



Occupation, Environment, and Mental Health

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Occupation, Environment, and Mental Health

Alexander Chu Wu

**A Dissertation Submitted to the Faculty of
The Harvard T.H. Chan School of Public Health
in Partial Fulfillment of the Requirements
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Occupation, Environment, and Mental Health

ABSTRACT

Despite a decades-old call for better understanding of the role of environmental pollutant influences on mental health, a comprehensive review of the literature on non-occupational exposures to environmental pollutants and adult mental health has not been performed. Second, the Germanwings Flight 9525 crash has brought the sensitive subject of airline pilot mental health to the forefront in aviation. Third, scientists use biomarkers to evaluate metal exposures. One biomarker, toenails, is easily obtained and minimally invasive, but less commonly used as a biomarker of exposure. Their utility will depend on understanding characteristics of their variation in a population over time. Fourth, toenails are less commonly used as a biomarker of exposure and has not been evaluated on its relationship with psychiatric outcomes; particularly depression and anxiety.

We reviewed the existing literature on environmental pollutant exposures and three specific mental health outcomes (depression, anxiety, and suicide) published on PubMed, Embase, Web of Science, and PsychINFO through the end of year 2016. Second, we conducted a descriptive cross-sectional study via an anonymous web-based survey administered to airline pilots between April and December 2015. Third, we utilized linear mixed models to assess correlation between toenail metal concentrations in multiple toenail samples from the same subject collected years apart among participants in the VA Normative Aging Study (NAS).

Fourth, we utilized multivariate linear and logistic mixed models to assess the association with five toenail metals and outcomes measured by the Brief Symptom Index (BSI).

The current literature, although limited, clearly suggests many kinds of environmental exposures may be risk factors for depression, anxiety, and suicide. Overall, the strongest studies appear to be of air pollution exposure. Second, hundreds of pilots currently flying are managing depressive symptoms perhaps without the possibility of treatment due to the fear of negative career impacts. Third, our results suggest that lead, arsenic, cadmium, manganese, and mercury levels from toenail clippings can reasonably reflect exposures over several years in elderly men in the NAS. Fourth, our study tentatively suggests that toenails from NAS participants may be an important biomarker to measure the association between metals and symptoms of depression or anxiety.

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CHAPTER 1

A Review of Non-occupational Exposures to Environmental Pollutants and Adult Mental Health: Depression, Anxiety, and Suicide.

Alexander C. Wu

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Marc G. Weisskopf

Abstract

Background: Despite a decades-old call for better understanding of the role of environmental pollutant influences on mental health, and the tremendous public health burden of mental health, this issue receives far less attention than cognitive effects of pollutants. A comprehensive review of the literature on non-occupational exposures to environmental pollutants and adult mental health has not been performed.

Objectives: We conducted a Scoping review of the body of literature on non-occupational environmental pollutant exposures and adult mental health—specifically depression, anxiety, and suicide—among four major journal databases.

Methods: We reviewed and summarized the existing literature on environmental pollutant exposures (including metals, air pollution, pesticides, noise, and secondhand smoke) and three specific mental health outcomes (depression, anxiety, and suicide) published on PubMed, Embase, Web of Science, and PsychINFO through the end of year 2016.

Results: There were 90 articles that met our criteria for further review. Of these, we found 68 articles on depression, 28 on anxiety, and 23 on suicide (some articles covered multiple outcomes). Majority (47 articles) of included articles were published after 2011 with the earliest article published in 1967.

Conclusion: The current literature, although limited, clearly suggests many kinds of environmental exposures may be risk factors for depression, anxiety, and suicide. Overall, the strongest studies appear to be of air pollution exposure. For other pollutants, while results are suggestive, important limitations exist with many of the studies. Gaps in the body of research include a need for more longitudinal studies, studies that can measure cumulative exposures as well as shorter-term ones, and studies that reduce the possibility of reverse causation.

Introduction

The burden of mental disorders on public health is tremendous. An estimated 905 million cases of mental disorders occurred worldwide in 2015 (G. B. D. Disease Injury, 2016).

Depression is the third most important cause of disease burden worldwide and affects about 300 million people globally (CDC, 2016; Mathers, Fat, Boerma, & World Health, 2008; WHO, 2017).

In 2010, depression accounted for the most disability-adjusted life years (DALYs) among mental and substance use disorders—accounting for approximately 74.5 million disability adjusted life years worldwide (Whiteford et al., 2013). In the US, 17% of people have Major Depressive Disorder (MDD) over their lifetime (Kessler, Berglund, et al., 2005) and 7% have experienced an MDD in the past year (Kessler, Chiu, Demler, & Walters, 2005; Reeves et al., 2011).

There are many potential risk factors for MDD: Women are at higher risk than men (Whiteford et al., 2013). Those age 30 to 59 years, in particular, have higher risk than other age groups (Kessler, Berglund, et al., 2005). Lower education attainment, unemployment, and adverse childhood experiences place people at higher risk (Blazer, Kessler, McGonagle, & Swartz, 1994; Chapman et al., 2004). Experiencing one episode of MDD puts an individual at 50% risk of experiencing another, and the subsequent risk increases with additional episodes (NIMH, 1985).

Improved understanding of the role of modifiable risk factors for symptoms of MDD could have great health, and associated financial, benefits. Financial costs from MDD to employers in the US in 2000 measured \$83 billion, with the majority (62% or \$52 billion) due to lost workplace productivity (P. E. Greenberg et al., 2003). Other studies estimate employers lose

27 workdays per worker per year due to MDD; two-thirds of which is due to “presenteeism”—workers are present but are less productive (Kessler et al., 2006). Furthermore, the cost of MDD to employers in lost work days is as great or greater than the cost of many other common medical conditions, including heart disease, diabetes, or back problems (Druss, Rosenheck, & Sledge, 2000). The personal costs from MDD include significant clinical morbidity, increased mortality from suicide, and loss of quality of life (P. S. Wang, Simon, & Kessler, 2003).

Anxiety disorders are the most common types of psychiatric disorder in the general population and affect around 270 million people worldwide (G. B. D. Disease Injury, 2016; Kessler, Berglund, et al., 2005). Anxiety disorders are characterized by disruptive fear, worry, and related behavioral disturbances such as avoidance or physical sensations of hyperarousal (Mathers et al., 2008). Approximately 29% of people have an anxiety disorder in their lifetime and 18% have experienced an anxiety disorder in the past year (Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005). Anxiety disorders are associated with reduced productivity and increased psychiatric and non-psychiatric medical care, absenteeism, and risk of suicide (Lépine, 2002). The monetary cost of anxiety disorders is also substantial; in the US, the annual direct cost of anxiety disorders in the 1990s has been estimated to be \$42.3bn (P. Greenberg et al., 1999).

Women have a higher prevalence of anxiety disorders than men (McLean, Asnaani, Litz, & Hofmann, 2011) and the onset for most anxiety disorders is commonly in adolescence or young adulthood. However, the incidence of anxiety disorders remains substantial in midlife, and new cases continue to arise into later life, especially in the case of generalized anxiety disorder (Kessler, Berglund, et al., 2005). Although numerous pharmacologic and non-pharmacologic

therapies are available, remission is not always possible. Many patients have persistent symptoms despite use of first line treatments (Lanouette & Stein, 2010).

In 2012, there was an estimated 804,000 suicide deaths worldwide with an annual age-standardized suicide rate of 11.4 per 100,000 people (15.0 for males, 8.0 for females) (WHO, 2014). Although suicides accounted for about 1.4% of deaths globally in 2012, it is the second leading cause of death after traffic accidents among young-adults age 15 to 29 years and the fifth leading cause of death among adults age 30 to 49 years (CDC, 2016). In 2009, suicides accounted for 36,909 deaths (age-adjusted rate of 11.75 per 100,000 people) in the U.S. and were the 10th leading cause of death among people 10 years and older (CDC, 2014). The most recent data from the CDC reports 44,193 deaths in 2015 and an age-adjusted rate of 13.0 per 100,000 were due to suicide in 2014, which represented 21.3% of all injury deaths (CDC, 2015, 2017a, 2017b).

