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RESEARCH ARTICLE

Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011–2012

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Abstract Links between environmental chemicals and human health have emerged, but the effects on mental health such as depression were less studied. Therefore, it was aimed to study the relationships between different sets of urinary environmental chemical concentrations and adult depression in a national and population-based setting in recent years. Data was retrieved from the US National Health and Nutrition Examination Survey in 2011–2012 including demographics, serum measurements, lifestyle factors, self-reported health conditions and urinary chemical concentrations. Depression was determined by using the Patient Health Questionnaire with a cutoff point at 9/10. Chi-square test, *t* test and survey-weighted logistic regression modeling were performed. Among 5560 American adults aged 20–80 years, 363 (7.8 %) people were classified as having depression (Patient Health Questionnaire score≥10). They tended to have history of health events. After full adjustment including urinary creatinine; demographic characteristics; lifestyle factors; health conditions (such as cardiovascular, neurological, respiratory, digestive and bone diseases, and injury); and subsample weighing; and higher levels of manganese, tin, and phthalates including mono-2-ethyl-5-carboxypentyl, mono-n-butyl, mono-isobutyl, and mono-benzyl were associated with adult depression. Similarly, urinary polyaromatic hydrocarbons including 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 1-hydroxypyrene, 1-hydroxynaphthalene (1-naphthol), 2-hydroxynaphthalene (2-naphthol) and 4-hydroxyphenanthrene were associated with depression. There were no associations observed in urinary arsenic, phenols, parabens, pesticides, perchlorate, nitrate, thiocyanate and polyfluorinated compounds. Urinary heavy metal, phthalates and polyaromatic hydrocarbons were associated with adult depression, being independent of health events. Further elimination of such harmful chemicals might need to be considered in future mental health and environmental policies.

Keywords Chemical · Risk factor · Depression · Hydrocarbon · Chronic disease · Phthalate · Heavy metal

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Introduction

Evidence before this study

Links between environmental chemicals and human health including hypertension, cardiovascular disease, respiratory disease, food allergy, oral health and cognitive function have emerged (Shiue 2013a, b, c; 2014a, b; 2015a, b, c) in American adults, but the effects from polyaromatic hydrocarbons (PAHs) were less studied, compared to other commonly known environmental chemicals such as heavy metals, arsenic, phenols, parabens, pesticides, phthalates, etc. PAHs constitute a group of chemicals that people could be exposed to via vehicle exhausts, asphalt, coal tar, wild fires, agricultural burning, soil, charbroiled foods, and tobacco smoke. PAH pollution may have significant health implications, and the

extent of damage to organisms from PAH exposure could be dependent on several factors including degree and type of PAH exposure (Ball and Truskewycz 2013). The potential for PAHs to adversely affect human immunologic health could have traditionally been evaluated in rodents, under laboratory conditions (Luebke et al. 1997). Recently, researchers have also found how PAHs could be linked to cardiovascular disease in American adults (Xu et al. 2010) or in pregnant women (Woodruff et al. 2011).

Knowledge gap

However, in addition to physical health, it is unclear about the role of PAHs and other environmental chemicals in mental health such as depression. Following this context, therefore, it was aimed to examine and provide further evidence on the relationships between different sets of urinary environmental chemical concentrations and adult depression using a large human sample to account for prior health events in a national and population-based setting in recent years.

Methods

Study sample

As described elsewhere (more details via http://www.cdc.gov/nchs/nhanes.htm), the US National Health and Nutrition Examination Surveys (NHANES) has been a national, population-based, multiyear, cross-sectional study since the 1980s. Study samples are a representative sample of the civilian, noninstitutionalized US population. Information on demographics, serum measurements, lifestyle factors, self-reported health conditions, and urinary environmental chemical concentrations was obtained by household interview. Depression status was measured using Patient Health Questionnaire (Spitzer et al. 1999), a nine-item screening instrument that asked questions about the frequency of symptoms of depression over the recent past 2 weeks. Response categories for the nine-item instrument such as "not at all," "several days," "more than half the days," and "nearly every day" were given a point ranging from 0 to 3 (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/DPQ_G.htm). The overall scoring ranges from 0 to 27 following answering nine items and could have categories from none, mild to moderate, and even severe (more details via http://www.phqscreeners.com/instructions/instructions.pdf). The current recommended cutoff in the clinical setting is 9/10 (Manea et al. 2012). In the current analysis, the 2011–2012 cohort as the most recent study cohort with available information mentioned above was selected for examination. Informed consents were obtained from participants by the NHANES researchers.

Biomonitoring

Urines were only collected in a subsample, being one third of the whole study cohort (still representative), to measure environmental chemical concentrations in urines. To be specific, participants were instructed to collect a partial void in a specimen cup during one morning when they first woke up and to mail it back to the contract laboratory (more details via http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/labdoc_g.htm). Urine specimens were then processed, stored under appropriate frozen (−20 °C) conditions, and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for laboratory analysis.

