.27)**	**1.1E-09***	**1.37**	**(0.93,2.03)**	**1.2E-01***
2-fluorene (ng/L)	**Polyaromatic Hydrocarbons (PAH)**	**1.26**	**(1.14,1.39)**	**7.8E-05***	**1.45**	**(0.92. 2.27)**	**1.1E-01***
Thallium, urine (ng/mL)	Metals	0.74	(0.66,0.86)	7.81E-05*	1.07	(0.66, 1.73)	7.8E-01
3-fluorene (ng/L)	Polyaromatic Hydrocarbons (PAH)	1.19	(1.09,1.30)	1.1E-04*	1.31	(0.85, 2.03)	2.2E-01
Blood Toluene (ng/ml)	**Volatile Organic Compounds (VOCs)**	**1.20**	**(1.09,1.32)**	**1.1E-04***	**1.62**	**(0.94, 2.78)**	**8.2E-02***
Enterolactone (ng/mL)	Phytoestrogens	0.89	(0.84, 0.95)	3.1E-04*	1.04	(0.80, 1.36)	7.8E-01
Cadmium, urine (ng/mL)	Metals	1.18	(1.07, 1.31)	9.7E-04*	0.93	(0.62, 1.39)	7.2E-01

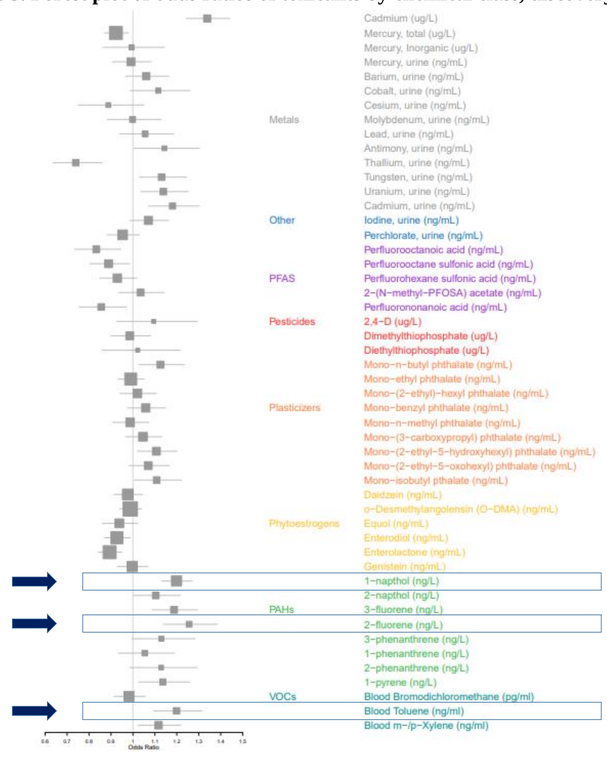
Bolded lines represent replicated results
Discovery covariates: sex, race/ethnicity, cotinine, marital status, education, poverty index, BMI, creatinine, and wave
Replication covariates: sex, marital status, cotinine
* p-value < 0.001
** replication p-value <0.05

Figure 2. Sample distribution of suggestive replicated toxicants in the discovery sample



- Discovery and replication datasets have higher percentage of depressive phenotype in women, 64.2% and 72.5%, respectively
- Based on a criteria of <0.001 we found 8 toxicants to be significant: blood cadmium (ug/L) , 1-napthol (ng/L), 2-fluorene (ng/L), urine thallium (ng/mL) , 3-fluorene (ng/L), blood toluene (ng/ml) , enterolactone (ng/mL) , and urine cadmium (ng/mL)
- When the regression was repeated in the replication dataset we observed a marginal significance in three exposures: blood toluene, 1-napthol, and 2-fluorine
- The chemical classes of the three marginally significant variables were VOCs (toluene) or PAH (1-napthol & 2-fluorene)

Figure 3. Forest plot of odds ratios of toxicants by chemical class, discovery



Conclusions

- This provides evidence that there is a relationship between toxicants and development of depressive symptoms
- There is further need for studies involving chemicals with short half-lives, like toluene, whose effects are hard to observe
- The association seen between depressive symptoms and 1-napthol is may potentially be due to extreme outliers

Future Directions

- Perform survey weighted logistic regression based on NHANES weighting recommendations in order to obtain results generalizable to the Adult U.S. population
- Perform sensitivity analysis adjusting for other comorbidities

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