Anxiety and MDD are somewhat lower in the elderly (each occur in an estimated 5% of persons over 65 (CDC, 2015, 2016) but much higher percentages of older people suffer from clinically relevant depressive (10-30%) or anxiety (~20%) symptoms that do not meet full diagnostic criteria (Druss et al., 2000; Kessler et al., 2006; Lépine, 2002; P. S. Wang et al., 2003). These symptoms are associated with excess morbidity and significant functional impairment (American Psychiatric & American Psychiatric Association, 2013; CDC, 2014, 2015; P. Greenberg et al., 1999; Mathers et al., 2008) and greater risk of subsequent depression and anxiety clinical diagnoses (Hasin, Fenton, & Weissman, 2011; Kessler et al., 2009; Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005; Whiteford et al., 2013). Furthermore, depression and anxiety increase the risk for suicide and all-cause mortality; substantially detrimentally affect physical, mental, and social functioning; are associated with worse cognitive

functioning; and lead to greater healthcare service use and costs (Blazer et al., 1994; Druss et al., 2000; P. E. Greenberg et al., 2003; Kessler et al., 2006; Stewart, Ricci, Chee, Hahn, & Morganstein, 2003; P. S. Wang et al., 2003).

Exposure to environmental contaminants may be important modifiable—individually and through public policy—risk factors for depression, anxiety, and suicide. Many environmental toxicants have known effects on neural systems that underlie such negative affects, and in many occupational and other high contaminant exposure settings strong associations between toxicants and mood or psychological distress have been seen (Chapman et al., 2004; Lépine, 2002; NIMH, 1985). Despite a decades old call by a panel convened by the National Institute for Mental Health to study the link between environmental pollution and mental health, this area of research has received limited attention (Williams, Leyman, Karp, & Wilson, 1973). We set out to systematically review the literature on non-occupational exposures to toxicants and risk of depression, anxiety, and suicide.

Methods

We conducted a scoping review (Arksey & O'Malley, 2005; Armstrong, Hall, Doyle, & Waters, 2011) by selecting, collecting, and summarizing the existing literature on environmental pollutants and mental health outcomes: depression, anxiety, and suicide. We defined “environmental” as a person’s surroundings, and “pollutants” as metals, pesticides, particles (air pollution, secondhand smoke), noise, and radiation that pollute a person’s surroundings. Our definition of “pollutants” did not include personal lifestyle factors such as diet, medications, or psychosocial factors, nor did we consider biological agents (e.g., viruses, bacteria, and mold). We initiated a search of journal article databases with guidance from an experienced research librarian from the Francis A. Countway Library of Medicine. We searched for English articles on

human subjects published through December 31, 2016. We utilized four databases: PubMed (US National Library of Medicine, Bethesda, Maryland), Web of Science (Thomson Reuters Corporation, New York, New York), PsychINFO (American Psychological Association, Washington, D.C.), and Embase (Elsevier, Amsterdam, Netherlands). Figure 1.1 details search terms used in each database.

After removing duplicates, we excluded articles that were the following: not human studies, did not study environmental pollutants, and did not study depression, anxiety, or suicide. We excluded articles with assessments in childhood (≤ 18 years) for depression and anxiety. Because of the smaller literature on suicide, we did not impose an age restriction on those articles. Other reasons for exclusion were studies on acute poisonings or workers, review papers, commentaries, conference abstracts, dissertations, and case studies. Additionally, we hand searched reference lists in review papers and journal articles captured by our search terms for additional relevant papers. We excluded articles on general psychological impacts because they lacked specific evaluation of the outcomes of interest in our review. We also excluded articles on perception of negative health outcomes from environmental exposure due to an environmental health incident or disaster in part because typically specific pollutant exposures are not identified. In addition, in such settings subjects are aware of the incident and it becomes hard to determine whether exposures to a pollutant—rather than the perception of living near the location of the incident where the pollutant was released—is associated with the mental health outcome. We decided to include noise due to growing public concern on its negative health effects despite the concern that this exposure is also perceived by the individuals.

PubMed Articles (n=1412) "Environmental Pollution"[Mesh] OR Pollut*[tw] OR ((Environment*[tw] OR water[tw] OR Hazardous[tw]) AND (waste[tw] OR radioactive*[tw] OR radiation[tw])) AND "Depression"[Mesh] OR "Depression"[tiab] OR "Depressions"[tiab] OR "Depressive"[tiab] OR "Anxiety"[Mesh] OR "Anxiety"[tiab] OR "Catastrophization"[tiab] OR "Hypervigilance"[tiab] OR "Suicide"[Mesh] OR "Suicide"[tiab] OR "Internalizing"[tiab] OR "externalizing"[tiab] AND "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] OR "Epidemiologic Research Design"[Mesh] OR "Epidemiologic Study Characteristics as Topic"[Mesh] OR "Depression/epidemiology"[Mesh] OR "Anxiety/epidemiology"[Mesh] NOT ("invertebrates"[Mesh] OR "Rodentia"[Mesh]) Filters: date to Dec. 31, 2016	Embase Articles (n=1292) 'pollution and pollution related phenomena'/exp OR 'pollut*':ab,ti OR (('environment*' OR 'water' OR 'hazardous') AND ('waste' OR 'radioactive*' OR 'radiation')) AND 'depression'/exp OR 'depression':ab,ti OR 'depressions':ab,ti OR 'depressive':ab,ti OR 'anxiety'/exp OR 'anxiety disorder'/exp OR 'anxiety':ab,ti OR 'catastrophization':ab,ti OR 'hypervigilance':ab,ti OR 'suicide'/exp OR 'suicidal behavior'/exp OR 'suicide':ab,ti OR 'internalizing':ab,ti OR 'externalizing':ab,ti AND 'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ab,ti OR 'compared':ab,ti OR 'groups':ab,ti OR 'case control':ab,ti OR 'multivariate':ab,ti AND (1952:py OR 1958:py OR 1959:py OR 1960:py OR 1961:py OR 1962:py OR 1963:py OR 1964:py OR 1965:py OR 1966:py OR 1967:py OR 1969:py OR 1970:py OR 1971:py OR 1972:py OR 1973:py OR 1974:py OR 1975:py OR 1976:py OR 1977:py OR 1978:py OR 1979:py OR 1980:py OR 1981:py OR 1982:py OR 1983:py OR 1984:py OR 1985:py OR 1986:py OR 1987:py OR 1988:py OR 1989:py OR 1990:py OR 1991:py OR 1992:py OR 1993:py OR 1994:py OR 1995:py OR 1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py)	Web of Science Articles (n=8455) TS=(Environmental pollution OR Pollut* OR air pollution OR water pollution OR pesticide* OR environmental exposure* OR environmental monitoring OR radiation OR noise OR waste water OR wastewater OR toxi* OR metal* OR pesticide* OR particle* OR particulate*) OR TS=((Environment* OR water OR Hazardous OR industrial OR solid OR radioactive) SAME (waste OR radioactive* OR radiation)) AND TS=(depression OR depressions OR depressive OR anxiety OR catastrophization OR hypervigilance OR hypervigilant OR suicid* OR internalizing OR externalizing) AND TS=((cohort NEAR/1 studies) OR (case NEAR/1 control) OR (comparative NEAR/1 study) OR (risk NEAR/1 factors) OR cohort OR compared OR groups OR multivariate OR (cross NEAR/1 sectional)) Filters: date 1900 - 2016	PsychINFO Articles (n=891) DE "Hazardous Materials" OR DE "Insecticides" OR DE "Teratogens" OR DE "Toxins" OR DE "Toxic Disorders" OR DE "Acute Alcoholic Intoxication" OR DE "Carbon Monoxide Poisoning" OR DE "Drug Induced Congenital Disorders" OR DE "Lead Poisoning" OR DE "Mercury Poisoning" OR DE "Narcosis" OR DE "Neuroleptic Malignant Syndrome" OR DE "Thyrototoxicosis" OR DE "Toxic Encephalopathies" OR DE "Toxic Hepatitis" OR DE "Toxic Psychoses" OR DE "Pollution" OR DE "Passive Smoking" OR DE "Prenatal Exposure" OR DE "Noise Effects" OR TX (pollut* OR ((Environment* OR water OR Hazardous) AND (waste OR radioactive* OR radiation))) AND DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Atypical Depression" OR DE "Bipolar Disorder" OR DE "Cyclothymic Personality" OR DE "Depression (Emotion)" OR DE "Euthymia" OR DE "Neurosis" OR DE "Childhood Neurosis" OR DE "Experimental Neurosis" OR DE "Occupational Neurosis" OR DE "Traumatic Neurosis" OR DE "Pseudodementia" OR DE "Seasonal Affective Disorder" OR DE "Anxiety" OR DE "Computer Anxiety" OR DE "Mathematics Anxiety" OR DE "Performance Anxiety" OR DE "Social Anxiety" OR DE "Speech Anxiety" OR DE "Test Anxiety" OR DE "Anxiety Disorders" OR DE "Acute Stress Disorder" OR DE "Castration Anxiety" OR DE "Death Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Separation Anxiety Disorder" OR DE "Anxiety Management" OR DE "Generalized Anxiety Disorder" OR DE "Panic" OR DE "Panic Attack" OR DE "Panic Disorder" OR DE "Externalization" OR DE "Internalization" OR DE "Introjection" OR DE "Suicide" OR DE "Assisted Suicide" OR DE "Attempted Suicide" OR DE "Suicidal Ideation" OR TX (depression OR depressions OR Depressive OR anxiety OR catastrophization OR hypervigilance OR suicide OR internalizing OR externalizing) AND TX ("case control" OR "comparative study" OR "comparative studies" OR "risk factor" OR "risk factors" OR cohort OR compared OR groups OR multivariate) Filters: publication year 1936-2016
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Figure 1.1. Journal database search terms utilized in reviewing studies on the associations between environmental contaminants and pollutants and mental health (depression, anxiety, suicide) among non-occupational cohorts.