The inductively coupled plasma-mass spectrometry (ICP-MS) method (Mulligan et al. 1990) was used to measure the following 12 elements of heavy metals in urine: beryllium (Be), cobalt (Co), molybdenum (Mo), cadmium (Cd), antimony (Sb), cesium (Cs), tungsten (W), tin (Sn), strontium (Sr), manganese (Mn), thallium (TI), lead (Pb), and uranium (U). Urine samples are diluted 1+9 with 2 % (*v*/*v*), double-distilled, concentrated nitric acid containing both iridium (Ir) and rhodium (Rh) for multi-internal standardization (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/UHM_G.htm). In addition, the test principle utilized high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS) for the quantitative detection in urine of the following phthalate metabolites: monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobutyl phthalate (MBP), mono-isobutyl phthalate (MIBP), mono (3-carboxypropyl) phthalate (MCPP), mono(2-ethylhexyl) phthalate (MEHP), monobenzyl phthalate (MBzP), monoisononyl phthalate (MNP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), monocarboxyoctyl phthalate (MCOP), monocarboxynonyl phthalate (MCNP), and cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester (MHNCH) (Silva et al. 2007). Urine samples are processed using enzymatic deconjugation of the glucuronidated metabolites followed by on-line solid-phase extraction (SPE) coupled with reversed phase HPLC-ESI-MS/MS. Assay precision is improved by incorporating isotopically labeled internal standards of the phthalate metabolites and MHNCH (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/PHTHTE_G.htm).

Total and specific urine arsenic concentrations were determined by using inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS) (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/UAS_G.htm). In this case, urine is analyzed because urinary excretion is the major pathway for eliminating arsenic from the mammalian body (Vahter 1988). A sensitive method for measuring two

dichlorophenols and several other phenols was developed in 2005 (Ye et al. 2005). The method used on-line solid-phase extraction (SPE) coupled to HPLC and tandem mass spectrometry (HPL/CMS/MS) (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/PP_G.htm and http://wwwn.cdc.gov/nchs/nhanes/2011-2012/EPH_G.htm).

To detect and measure metabolites of PAHs (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/PAH_G.htm), the procedure involved enzymatic hydrolysis of glucuronidated/sulfated OH-polyaromatic hydrocarbons metabolites in urine, extraction, derivatization, and analysis using isotope dilution capillary gas chromatography tandem mass spectrometry (GC-MS/MS). Ion transitions specific to each analyte and carbon-13 labeled internal standards are monitored, and the abundances of each ion are measured. Moreover, solid-phase extraction coupled to high-performance liquid chromatography-turbo ion spray ionization-tandem mass spectrometry (on-line SPE-HPLC-TIS-MS/MS) was used for the quantitative detection of perfluorooctane sulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamido), acetic acid (Me-PFOSA-AcOH), 2-(N-ethyl-perfluorooctane sulfonamido), acetic acid (Et-PFOSA-AcOH), perfluorobutane sulfonate (PFBuS), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluoroheptanoate (PFHpA), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDeA), perfluoroundecanoate (PFUA), and perfluorododecanoate (PFDoA).

For phenols and parabens that could come from industrial pollution, pesticide use, food consumption, or use of personal care products (more details via: http://wwwn.cdc.gov/nchs/nhanes/2011-2012/EPH_G.htm), a sensitive method for measuring BPA, BP-3, triclosan, and four parabens was developed in 2005 (Ye et al. 2005, 2006). The method uses on-line solid-phase extraction (SPE) coupled to HPLC and tandem mass spectrometry (HPLC-MS/MS). While drinking water, milk, and certain plants with high water content can be the main sources of perchlorate intake for humans, nitrate and thiocyanate are polyatomic anions that can disrupt thyroid function by competitively inhibiting iodide uptake, similar to the action of perchlorate (more details via http://wwwn.cdc.gov/nchs/nhanes/2011-2012/PERNT_G.htm). The laboratory method used was ion chromatography coupled with electrospray tandem mass spectrometry (more details via http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/PERNT_G_met.pdf).

Statistical analysis

Adults aged 20 years and above were included in the current statistical analysis since adult depression status was asked in such age group. For statistical analysis purpose in the present study, urinary chemicals were all log transformed due to the fact that they were highly skewed to one side. In the first step, associations of historical health events and adult depression were investigated in order to see which disease might be more likely to result in depression. In the second step, associations of urinary different sets of environmental chemical concentrations and adult depression were examined by using t test and survey-weighted logistic regression models, with $P<0.05$ considered statistically significant. Covariates including urinary creatinine, age, sex, ratio of family income to poverty (proxy of socioeconomic status), body mass index, serum cotinine (biomarker of smoking status), alcohol habit, physical activity level, and educational level were adjusted. In the third step, significant prior health events were additionally adjusted in the modeling to rule out the possibility of the potential cause to adult depression. Statistical software STATA version 13.0 (STATA, College Station, Texas, USA) was used to perform all the statistical analyses. Since the present study is only a secondary data analysis by extracting data from the NHANES website, no further ethics approval was required.

Results

Among 5560 American adults aged 20–80 years, 363 (7.8 %) people were classified as having depression (Patient Health Questionnaire score≥10). They tended to have history of health events. Table 1 presents associations of historical health events and adult depression. It is clear to see that health conditions such as cardiovascular, neurological, respiratory, digestive and bone diseases, and injury were significantly associated with depression. Tables 2 and 3 show associations of urinary heavy metals and adult depression and by accounting for health events, respectively, while Tables 4 and 5 show associations of urinary phthalates and adult depression and by accounting for health events, respectively. It is clear to see that higher levels of manganese, tin, mono-2-ethyl-5-carboxypentyl, mono-n-butyl, mono-isobutyl, and mono-benzyl were associated with adult depression.

Similarly, Tables 6 and 7 show associations of urinary PAHs and adult depression and by accounting for health events, respectively. It is clear to see that urinary 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 1-hydroxypyrene, 1-hydroxynaphthalene (1-naphthol), 2-hydroxynaphthalene (2-naphthol), and 4-hydroxyphenanthrene were also associated with depression. However, there were no associations observed in urinary arsenic, phenols, parabens, pesticides, perchlorate, nitrate, thiocyanate, and polyfluorinated compounds.

Table 1 Associations between health conditions and adult depression aged 20–80 years (n=5560)

	No depression (n=4292, 92.2 %)	Depression (n=363, 7.8 %)	OR (95 % CI)[a]	P value
High blood pressure	342 (92.9 %)	26 (7.1 %)	0.84 (0.36–1.95)	0.662
No	3285 (92.2 %)	280 (7.9 %)	1.00	
Psoriasis	118 (84.9 %)	21 (15.1 %)	2.18 (0.95–5.00)	0.063
No	4170 (92.4 %)	342 (7.6 %)	1.00	
Celiac disease	13 (81.3 %)	3 (18.8 %)	1.56 (0.27–8.99)	0.600
No	4276 (92.2 %)	360 (7.8 %)	1.00	
Blood disorder	526 (88.4 %)	69 (11.6 %)	1.72 (0.87–3.44)	0.112
No	3729 (92.8 %)	288 (7.2 %)	1.00	
Gout disease	190 (90.5 %)	20 (9.5 %)	1.19 (0.37–3.85)	0.760
No	4101 (92.3 %)	343 (7.7 %)	1.00	
Heart failure	133 (83.1 %)	27 (16.9 %)	**1.72 (1.02–2.91)**	**0.042**
No	4153 (92.6 %)	332 (7.4 %)	1.00	
Coronary heart disease	147 (89.1 %)	18 (10.9 %)	1.08 (0.51–2.32)	0.824
No	4136 (92.4 %)	339 (7.6 %)	1.00	
Angina	92 (85.2 %)	16 (14.8 %)	1.51 (0.57–4.04)	0.388
No	4189 (92.4 %)	345 (7.6 %)	1.00	
Heart attack	147 (85.0 %)	26 (15.0 %)	1.26 (0.56–2.83)	0.555
No	4142 (92.5 %)	337 (7.5 %)	1.00	
Emphysema	70 (81.4 %)	16 (18.6 %)	1.22 (0.48–3.08)	0.658
No	4218 (92.5 %)	344 (7.5 %)	1.00	
Liver disease	159 (83.7 %)	31 (16.3 %)	**1.67 (1.01–2.77)**	**0.046**
No	4131 (92.6 %)	331 (7.4 %)	1.00	
Cancer	371 (90.1 %)	41 (10.0 %)	1.53 (0.86–2.72)	0.139
No	3918 (92.4 %)	321 (7.6 %)	1.00	
Infection	809 (89.0 %)	100 (11.0 %)	**1.59 (1.14–2.21)**	**0.009**
No	1958 (92.6 %)	156 (7.4 %)	1.00	
Injury	312 (81.5 %)	71 (18.5 %)	**3.10 (2.04–4.71)**	**<0.001**
No	2470 (93.0 %)	187 (7.0 %)	1.00	
Asthma	615 (88.2 %)	82 (11.8 %)	**1.44 (1.03–2.00)**	**0.034**
No	3674 (92.9 %)	281 (7.1 %)	1.00	
Chronic bronchitis	209 (78.3 %)	58 (21.7 %)	**2.33 (1.54–3.53)**	**<0.001**
No	4077 (93.1 %)	304 (6.9 %)	1.00	
Taste disorder	149 (77.6 %)	43 (22.4 %)	**3.99 (1.87–8.51)**	**0.001**
No	2636 (92.5 %)	215 (7.5 %)	1.00	
Diabetes	3670 (93.2 %)	267 (6.8 %)	**1.71 (1.18–2.46)**	**0.007**
No	621 (86.7 %)	95 (13.3 %)	1.00	
Thyroid disorder	405 (89.0 %)	50 (11.0 %)	1.46 (0.92–2.30)	0.101
No	3880 (92.7 %)	308 (7.4 %)	1.00	
Eye complaint	710 (81.5 %)	161 (18.5 %)	**3.13 (2.15–4.56)**	**<0.001**
No	3581 (94.7 %)	202 (5.3 %)	1.00	
Arthritis	1024 (86.6 %)	159 (13.4 %)	**2.34 (1.75–3.13)**	**<0.001**
No	3264 (94.2 %)	202 (5.8 %)	1.00	
Stroke	141 (79.7 %)	36 (20.3 %)	**2.42 (1.42–4.10)**	**0.003**
No	4149 (92.7 %)	327 (7.3 %)	1.00	
Smell disorder	255 (80.7 %)	61 (19.3 %)	**3.32 (1.86–5.94)**	**<0.001**
No	2530 (92.8 %)	197 (7.2 %)	1.00	
Sleep disorder	315 (75.2 %)	104 (24.8 %)	**4.42 (2.87–6.82)**	**<0.001**
No	3974 (93.9 %)	258 (6.1 %)	1.00	