Results

We identified 12050 articles: 1412, 1292, 8455, and 891 articles by searching PubMed, Embase, Web of Science, and PsychINFO, respectively. Of these, we found 11245 unique articles.

Following exclusions and hand searches among references we ended with 90 articles for further review (Figure 1.2.). Of these, we found 68 articles on depression, 28 on anxiety, and 23 on suicide (some articles covered multiple outcomes). Majority (47 articles) of included articles were published after 2011 with the earliest article published in 1967 (Figure 1.3). We present these articles organized by outcome and subdivided by exposure. We considered general quality of the articles, considering aspects such as type of study, sample size in determining measurement of association, exposure measurement, outcome measurement, adjusting for confounding variables, and potential for biases.

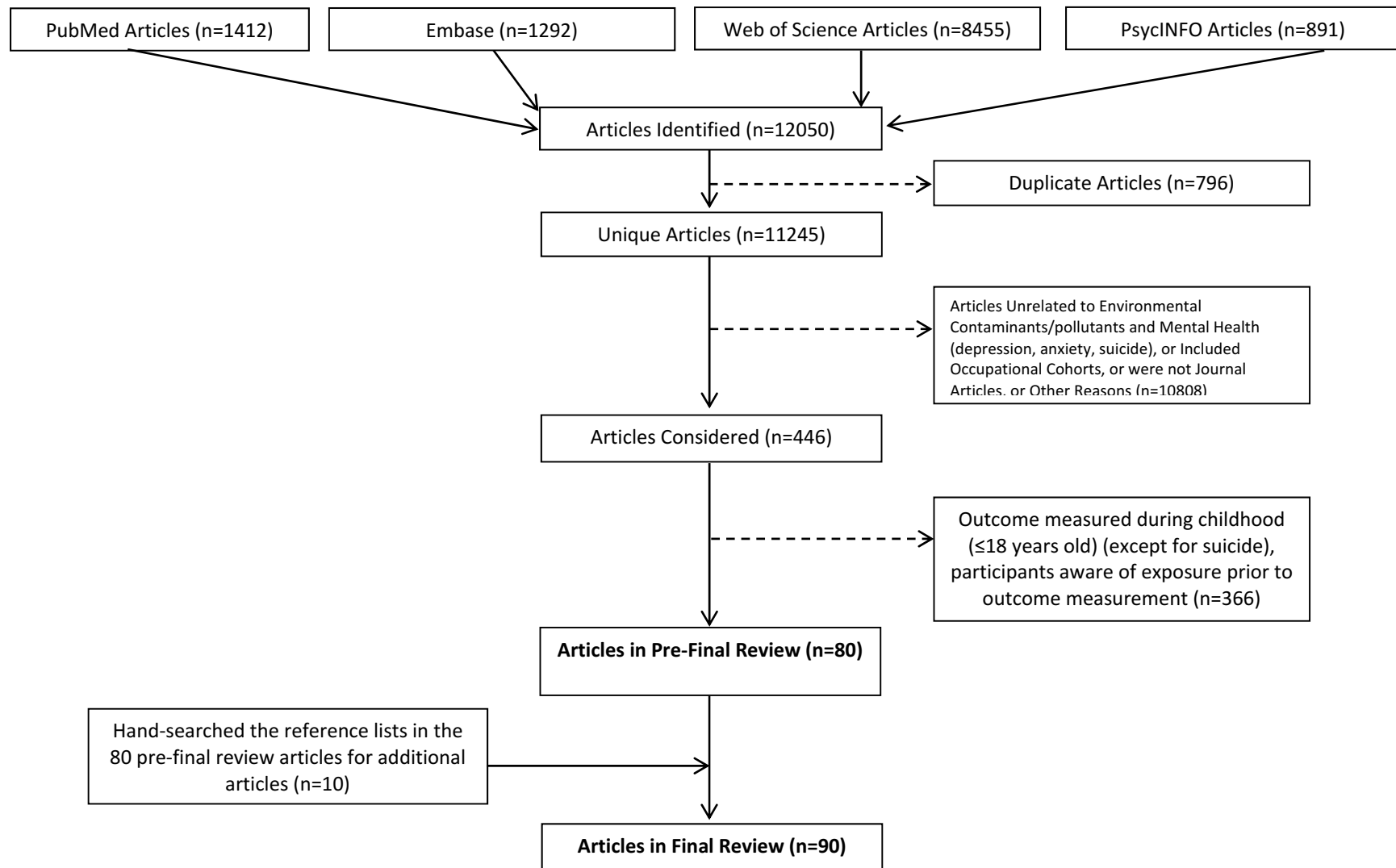


Figure 1.2. Article search and selection method utilized in reviewing studies on the associations between environmental contaminants/pollutants and mental health (depression, anxiety, suicide) among non-occupational cohorts. Solid lines represent articles kept and dashed lines denote dropped articles. Selection only included articles published up to Dec. 31, 2016.