Numbers highlighted in bold denote significance.

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

Table 2 Associations between urinary heavy metals (one third of the study population) and adult depression

(μg/L)	No depression (n=1395)	Depression (n=113)	OR (95 % CI)[a]	P value
Barium	1.7±3.1	1.8±2.0	0.91 (0.57–1.46)	0.676
Cadmium	0.4±0.5	0.5±0.6	1.20 (0.80–1.80)	0.366
Cobalt	0.4±1.0	0.5±0.6	1.41 (0.94–2.11)	0.088
Cesium	4.8±3.1	4.3±2.6	0.80 (0.47–1.37)	0.394
Manganese	0.2±0.2	0.2±0.1	**1.47 (1.01–2.15)**	**0.047**
Molybdenum	51.7±48.1	54.3±49.8	1.18 (0.82–1.71)	0.339
Lead	0.6±1.3	0.7±1.3	1.18 (0.78–1.79)	0.400
Antimony	0.1±0.1	0.1±0.1	1.25 (0.93–1.69)	0.132
Strontium	116.3±122.7	125.1±115.7	0.97 (0.56–1.69)	0.916
Thallium	0.2±0.1	0.2±0.1	0.81 (0.50–1.32)	0.378
Tin	1.4±3.4	1.3±1.5	**1.30 (1.00–1.68)**	**0.048**
Tungsten	0.1±0.9	0.2±0.4	1.14 (0.82–1.58)	0.411
Uranium	0.01±0.03	0.01±0.02	1.11 (086–1.42)	0.396

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

Discussion

Previous research synthesis

Evidence of risk effects of chemicals on mental health has gradually emerged in recent years, in particular on the effects of endocrine-disrupting chemicals on brain function, concomitantly with an increase in neuropsychiatric disorders including autism, attention deficit, hyperactivity disorder, learning disabilities, and aggressiveness (Kajta and Wójtowicz 2013). Even low doses might increase the risk of depression and consequently neural degeneration. Depression is a leading cause of disability worldwide and occurs in people of all ages and backgrounds (Bromet et al. 2011). However, studies looking into this emerging area, namely chemicals and depression or general mental health, are still limited.

Urinary heavy metals such as manganese and tin were associated with adult depression in the present study. Manganese is an often overlooked but important nutrient, required in small amounts for multiple essential functions in the body. However, too much of it could promote toxicity in the brainstem, leading to mental health conditions and improper cognitive performance (Samsel and Seneff 2015; Jain and Ferrando 2011; Solís-Vivanco et al. 2009). The underlying mechanism is likely through oxidative stress and excitotoxicity in the cerebellum, frontal cortex, caudate, globus pallidus, olfactory cortex, and putamen (Erikson et al. 2008). Tin, as a stannous chloride, can facilitate the neuromuscular transmission by accelerating the transmitter release from the nerve terminals in the mouse, in vitro and in vivo (Silva et al. 2002). It could, therefore, produce stimulation or depression of the central nervous system.

The neurotoxicity of phthalates could also be linked with mental health state such as anxiety or depression. In the limited animal research, it was preliminarily observed that benzyl butyl phthalate exposure caused a decrease in the number of

Table 3 Associations between urinary heavy metals and adult depression accounting for health events

	OR (95 % CI)[a]					
	Stroke	Liver disease	Infection	Injury	Asthma	Chronic bronchitis
Manganese	1.46 (0.99–2.16)	**1.47 (1.01–2.14)**	1.59 (0.92–2.74)	1.60 (0.94–2.71)	**1.49 (1.01–2.21)**	**1.51 (1.04–2.17)**
Tin	1.30 (0.99–1.70)	**1.31 (1.02–1.69)**	1.33 (0.93–1.90)	1.33 (0.94–1.87)	**1.30 (1.00–1.71)**	**1.31 (1.00–1.71)**
	Taste disorder	Smell disorder	Diabetes	Thyroid disorder	Heart failure	Arthritis
Manganese	1.64 (0.92–2.93)	1.43 (0.84–2.44)	**1.50 (1.02–2.21)**	1.45 (0.99–2.12)	**1.48 (1.01–2.15)**	**1.49 (1.01–2.21)**
Tin	1.35 (0.94–1.92)	**1.34 (1.01–1.77)**	1.30 (0.99–1.69)	1.28 (0.98–1.68)	1.30 (0.99–1.70)	1.30 (0.98–1.72)

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

Table 4 Associations between urinary phthalates (one third of the study population) and adult depression

(ng/L)	No depression (n=1395)	Depression (n=113)	OR (95 % CI)[a]	P value
Mono(carboxyoctyl)	52.1±119.3	34.7±59.6	1.04 (0.87–1.24)	0.669
Mono(carboxynonyl)	4.6±13.2	8.1±56.6	1.09 (0.89–1.34)	0.399
Mono-2-ethyl-5-carboxypentyl	24.9±65.3	25.0±60.7	**1.22 (1.00–1.48)**	**0.051**
Mono-n-butyl	20.3±84.3	30.6±56.9	**1.33 (1.14–1.54)**	**0.001**
Mono-(3-carboxypropyl)	15.6±105.0	7.6±19.6	1.04 (0.87–1.23)	0.665
Mono-ethyl	210.7±991.0	196.5±441.4	1.11 (0.91–1.36)	0.268
Mono-(2-ethyl-5-hydroxyhexyl)	17.5±55.6	16.2±39.4	1.22 (0.95–1.58)	0.111
Mono-(2-ethyl)-hexyl	3.3±8.3	3.3±11.6	1.11 (0.87–1.42)	0.386
Mono-isobutyl	11.5±22.8	15.4±19.0	**1.23 (0.99–1.51)**	**0.055**
Mono-n-methyl	3.4±20.3	4.7±11.4	1.02 (0.84–1.25)	0.805
Mono-isononyl	4.2±14.3	3.5±9.7	1.01 (0.81–1.26)	0.924
Mono-(2-ethyl-5-oxohexyl)	10.5±27.5	10.4±26.0	1.17 (0.91–1.50)	0.211
Mono-benzyl	8.7±15.9	13.8±26.0	**1.29 (1.00–1.67)**	**0.047**
Cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester	0.4±0.9	0.8±3.8	0.81 (0.46–1.40)	0.421

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

neurotransmitters, which in turn downregulates the levels of CREB phosphorylation by the cAMP/protein kinase A (PKA)-mediated signaling (Min et al. 2014). In the present study, further observations were made on other phthalate metabolites including mono-2-ethyl-5-carboxypentyl, mono-n-butyl, mono-isobutyl, and mono-benzyl that would need future experimental research to confirm or refute. In addition, urinary PAHs were found to be associated with adult depression by using a large human sample for the first time. It is known that exposure to PAHs occurs through one of the following routes: inhalation, ingestion with or without aspiration, or dermal exposure. Inhalational abuse is associated with central nervous system depression, metabolic acidosis, and arrhythmia, although the exact mechanism of the CNS depression is unknown (Tormoehlen et al. 2014). Some experimental evidence could have also suggested effects on NMDA, dopamine and GABA receptors.

Strengths and limitations

The present study has a few strengths. First, this study was conducted in a large and nationally representative human

Table 5 Associations between urinary phthalates and adult depression accounting for health events

	OR (95 % CI)[a]					
	Stroke	Liver disease	Infection	Injury	Asthma	Chronic bronchitis
Mono-2-ethyl-5-carboxypentyl	**1.22 (1.00–1.48)**	**1.23 (1.00–1.51)**	1.27 (0.86–1.86)	1.27 (0.88–1.82)	**1.22 (1.00–1.48)**	**1.24 (1.01–1.52)**
Mono-n-butyl	**1.32 (1.14–1.54)**	**1.34 (1.15–1.57)**	**1.23 (1.02–1.48)**	**1.23 (1.02–1.47)**	**1.33 (1.14–1.54)**	**1.32 (1.13–1.55)**
Mono-isobutyl	**1.23 (1.00–1.51)**	**1.25 (1.02–1.52)**	1.25 (0.92–1.71)	1.25 (0.93–1.69)	**1.23 (1.00–1.51)**	1.23 (0.98–1.54)
Mono-benzyl	**1.30 (1.01–1.68)**	**1.31 (1.01–1.70)**	1.34 (0.93–1.93)	1.32 (0.92–1.90)	**1.29 (1.00–1.67)**	**1.32 (1.01–1.71)**
	Taste disorder	Smell disorder	Diabetes	Thyroid disorder	Heart failure	Arthritis
Mono-2-ethyl-5-carboxypentyl	1.33 (0.89–1.98)	1.29 (0.91–1.84)	**1.23 (1.00–1.51)**	**1.21 (1.01–1.46)**	**1.23 (1.01–1.50)**	**1.21 (1.00–1.45)**
Mono-n-butyl	**1.26 (1.03–1.53)**	**1.23 (1.00–1.50)**	**1.34 (1.13–1.57)**	**1.34 (1.15–1.56)**	**1.34 (1.15–1.55)**	**1.35 (1.17–1.57)**
Mono-isobutyl	1.27 (0.93–1.72)	1.28 (0.94–1.74)	**1.25 (1.00–1.56)**	**1.25 (1.01–1.55)**	**1.23 (1.00–1.52)**	1.24 (0.99–1.54)
Mono-benzyl	1.34 (0.92–1.96)	1.34 (0.95–1.90)	1.30 (0.99–1.72)	**1.30 (1.02–1.65)**	**1.29 (1.00–1.67)**	**1.28 (1.01–1.63)**