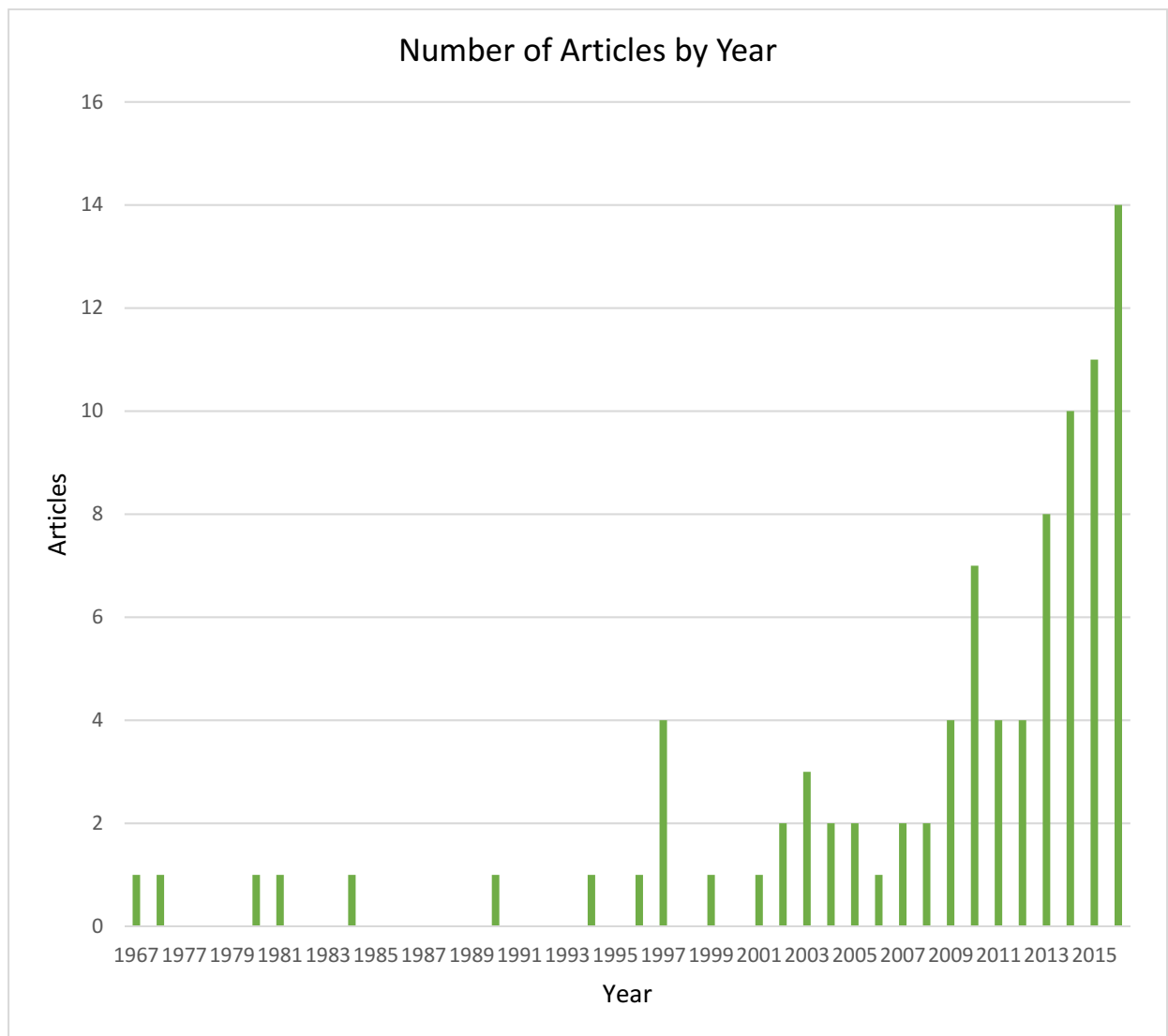


Figure 1.3. Number of articles included in the review by year (90 total articles, no articles from 1968-1975).

Depression

Metals

There were studies that examined exposure to metals and depression, and most involved concurrent assessment of exposure and outcome. All studies generally attempted to control for key variables like age, sex, and socioeconomic status (SES). Most of the studies utilized the National Health and Nutrition Examination Survey (NHANES) data for adults over 18 with metals measured in blood. The two studies that examined cadmium found positive associations with depression (Berk et al., 2014; Scinicariello & Buser, 2015). Two studies to examine mercury found negative associations with depression that one study suggested could be related to protection from fish consumption (Berk et al., 2014), although the other study attempted to control for fish consumption and fish oil intake (T. H. H. Ng, Mossey, & Lee, 2013). Manganese and tin, but not arsenic were found associated with depression in the one study to explore these metals (Shiue, 2015). Three studies examined lead with mixed results (Berk et al., 2014; Golub, Winters, & van Wijngaarden, 2010; Shiue, 2015). Two studies found no association, while one found risk of depression to increase slightly over the first three quartiles of blood lead, but decrease a bit in the highest quartile (Golub et al., 2010). All of these studies used the Patient Health Questionnaire (PHQ) 9 item scale to identify depression. Bouchard et al. (2009) was the only NHANES study of blood lead that used the Composite International Diagnostic Interview (CIDI)-defined major depressive disorder (MDD) as the outcome. A significant association was found between lead and MDD, although the association was much stronger when restricted to non-smokers. This could relate to increased exposure from more hand to mouth activity among smokers, but the smoking being a form of self-medication to reduce symptoms (and therefore

their CIDI score), highlighting the concern with such cross-sectional studies of the possibility of reverse causation.

Six other studies examined concurrent metal biomarkers in other settings. One study considered Hg among 83 women, forty of whom were recruited specifically for being amalgam sensitive based on their reported belief that Hg from their fillings affected their health (Bailer et al., 2001). Mental health was assessed with the SCL-90-R, and although depression was assessed, no results were reported for associations with blood, urine, or saliva Hg concentrations, presumably because no significant results were found. Another study recruited 50 people who complained of oral galvanism or mercury poisoning related to dental amalgams and 50 age, sex and zip code matched controls and considered depression symptoms measured by several different scales and blood, hair, and urine mercury levels (Bratel, Haraldson, & Ottosson, 1997). However, researchers found no difference in Hg levels in blood, urine, and hair between these groups. Reported symptoms thus were thought to be part of a broad spectrum of underlying mental disorders instead of mercury levels (Bratel et al., 1997). Although the authors reported no association between Hg levels and symptoms, they did not analyze the group as a whole, but rather the symptomatic patients and matched controls separately. A study in Southwestern Quebec among 273 men and women found an association between manganese and profile of mood states (POMS) and Brief Symptom Inventory (BSI) depression scores, but only among men over 50 (R. M. Bowler, Mergler, Sassine, Larribe, & Hudnell, 1999). A subsequent study of the same population suggested that there was an interaction with risk for alcohol use disorder such that those at higher risk showed a significant positive association between blood Mn and depression (Sassine, Mergler, Bowler, & Hudnell, 2002). Rhodes, Spiro, Aro, and Hu (2003) did not find an association between higher blood lead and BSI depression scores among older men in

the Normative Aging Study (NAS), but did find a significant positive association with a combined depression and anxiety score. The other study, among 395 elderly residents of Seoul, South Korea, found inconsistent associations between blood Cd and depression measured with the Short Form Generic Depression Scale test (SGDS-K) (Han, Lim, & Hong, 2016).

Three studies examined the association between drinking water arsenic and depression. Assuming measured drinking water levels reflect those in the past, these studies will capture past exposures somewhat better than concurrent blood concentrations. One in Wisconsin among 1185 residents older than 35 who reported drinking their well water for >20 years found people with drinking water arsenic concentration over 2 micrograms per liter (ug/L) had a higher likelihood of a self-reported history of depression (Zierold, Knobeloch, & Anderson, 2004). The other in India among 654 women found that those living in areas with high levels of endemic water arsenic (n=342) reported significantly worse scores on the Beck Depression Inventory Second Edition (BDI-II) compared with women in a non-endemic arsenic area (Mukherjee, Bindhani, Saha, Sinha, & Ray, 2014). The authors reported that the women were similar on many demographic and socioeconomic status variables, but those in the endemic arsenic area had a higher prevalence of several health conditions. Another study looked at groundwater selenium levels and depression among participants of Project FRONTIER, a cross sectional study of 585 participants in rural Texas (Johnson et al., 2013). Selenium levels in groundwater at residences were estimated based on Texas Water Development Board groundwater measurements with interpolation to residences using inverse distance weighting and depression was measured via the Geriatric Depression Scale (GDS-30). After adjusting for potential confounders, the findings showed significantly lower depression scores with higher selenium levels (Johnson et al., 2013).

One study compared 100 residents of a town in Ohio with identified elevated Mn air emissions from industrial emissions with 90 residents of a control town (Rosemarie M. Bowler et al., 2012). No difference between the groups was found in depression assessed with the Symptom Checklist-90-Revised (SCL-90-R).

Only three studies have used biomarkers of exposure that captured past exposures and the relation with depression. McFarlane et al. (2013) was a prospective study of 210 participants from the Port Pirie cohort study. Blood lead samples were collected from participants as children up to age 7 years and they were assessed for psychiatric disorders at 25-29 years of age via the CIDI. No significant adjusted association between average childhood blood lead levels and depression in adulthood was found. Rhodes et al. (2003), in addition to the blood lead results mentioned above, found that higher patella bone lead levels measured via K-shell X-Ray Fluorescence (KXRF) were associated with worse depression scores on the BSI among older men in the NAS, although not quite statistically significant. The study also found no association in tibia bone lead (a longer-term cumulative exposure measure). Lead in both bone types was significantly associated with a combined anxiety and depression measure. Eum et al. (2012) found that higher tibia bone lead concentrations measured with KXRF were associated with greater depression as measured via the Mental Health Index 5-item scale (MHI-5) among 617 older women consistently on hormone replacement therapy between menopause and the KXRF measurement (to limit variance in the relation between KXRF measurement and past lead exposure) in the Nurses' Health Study (NHS). Table 1.1 outlines the studies on depression and metals.

Table 1.1. Depression and exposure to metals

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bailer, 2001 Adverse health effects related to mercury exposure from dental amalgam fillings: Toxicological or psychological causes?	Women who had three or more amalgam fillings at time of examination (Jan 1997 to Dec 1998)	83, Women age 18-55 years	Symptoms of depression via Beck Depression Inventory (BDI)	Mercury in blood, urine, and saliva	None, utilized non-parametric analyses	Mann–Whitney U for non-parametric tests, chi-square for frequency comparisons, Pearson’s correlations	BDI Depression (global score) Amalgam sensitive: Mean 9.2 (SD 6.5) Non-sensitive: Mean 4.7 (SD 5.7) ANCOVA F= 9.75 p<0.05
Berk, 2014 Pop, heavy metal and the blues: Secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES national epidemiological survey	Adults who participated in one of the three waves (2005–2006, 2007–2008 and 2009–2010) of the NHANES	15140, Age 31-63 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Heavy metals in blood	Demographics and socioeconomic status (age, sex, poverty, family income, ethnicity and country of birth), cotinine levels and chronic medical illness, blood levels of cholesterol, glucose and creatinine	Binary Poisson regression with robust estimation of SE	Risk ratios for blood heavy metals and depression: Cadmium 1.48 (95% CI: 1.16,1.90) Lead 0.81 (95% CI: 0.64, 1.02), Mercury 0.62 (95% CI: 0.50, 0.78), frequency of fish consumption was associated with total circulating mercury (n=5500, r=0.366, p<0.001)
Bouchard, 2009 Blood lead levels and major depressive disorder, panic disorder, and generalized anxiety disorder in US young adults	Adults who participated in the 1999-2004 NHANES	1987, Age 20-39 years	Meeting criteria of DSM-IV of major depression via the World Health Organization Composite International Diagnostic Interview (CIDI)	Lead in blood	Age, sex, race/ethnicity, education, poverty income ratio	Logistic regression	Meeting DSM-IV criteria for major depression: Highest blood lead quintile vs. lowest OR= 2.32 (95% CI: 1.13, 4.75) Among non-smokers: Highest blood lead quintile vs. lowest OR= 2.93 (95% CI: 1.24, 6.92)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bowler, 1999 Neuropsychiatric effects of manganese on mood	Residents who live in Southwest Qué bec downwind of point source, study results focused on men	273, Age 20-70	Depression measured via profile of mood states (POMS), Brief Symptom Inventory (BSI)	Manganese in blood	Age, education level, smoking status, alcohol intake, interaction of blood manganese and gender, interaction of blood manganese and age, fish consumption	T-tests, general linear model MANOVA	POMS: Men <50yrs and higher blood manganese (≥ 7.5 ug/L): significantly lower scores on Anxiety, no sig. difference for Depression Men ≥ 50yrs and ≥ 7.5 ug/L: significantly higher scores on Depression and Anxiety BSI: Men <50yrs and higher blood manganese (≥ 7.5 ug/L): significantly lower scores on Anxiety, no sig. difference for Depression Men ≥ 50yrs and ≥ 7.5 ug/L: significantly higher scores on Depression and Anxiety

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bratel, 1997 Potential side effects of dental amalgam restorations. (II). No relation between mercury levels in the body and mental disorders	50 patients from Department of Oral Diangosis Gotenborg University complaining of oral galvanism or mercury poisoning. 50 controls matched to age, sex, and postal zip code	50 exposed, 50 controls	ICD-9 for psychiatric outcomes Comprehensive psychopathological rating scale (CPRS), Zung scale, Karolinska scales of personality (KSP), mood adjective checklist (MACL), multidimensional health locus of control (MHLC) scales, illness behavior questionnaire (IBQ), and life event scale.	Mercury levels determined in whole blood, plasma, urine, and hair.	Matched on age, sex, postal zip code	Student paired t-test, Wilcoxon test, Pearson correlation	Higher incidence of psychiatric diagnosis in individuals with the amalgam restorations than in the control group. However, no difference in mercury levels and no correlation between mercury levels and severity of reported symptoms. Reported symptoms thus are thought to be part of a broad spectrum of mental disorders instead of mercury levels.
Eum, 2012 Relation of Cumulative Low-Level Lead Exposure to Depressive and Phobic Anxiety Symptom Scores in Middle-Age and Elderly Women	Nurses' Health Study	617 Women, Age 45-79 years	Symptoms of depression via Mental Health Index 5-item scale (MHI-5) Phobic anxiety scale of the Crown-Crisp Index (CCI) assessment	Tibia and patella bone lead measurements via K-shell X-ray fluorescence (KXRF)	Age at bone lead and at MHI-5 measurement, education, husband's education, alcohol consumption, pack-years of smoking, and employment status at MHI-5 measurement	Generalized linear mixed model	Among women who were either premenopausal or postmenopausal and consistently on hormone replacement therapy: Difference in MHI-5 scores between highest vs. lowest tertile of tibia lead concentration = -7.78 (95% CI: -11.73, -3.83) (lower score indicates worse symptoms) OR for severe depression = 3.71 (95% CI: 1.18, 11.64); p-trend = 0.02)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Golub, 2010 A population-based study of blood lead levels in relation to depression in the United States	Adults who participated in the 2005-2006 NHANES	4159, Age ≥ 20 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Lead in blood	Age, sex, education level, ethnicity, poverty income ratio	Poisson regression	Relative risk of depression when blood lead level modeled as categorical variable: 0–0.88 ug/dL Reference 0.89–1.40 ug/dL RR= 1.16 (95% CI: 0.99, 1.36) 1.41–2.17 ug/dL RR= 1.20 (95% CI: 1.07, 1.36) 2.18–26.4 ug/dL RR= 1.16 (95% CI: 0.87, 1.54)
Han, 2016 Does cadmium exposure contribute to depressive symptoms in the elderly population?	Elderly participants in the Korean Elderly Environmental Panel (KEEP) study residing in Seoul, Korea	395	Korean Version of the Short Form Generic Depression Scale test (SGDS-K)	Cadmium in blood	Model 1: adjusted by age, sex, fasting glucose, urinary cotinine Model 2: adjusted by age, sex, fasting glucose, urinary cotinine, alcohol drinking, hypertension, regular exercise	Logistic regression	By analysing the first visit data, the highest quartile blood cadmium group (Q4) showed increased risk for depressive symptoms compared to the lowest quartile group (Q1) (OR 3.50, 95% CI 1.22 to 10.00). Data of the second and third visits suggested that blood cadmium may be protective against depressive symptoms (second visit data, Q4 vs Q1, OR 0.78, 95% CI 0.19 to 3.14; third visit data, Q4 vs Q1, OR 0.58, 95% CI 0.04 to 8.77).
Johnson, 2013 The impact of GPX1 on the association of groundwater selenium and depression: a project FRONTIER study	Adults from the Project FRONTIER, a study of rural health in West Texas	585 adult (183 men, 402 women), age 40-96 (mean 61)	Geriatric depression scale (Qx)	GIS-based selenium concentrations derived from well measurements and modeling	Linear regression: age, gender, education, and language of administration	Linear and logistic regression	Higher Se significantly ($\beta = -0.34$, $p < 0.001$) associated with lower depression score (Change in total GDS-30 Score per unit increase of Selenium levels)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
McFarlane, 2013 Prospective associations between childhood low-level lead exposure and adult mental health problems: the Port Pirie cohort study	Port Pirie cohort	210, Mean age 26 years	Lifetime prevalence of DSM–IV disorder as an adult via Composite International Diagnostic Interview (WMH-CIDI 3.0), Adult Self-Report (ASR), the adult version of the Child Behaviour Checklist	Childhood (age 7 years) blood lead levels	For Females: HOME scores, Mothers' age at birth, paternal occupation, breastfeeding For Males: HOME scores, paternal education and maternal education for depressive problems	Logistic and linear regression	Major depressive disorder Females OR=0.31 (95% CI: 0.07, 1.22) Males OR=0.31 (95% CI: 0.02, 4.05) Depressive symptoms Females Beta= -0.1 (0.9), p>0.10 Males Beta= -0.9 (0.8), p>0.10
Mukherjee, 2014 Platelet hyperactivity, neurobehavioral symptoms and depression among Indian women chronically exposed to low level of arsenic	Women chronically exposed to low levels of arsenic in India	654, Women age 23-45 years	Symptoms of depression via Beck Depression Inventory Second Edition (BDI-II)	Arsenic in drinking water	Age, education, cooking years, menstrual length, adverse reproductive outcome experienced in past 1 year and family income	Chi-square test, Logistic regression	Prevalence of depressive symptoms: Residing in endemic areas 39.8% vs. control areas 19.9% (p < 0.001) Arsenic in groundwater and depression in adjusted logistic regression model: OR= 1.37 (95% CI: 1.11, 1.97)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Ng, 2013 Total Blood Mercury Levels and Depression among Adults in the United States: National Health and Nutrition Examination Survey 2005-2008	Adults who participated in the 2005-2008 NHANES	6911, Age ≥ 20 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Mercury in blood	Age, sex, race/ethnicity, family income-poverty ratio, educational attainment, marital status, current smoking status, BMI, fish consumption and fish oil	Logistic regression	Depression among: Total sample population highest quintile vs lowest (reference) of Hg: OR= 0.73 (95% CI: 0.53, 1.00) Younger adults (20-39 years) highest quintile vs lowest (reference) of Hg: OR= 0.86 (95% CI: 0.50, 1.50) Older adults ≥ 40 years highest quintile vs lowest (reference) of Hg: OR= 0.58 (95% CI: 0.40, 0.83)
Rhodes, 2003 Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study	Veterans who participated in the Normative Aging Study	526, Men age 48-70 years	Symptoms of depression via the Brief Symptoms Inventory	Lead in blood and bone	Age, age-squared, alcohol, education, and employment variables	Logistic regression	For depression: Blood lead OR= 1.028 (95% CI: 0.972, 1.087) Tibia lead OR= 1.007 (95% CI: 0.989, 1.025) Patella lead OR= 1.011 (95% CI: 0.999, 1.023)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Sassine, 2002 Manganese accentuates adverse mental health effects associated with alcohol use disorders	Current drinkers of alcohol who live in Southwest Qué bec downwind of point source	253, Age 20-69 years	Alcoholism via CAGE, Depression measured via French Canadian version of the Brief Symptom Inventory (BSI)	Manganese in blood	None, utilized non-parametric analyses	Mann–Whitney U or t-tests for non-parametric analysis, chi-square, Spearman rank correlations, (ANOVA) or Kruskal-Wallis	Brief Symptom Inventory relative scores: Difference among all three risk levels for alcohol use disorders $p < 0.001$ High risk for alcohol use disorders had greatest BSI relative depression scores mean = 57.9 (SE 1.9). Differences in BSI relative score for anxiety were greatest among the three levels than the differences in the three levels in depression scores. Stratified by blood manganese levels, there was a significant difference ($p < 0.001$) in BSI relative score for anxiety and depression among the levels of risk for alcohol use disorders in the high blood manganese level group (≥ 7.5 ug/L), while the low blood manganese level group (< 7.5 ug/L) did not.