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

Table 6 Associations between urinary polyaromatic hydrocarbons (one third of the study population) and adult depression

(ng/L)	No depression (n=1395)	Depression (n=113)	OR (95 % CI)[a]	P value
2-Hydroxyfluorene	554.9±1013.5	1083.7±1466.7	**1.45 (1.23–1.70)**	**<0.001**
3-Hydroxyfluorene	273.2±583.6	513.3±781.6	**1.37 (1.18–1.58)**	**<0.001**
9-Hydroxyfluorene	498.8±877.8	744.5±994.8	**1.40 (1.13–1.72)**	**0.004**
1-Hydroxyphenanthrene	198.3±299.3	230.2±212.9	**1.30 (1.06–1.59)**	**0.015**
2-Hydroxyphenanthrene	107.6±160.1	130.4±119.2	**1.35 (1.08–1.69)**	**0.012**
3-Hydroxyphenanthrene	119.4±239.0	158.8±190.4	**1.38 (1.15–1.65)**	**0.001**
1-Hydroxypyrene	200.4±345.8	257.7±308.5	**1.36 (1.12–1.65)**	**0.004**
1-Hydroxynaphthalene (1-naphthol)	21818.3±372562.3	278161.2±1923832.0	**1.32 (1.13–1.55)**	**0.002**
2-Hydroxynaphthalene (2-naphthol)	8514.7±11812.2	11598.4±12717.3	**1.31 (1.02–1.70)**	**0.037**
4-Hydroxyphenanthrene	34.4±52.0	42.0±39.5	1.35 (0.99–1.85)	0.060

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

sample with mixed ethnicities and socioeconomic status in recent years. Second, this is the first time examining the associations of urinary PAHs and phthalates and adult depression. However, there are still some limitations that cannot be ignored. First, there could still be other emerging chemicals from the living environments that we might not yet know

Table 7 Associations between urinary polyaromatic hydrocarbons and adult depression accounting for health events