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Scinicariello, 2015 Blood cadmium and depressive symptoms in young adults (aged 20-39 years)	Adults who participated in the 2007-2010 NHANES	2892, Age 20-39 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Cadmium in blood	Age, sex, race/ethnicity, education, poverty income ratio, obesity, alcohol consumption, smoking status, and blood lead	Logistic regression	Depressive symptoms: Highest blood cadmium quartile vs. lowest quartile OR= 2.79 (95% CI: 1.84, 4.25) Depressive symptoms among non-smokers: Highest blood cadmium quartile vs. lowest quartile OR= 2.91 (95% CI: 1.12, 7.58) Depressive symptoms among current smokers: Highest blood cadmium quartile vs. lowest quartile OR= 2.69 (95% CI: 1.13, 6.42)
Shiue, 2015 Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011-2012	Adults who participated in the 2011-2012 NHANES	5560, Age 20-80 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Heavy metals in urine	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	Survey-weighted logistic regression	Depressed vs. not among urinary levels: Manganese OR= 1.47 (95% CI: 1.01, 2.15) Tin OR= 1.30 (95% CI: 1.00, 1.68) Lead OR= 1.18 (95% CI: 0.78, 1.79)

Table 1.1. Depression and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Zierold, 2004 Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water	Homeowners surveyed July 2000 to January 2002 as part of well-water testing in Wisconsin	1185, Age ≥ 35 years	Self-reported depression via survey included in water sampling kit	Arsenic in drinking water	Age, sex, smoking status, and BMI	Logistic regression	Self-reported depression and arsenic levels between: 2-10 $\mu\text{g/L}$ vs. $<2 \mu\text{g/L}$: OR= 2.74 (95% CI: 1.14, 6.63) >10 $\mu\text{g/L}$ vs. $<2 \mu\text{g/L}$: OR= 2.32 (95% CI: 0.08, 6.82)

Air Pollution

There were ten studies on exposure to air pollution and depression. Four of these studies examined the association between air pollutants and emergency department (ED) visits for depression as identified via International Classification of Disease (ICD) hospital discharge codes using a time-series or case-crossover approach, study designs that help avoid confounding by time-invariant factors. A Canadian study (Mieczyslaw Szyszkowicz (2007) used daily ambient monitor data of carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), and particulate matter with a median aerodynamic diameter of less than 2.5 (PM_{2.5}) and 10 (PM₁₀) micrometers and examined 15,556 ED visits from 1992-2002 in five area hospitals for depression. Overall, the percentage of daily ED visits significantly increased with higher NO₂. There were additional significant findings with different pollutants when results were stratified by sex and season, with other significant results only found among women for CO, NO₂, PM_{2.5} and PM₁₀ in different seasons. All significant findings of increased relative risk of daily ED visits were in same day pollutant levels. A second similar study was conducted of 27,047 visits to the ED in six Canadian cities over about two years (Mieczyslaw Szyszkowicz, Rowe, & Colman, 2009). Overall, for same day exposure, the relative risk for daily ED visits significantly increased with higher levels of CO, NO₂, and PM₁₀, and significantly decreased with increasing O₃ in cold weather months (October to March). No association was seen overall with SO₂ or PM_{2.5}, although for SO₂ there was a significant increase with higher levels in warm weather months (April-September).

A case-crossover study in Seoul, Republic of Korea (Cho et al., 2014) examined the association between daily ambient concentrations of air pollutants and ED visits for depression among 4,985 patients who visited the ED for a depressive episode from 2005 through 2009. The

risk of ED visits for depressive episode significantly increased with higher exposure over the previous three days (in particular the average of those) to all pollutants (SO₂, PM₁₀, O₃, NO₂, CO), although for O₃ the association did not reach significance (Cho et al., 2014). Elevated OR were also seen specifically among those patients with various underlying chronic conditions. In two-pollutant models, PM₁₀ and SO₂ emerged as the significant predictors of depression visits. A second case crossover study investigated 404 females visiting the ED for depression and daily levels of sulfur dioxide (SO₂); other air pollutants (that might be correlated with SO₂) were not considered (Mieczyslaw Szyszkowicz, 2011). There was a significant positive association between SO₂ and visiting the ED for depression, especially among females 35 years and older (Mieczyslaw Szyszkowicz, 2011).

Six studies examined the association between air pollutants and depression symptoms. Lim et al. (2012) followed 537 participants who frequented an elderly community center for three years and were surveyed three times for depression symptoms via the Korean version of the Geriatric Depression Scale-Short Form, or SGDS-K. Daily mean values of PM₁₀, SO₂, and NO₂, and daily maximum values of CO and O₃ were obtained from the nearest monitor to the subjects' residence (the same monitor for 90% of the participants). The study found a significant positive association between depressive symptoms and increasing concentrations of PM₁₀, NO₂, and O₃ in several different averages of days before up to 28. Y. Wang et al. (2014) investigated ambient air pollution and traffic pollution and its association with depressive symptoms among 732 adults age 65 years and older from the Boston, Massachusetts, area as part of the MOBILIZE Boston Study. Depressive symptoms were assessed during home interviews via the Revised Center for Epidemiological Studies Depression Scale (CESD-R). PM_{2.5}, black carbon (BC), ultrafine particles (UFP), and sulfates (SO₄²⁻) were measured at one monitor (within

20km of all participants' residences), while O₃, CO, NO, and NO₂ were averaged over several Boston area monitors. Moving averages of up to 14 days before the CESD-R were calculated. Long-term exposure to traffic pollution was estimated by residential distance to nearest major roadway. After adjusting for potential confounders, the study did not find evidence of a positive association between depressive symptoms and long-term exposure to traffic pollution or short-term changes in any of the ambient pollutant levels (Y. Wang et al., 2014). In contrast, the authors did find a statistically significant lower odds of worse CESD-R score with high PM_{2.5} levels over the prior 2 weeks. A study of 406 people in the Los Angeles, USA area used the CES-D to assess depression and assigned ozone and NO₂ exposure based on residential zip code and nearest air monitor measurements (Jacobs, Evans, Catalano, & Dooley, 1984). No association was found with NO₂ over the prior 7 days, while higher ozone was associated with worse depression, although this did not persist when perceived smog was included in the model.

Zijlema et al. (2016) combined data from four European cohorts (n=70,928) to analyze the association between particles and NO₂ estimated from land use regression models and depressive symptoms assessed via face-to-face interviews or questionnaire depending on the cohort using the Mini-International Neuropsychiatric Interview (MINI), PHQ-9, HADS, or CES-D. No consistent associations were found, although differences by cohort were seen with some cohorts showing significant adverse associations and others significant protective ones. Kim, Lim, et al. (2016) examined the association between PM_{2.5} measured at district monitors and hospital diagnosis of Major Depressive Disorder (MDD) among 27,270 people ages 15-79 who lived in Seoul, South Korea for the entire period of 2002-2010 and who did not have a diagnosis of MDD at the start. A significantly elevated risk of MDD with greater exposure to PM_{2.5} was found.

Banerjee, Siddique, Dutta, Mukherjee, and Ray (2012) was the only study to consider indoor air, examining PM10 and PM2.5 primarily from combustion of biomass used for cooking in rural India. Thus, exposure levels were far higher than are typically found for outdoor ambient air and in indoor air in regions where biomass is not used for cooking. The study included 952 women who cooked with biomass and 804 age-matched women who used a cleaner fuel, liquefied petroleum gas and depression was assessed with a local translation of the Beck Depression Inventory Second Edition (BDI-II). Women using biomass differed significantly from women using cleaner fuel on several aspects including higher abnormal menstrual cycle length, more fetal loss in the past year, and greater prevalence of respiratory symptoms in the past three months. However, even after adjusting for these conditions biomass users had a significantly higher risk of depression than those cooking with liquefied petroleum gas (Banerjee et al., 2012). Increasing PM10 and PM2.5 concentrations were significantly associated with having a mild to severe depression severity score on the BDI-II. Table 1.2 outlines the studies on depression and air pollution.

Table 1.2. Depression and exposure to air pollution

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Banerjee, 2012 Cooking with biomass increases the risk of depression in pre-menopausal women in India	Women (median age 37 years) cooked regularly with biomass	952	Depression assessed using the second edition of Beck's depression inventory (BDI-II). Platelet P-selectin expression was assessed by flow cytometry and platelet serotonin was measured by ELISA.	Indoor air pollution from biomass burning. PM(10) and PM(2.5) were measured by real-time aerosol monitor. Carbon monoxide (CO) in exhaled breath was measured by CO monitor.	Age, education, income, fetal loss	Controlled for confounding variables in logistic regression	Compared with the control group (women who cooked with cleaner fuel—liquefied petroleum gas), had a higher prevalence of depression and depleted platelet serotonin. Controlling potential confounders, cooking with biomass was found to be an independent and strong risk factor for depression. Cooking with biomass associated with depression (OR 1.67, 95% CI 1.18, 2.95).
Cho, 2014 Air pollution as a risk factor for depressive episode in patients with cardiovascular disease, diabetes mellitus, or asthma	People in Seoul, South Korea, with claims data in the Health Insurance Review and Assessment Service, years 2005 to 2009	4985, Ages <19 to >65 years	Depressive episode, ICD-10	CO, NO ₂ , O ₃ , SO ₂ , PM ₁₀ Monitoring data from Ministry of Environment	Case-crossover design National holidays, sunlight hours, and the natural cubic splines for temperature, relative humidity, and air pressure Air pollutant and weather data matched to ED visit period, and ED visit period matched to control period by using the same days of the week as the case period within the same month	Cox proportional hazard models, conditional logistic regression, single and distributed lag models	Adjusted OR for ED visits for depressive episode among patients without underlying five diseases (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, depressive disorder): SO ₂ , lag 0-3 days: 1.103 (1.019–1.193) PM ₁₀ , lag 0-3 days: 1.023 (0.950–1.103) O ₃ , lag 0-2 days: 1.248 (1.145–1.361) NO ₂ , lag 0-2 days: 1.053 (0.987–1.124) CO, lag 0-2 days: 0.985 (0.921–1.053)

Table 1.2. Depression and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Jacobs, 1984 Air pollution and depressive symptomatology: Exploratory analyses of intervening psychosocial factors	Participants from the Los Angeles-Long Beach metropolitan area from 1978-1982	406 randomly selected from 6000	Depression measured by Center for Epidemiologic Studies Depression Scales (CES-D).	Evaluated many exposures in addition to air pollutants (NO ₂ , Ozone)	Step-wise multivariate regression.	SES, sex, age, temperature, humidity, NO ₂ , prior symptoms of depression, life events, visibility, ozone, perceived smog	No significant relationship between NO ₂ , Ozone, and depression. However, "...objective air quality affects depression through an effect of perceived air quality." (267).
Kim et al., 2016 Long-Term Fine Particulate Matter Exposure and Major Depressive Disorder in a Community-Based Urban Cohort	Residents living in same area in Seoul, Korea, 2002-2010	27,270 individuals (Age 15-79 years)	Diagnosis of Major Depressive Disorder from ICD-10 codes and prescription of antidepressants	Monitoring data of PM _{2.5} of Seoul were obtained from the Research Institute of Public Health and Environment in Seoul	Stratified by age and sex and adjusted for: household income, smoking status, alcohol consumption, and regular exercise	Cox-proportional hazards model and sensitivity analyses	Long-term PM _{2.5} exposure increased the risk of MDD among the general population. Individuals with underlying chronic diseases are more vulnerable to long-term PM _{2.5} exposure.