	OR (95 % CI)[a]					
	Stroke	Liver disease	Infection	Injury	Asthma	Chronic bronchitis
2-Hydroxyfluorene	**1.46 (1.24–1.72)**	**1.46 (1.25–1.70)**	**1.37 (1.02–1.85)**	**1.36 (1.02–1.82)**	**1.45 (1.24–1.70)**	**1.42 (1.18–1.71)**
3-Hydroxyfluorene	**1.37 (1.18–1.60)**	**1.38 (1.19–1.60)**	1.27 (0.95–1.68)	1.26 (0.96–1.64)	**1.37 (1.19–1.58)**	**1.34 (1.13–1.59)**
9-Hydroxyfluorene	**1.41 (1.14–1.73)**	**1.41 (1.15–1.73)**	**1.43 (1.08–1.89)**	**1.42 (1.06–1.91)**	**1.42 (1.15–1.76)**	**1.39 (1.14–1.71)**
1-Hydroxyphenanthrene	**1.31 (1.07–1.60)**	**1.32 (1.09–1.59)**	1.27 (0.94–1.71)	1.26 (0.93–1.72)	**1.32 (1.07–1.64)**	**1.30 (1.06–1.59)**
2-Hydroxyphenanthrene	**1.37 (1.10–1.71)**	**1.37 (1.09–1.72)**	1.33 (0.93–1.91)	1.33 (0.93–1.88)	**1.37 (1.08–1.73)**	**1.34 (1.06–1.68)**
3-Hydroxyphenanthrene	**1.40 (1.17–1.66)**	**1.40 (1.17–1.67)**	1.30 (0.95–1.77)	1.28 (0.95–1.73)	**1.40 (1.16–1.69)**	**1.38 (1.15–1.66)**
1-Hydroxypyrene	**1.37 (1.13–1.67)**	**1.37 (1.13–1.66)**	1.30 (0.93–1.80)	1.28 (0.94–1.74)	**1.37 (1.13–1.67)**	**1.35 (1.09–1.66)**
1-Hydroxynaphthalene (1-naphthol)	**1.31 (1.11–1.55)**	**1.33 (1.12–1.57)**	**1.36 (1.11–1.68)**	**1.35 (1.09–1.68)**	**1.32 (1.12–1.56)**	**1.32 (1.12–1.55)**
2-Hydroxynaphthalene (2-naphthol)	**1.32 (1.01–1.71)**	**1.32 (1.03–1.70)**	1.37 (0.96–1.96)	1.35 (0.95–1.91)	**1.32 (1.03–1.70)**	**1.30 (1.00–1.69)**
4-Hydroxyphenanthrene	**1.37 (1.01–1.86)**	1.36 (0.99–1.88)	1.35 (0.89–2.06)	1.34 (0.87–2.07)	1.36 (0.99–1.88)	1.34 (0.97–1.84)
	Taste disorder	Smell disorder	Diabetes	Thyroid disorder	Heart failure	Arthritis
2-Hydroxyfluorene	**1.34 (1.001–79)**	**1.35 (1.01–1.80)**	**1.45 (1.22–1.73)**	**1.47 (1.26–1.72)**	**1.45 (1.23–1.71)**	**1.47 (1.24–1.74)**
3-Hydroxyfluorene	1.23 (0.95–1.61)	1.27 (0.98–1.64)	**1.37 (1.17–1.61)**	**1.39 (1.19–1.62)**	**1.37 (1.18–1.59)**	**1.38 (1.19–1.60)**
9-Hydroxyfluorene	**1.40 (1.06–1.85)**	**1.41 (1.04–1.90)**	**1.41 (1.15–1.75)**	**1.39 (1.14–1.70)**	**1.41 (1.15–1.72)**	**1.41 (1.14–1.75)**
1-Hydroxyphenanthrene	1.23 (0.94–1.62)	1.26 (0.92–1.73)	**1.31 (1.06–1.61)**	**1.29 (1.07–1.55)**	**1.31 (1.08–1.60)**	**1.31 (1.07–1.59)**
2-Hydroxyphenanthrene	1.32 (0.93–1.87)	1.31 (0.91–1.90)	**1.35 (1.06–1.72)**	**1.36 (1.10–1.68)**	**1.36 (1.09–1.70)**	**1.36 (1.08–1.72)**
3-Hydroxyphenanthrene	1.28 (0.94–1.73)	1.29 (0.96–1.74)	**1.39 (1.14–1.69)**	**1.40 (1.19–1.65)**	**1.40 (1.17–1.66)**	**1.38 (1.16–1.66)**
1-Hydroxypyrene	1.28 (0.93–1.76)	1.31 (0.94–1.83)	**1.38 (1.13–1.67)**	**1.36 (1.14–1.63)**	**1.36 (1.12–1.65)**	**1.36 (1.12–1.64)**
1-Hydroxynaphthalene (1-naphthol)	**1.32 (1.10–1.59)**	**1.28 (1.12–1.46)**	**1.34 (1.14–1.57)**	**1.34 (1.14–1.59)**	**1.32 (1.13–1.55)**	**1.33 (1.13–1.56)**
2-Hydroxynaphthalene (2-naphthol)	1.35 (0.94–1.95)	1.36 (0.95–1.96)	**1.33 (1.03–1.72)**	**1.33 (1.05–1.69)**	**1.32 (1.03–1.70)**	**1.32 (1.01–1.73)**
4-Hydroxyphenanthrene	1.32 (0.88–1.97)	1.39 (0.90–2.15)	1.35 (0.98–1.86)	**1.35 (1.00–1.84)**	**1.37 (1.00–1.88)**	1.36 (0.99–1.88)

Numbers highlighted in bold denote significance

[a] Adjusted for age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine, and survey design

and would need future research to further identify and examine. Second, the data on recurrence of depression was not available (Michel et al. 2007). Third, the causality cannot be established in the present study due to the cross-sectional study design in nature. Therefore, future studies with longitudinal and/or experimental study designs to confirm or refute the observations obtained in the present study and, if at all, to understand the persisting risk effects along the life course from those mentioned above environmental chemicals would be suggested.

Conclusion

Urinary heavy metals (manganese and tin), phthalates, and PAHs but not arsenic, phenols, parabens, pesticides, perchlorate, nitrate, thiocyanate and polyfluorinated compounds were associated with adult depression, being independent of historical health events. Further elimination of such harmful chemicals might need to be considered in future mental health and environmental policies.

Conflict of interest None.

References

Ball A, Truskewycz A (2013) Polyaromatic hydrocarbon exposure: an ecological impact ambiguity. Environ Sci Pollut Res Int 20: 4311–4326

Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lépine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC (2011) Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 9:90–106

Erikson KM, Dorman DC, Lash LH, Aschner M (2008) Duration of airborne-manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. Neurotoxicology 29:377–385

Jain S, Ferrando SJ (2011) Manganese neurotoxicity presenting with depression, psychosis and catatonia. Psychosomatics 52:74–77

Kajta M, Wójtowicz AK (2013) Impact of endocrine-disrupting chemicals on neural development and the onset of neurological disorders. Pharmacol Rep 65:1632–1639

Luebke RW, Hodson PV, Faisal M, Ross PS, Grasman KA, Zelikoff J (1997) Aquatic pollution-induced immunotoxicity in wildlife species. Fundam Appl Toxicol 37:1–15

Manea L, Gilbody S, McMillan D (2012) Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. CMAJ 184:E191–E196

Michel TM, Frangou S, Thiemeyer D, Camara S, Jecel J, Nara K, Brunklaus A, Zoechling R, Riederer P (2007) Evidence for oxidative stress in the frontal cortex in patients with recurrent depressive disorder—a postmortem study. Psychiatry Res 151:145–150

Min A, Liu F, Yang X, Chen M (2014) Benzyl butyl phthalate exposure impairs learning and memory and attenuates neurotransmission and CREB phosphorylation in mice. Food Chem Toxicol 71:81–89

Mulligan KJ, Davidson TM, Caruso JA (1990) Feasibility of the direct analysis of urine by inductively coupled argon plasma mass-spectrometry for biological monitoring of exposure to metals. J Anal At Spectrom 5:301–306

Samsel A, Seneff S (2015) Glyphosate, pathways to modern diseases III: manganese, neurological diseases, and associated pathologies. Surg Neurol Int 6:45

Shiue I (2013a) Urine phthalate concentrations are higher in people with stroke: United States National Health and Nutrition Examination Surveys (NHANES), 2001–2004. Eur J Neurol 20:728–731

Shiue I (2013b) Association of urinary arsenic, heavy metal, and phthalate concentrations with food allergy in adults: National Health and Nutrition Examination Survey, 2005–2006. Ann Allergy Asthma Immunol 111:421–423

Shiue I (2013c) Urinary environmental chemical concentrations and vitamin D are associated with vision, hearing, and balance disorders in the elderly. Environ Int 53:41–46

Shiue I (2014a) Urinary thiocyanate concentrations are associated with adult cancer and lung problems: US NHANES, 2009–2012. Environ Sci Pollut Res Int. doi:10.1007/s11356-014-3777-8

Shiue I (2014b) Higher urinary heavy metal, phthalate, and arsenic but not parabens concentrations in people with high blood pressure, U.S. NHANES, 2011–2012. Int J Environ Res Public Health 11:5989–5999

Shiue I (2015a) Are urinary polyaromatic hydrocarbons associated with adult hypertension, heart attack, and cancer? USA NHANES, 2011–2012. Environ Sci Pollut Res Int. doi:10.1007/s11356-015-4922-8

Shiue I (2015b) Urinary heavy metals, phthalates, phenols, thiocyanate, parabens, pesticides, polyaromatic hydrocarbons but not arsenic or polyfluorinated compounds are associated with adult oral health: USA NHANES, 2011–2012. Environ Sci Pollut Res Int. doi: 10.1007/s11356-015-4749-3

Shiue I (2015c) Arsenic, heavy metals, phthalates, pesticides, hydrocarbons and polyfluorinated compounds but not parabens or phenols are associated with adult remembering condition: US NHANES, 2011–2012. Environ Sci Pollut Res Int 22:6381–6386

Silva CR, Oliveira MB, Melo SF, Dantas FJ, de Mattos JC, Bezerra RJ, Caldeira-de-Araujo A, Duatti A, Bernardo-Filho M (2002) Biological effects of stannous chloride, a substance that can produce stimulation or depression of the central nervous system. Brain Res Bull 59:213–216

Silva MJ, Samandar E, Preau JL Jr, Reidy JA, Needham LL, Calafat AM (2007) Quantification of 22 phthalate metabolites in human urine. J Chromatogr B Analyt Technol Biomed Life Sci 860:106–112

Solís-Vivanco R, Rodríguez-Agudelo Y, Riojas-Rodríguez H, Ríos C, Rosas I, Montes S (2009) Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. Environ Toxicol Pharmacol 28:172–178

Spitzer RL, Kroenke K, Williams JB (1999) Validation and utility of a self-report version of prime MD: the PHQ primary care study. JAMA 282:1737–1744

Tormoehlen LM, Tekulve KJ, Nañagas KA (2014) Hydrocarbon toxicity: a review. Clin Toxicol (Phila) 52:479–489

Vahter ME (1988) Arsenic. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR (eds) Biological monitoring of toxic metals. Plenum Press, New York, pp 303–21

Woodruff TJ, Zota AR, Schwartz JM (2011) Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect 119(6):878–85

Xu X, Cook RL, Ilacqua VA, Kan H, Talbott EO, Kearney G (2010) Studying associations between urinary metabolites of polycyclic aromatic hydrocarbons (PAHs) and cardiovascular diseases in the United States. Sci Total Environ 408:4943–4948

Ye X, Kuklenyik Z, Needham LL, Calafat AM (2005) Automated on-line column-switching HPLC-MS/MS method with peak focusing for the determination of nine environmental phenols in urine. Anal Chem 77:5407–5413

Ye X, Kuklenyik Z, Bishop AM, Needham LL, Calafat AM (2006) Quantification of the urinary concentrations of parabens in humans by on-line solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 844:53–59