Table 1.2. Depression and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Lim, 2012 Air pollution and symptoms of depression in elderly adults	Elderly Adults in Seoul	537, adults	Korean version of the Geriatric Depression Scale-Short Form (SGDS-K)	Air pollution	Longitudinal study, attempted to control for confounders	Generalized estimating equations	17.0% (95%CI 4.9%, 30.5%) with IQR increases in the 3-day moving average of concentration of PM10. 32.8% (95%CI 12.6%, 56.6%) with IQR increase in the 0–7 day moving average of NO concentrations. 43.7% (95%CI 11.5%, 85.2%) with IQR increase in the 3-day moving average of Ozone. 132.5% (95%CI 32.0, 309.3) with increase of Ozone. 118.2% (95% CI 37.9%, 245.3%) with increase in NO2. 38.2% (95% CI –3.6%, 98.1%) with increase in PM10.
Szyszkowicz, 2007 Air pollution and emergency department visits for depression in Edmonton, Canada.	People in Edmonton, Canada, served by five hospitals, years 1992 and 2002	15556 ED visits, Ages from <20 to >80 years	Diagnosis of depression, International Classification for Diseases, 9th revision (ICD-9), rubric 311	CO, NO2, O3, SO2, PM10, PM2.5 Monitoring data from Environment Canada	Temperature and relative humidity	Generalized linear mixed models (Poisson), fixed slope, random intercept	Percentage increase in daily ED visits per increase in increase in interquartile range of ambient air pollutants: CO 6.9% (95% CI: 1.3, 12.9) for all patients in warm season NO2 3.9% (95% CI: 1.3, 6.6) for all patients for whole period SO2 4.5% (95% CI: 0.1, 9.1) for female patients in warm season O3, 1-day lagged 6.9% (95% CI: 0.6, 13.6) for female patients in warm season PM10 7.2% (95% CI: 2.7, 12.0) for females in cold season PM2.5 7.2% (95% CI: 2.0, 12.8) for females in cold season

Table 1.2. Depression and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Szyszkowicz, 2009 Air pollution and daily emergency department visits for depression.	People in six Canadian cities served by area hospitals	27047 ED visits, Age not specified	Diagnosis of depression, International Classification for Diseases, 9th revision (ICD-9), rubric 296	CO, NO ₂ , O ₃ , SO ₂ , PM ₁₀ , PM _{2.5} Monitoring data from Environment Canada	Temperature and relative humidity	Generalized linear mixed models (Poisson), fixed slope, random intercept	Percentage increase in daily ED visits per increase in the mean concentration for same day exposure in the warm weather period (April–September): CO 15.5% (95% CI: 8.0, 23.5) per 0.8 ppm NO ₂ 20.0% (95% CI: 13.3, 27.2) for per 20.1 ppb For the cold weather period (October–March): PM ₁₀ 7.2% (95% CI: 3.0–11.6) per 19.4 ug/m ³
Szyszkowicz. 2011 Ambient sulfur dioxide and female ED visits for depression	People in Toronto, Canada, served by a hospital, years 1999 to 2002	404 ED visits, Females 0 to 85 years	Diagnosis of depression, International Classification of Diseases, 9th Revision (ICD-9), rubric 296	SO ₂ monitoring data from Ministry of Environment	Case-crossover design Period when ED visits for depression occurred matched to control period by using the same days of the week as the case period within the same month	Cox proportional hazard models, conditional logistic regression	ED visit for depression per increase of one IQR in SO ₂ levels: Females, all ages, OR=1.12 (95% CI: 0.99, 1.25) Female patients 35 years of age and older, OR=1.27 (95% CI: 1.10, 1.47)

Table 1.2. Depression and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Wang, 2014 Ambient air pollution and depressive symptoms in older adults: results from the MOBILIZE Boston study	Adults ≥ 65 years of age (78.1 ± 5.5 years, mean $\pm$ SD).	732 adults	Depressive symptoms during home interviews using the Revised Center for Epidemiological Studies Depression Scale (CESD-R).	Residential distance to the nearest major roadway as a marker of long-term exposure to traffic pollution, and assessed short-term exposure to ambient fine particulate matter (PM _{2.5}), sulfates, black carbon (BC), ultrafine particles, and gaseous pollutants, averaged over the 2 weeks preceding each assessment.	Cross-sectional study	Controlled for confounding variables	No evidence of a positive association between depressive symptoms and long-term exposure to traffic pollution or short-term changes in pollutant levels Found an OR of CESD-R score ≥ 16 of 0.67 (95% CI: 0.46, 0.98) per interquartile range (3.4 $\mu\text{g}/\text{m}^3$) increase in PM_{2.5} over the 2 weeks preceding assessment

Table 1.2. Depression and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Zijlema, 2016 The association of air pollution and depressed mood in 70,928 individuals from four European cohorts	Individuals from four European cohorts	70,928 individuals	Depression assessed via the following based on which cohort: Mini-International Neuropsychiatric Interview (MINI), Patient Health Questionnaire-9 (PHQ-9), Hospital Anxiety Depression Scale (HADS), and Center for Epidemiological Studies Depression Scale (CES-D)	Residential exposure to particles (PM2.5, PM2.5 absorbance, PM10) and nitrogen dioxide (NO2) was estimated using land use regression (LUR) models developed for the European Study of Cohorts for Air Pollution Effects (ESCAPE) and using European wide LUR models.	Adjusted for demographic factors, health factors, and noise	Logistic regression	Found no consistent evidence for an association between ambient air pollution and depressed mood.

Pesticides

There were six studies of exposure to pesticides and depression. One was an ecologic study in Brazil that compared hospitalization rates for mood disorders (but not specifically depression) between a high pesticide use agricultural region to that of the city of Rio de Janeiro or Rio de Janeiro state (Meyer et al., 2010). As such this evidence must be viewed with great caution, but they did report more mood disorders in the more exposed region. Using NHANES data, Berk et al. (2014) found no cross sectional association between urinary pesticides and organophosphates and depression assessed by the PHQ-9. In the Agricultural Health Study (AHS) exposure to pesticides among 29,074 female spouses of pesticide applicators was assessed by questionnaire at enrollment, including whether they had ever been diagnosed with pesticide poisoning by a doctor (Beseler et al., 2006). Depression was determined by asking if a doctor ever diagnosed them with depression requiring medication. After adjusting for potential confounders, a significant positive association was found between having a history of pesticide poisoning and depression, but not with self-reported cumulative pesticide exposure. A second study in the AHS that considered only incident depression during an average 11.9 years of follow-up of wives who had not reported depression at enrollment found similar results: an association with pesticide poisoning, but not cumulative exposure (Beard et al., 2013). Among 869 residents of a rural agricultural area of Brazil self-reported pesticide exposure prior to age 15 was associated with increased odds of depression (Campos, da Silva, de Mello, & Otero, 2016). One study used red blood cell acetylcholinesterase (AChE) activity as an indicator of exposure to organophosphate (OP) pesticides in a study of 149 patients with MDD and 64 patients without (Altinyazar, Sirin, Sutcu, Eren, & Omurlu, 2016). AChE activity did not differ between controls and MDD patients who had not attempted suicide (n=76).

Of note, we excluded two studies whose populations included farm operators and their spouses (and also farm residents in one) because whether the results applied specifically to non-workers could not be determined. These studies, though, did report significant positive associations between depression measured with the Center for Epidemiological Studies-Depression (CES-D) scale and both having a self-reported pesticide-related illnesses (Stallones & Beseler, 2002) and a pesticide poisoning (Beseler & Stallones, 2008). Table 1.3 outlines the studies on depression and pesticides.

Table 1.3. Depression and exposure to pesticides

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis, Results
Altinyazar, 2016 The Red Blood Cell Acetylcholinesterase Levels of Depressive Patients with Suicidal Behavior in an Agricultural Area	Patients suffering from depression and healthy controls in rural agriculture area in Turkey	149 patients diagnosed with major depressive disorder and had or did not have suicide attempts, 64 health controls who lived in the same rural district for at least 1 year	Red blood cell acetylcholine esterase (RBC-AChE) activity as proxy of exposure to Organophosphate pesticide residues, AChE activity determined from blood sample and colorimetric method defined by Ellman et al	Diagnosis of depression via Beck's Depression Inventory [18] Anxiety via Beck's Anxiety Inventory	Occupations	Logistic Regression Adjusted for occupations: OR between AChE activity and suicide attempt was 0.394 (95% CI 0.214-0.727), $p = 0.003$ Correlation between the number of suicide attempts of the patients in the past and their AChE activity levels ($r = -0.227$, $p = 0.001$). AChE activity and suicide attempts in the past correlation $r = -0.227$, $p = 0.001$) No correlation was found between patient group AChE activity levels and the Beck depression scale ($p = 0.189$), the Beck anxiety scale ($p = 0.767$) and the Impulsiveness scale ($p = 0.258$).
Beard, 2013 Pesticide exposure and self-reported incident depression among wives in the Agricultural Health Study	Participants enrolled in the Agricultural Health Study	16893 Female spouses age <25 to >60 years	Physician-diagnosed depression requiring medication, asked as part of questionnaire at enrollment and at follow-up via telephone interview	Pesticides, asked via self-administered survey at enrollment	Age at enrollment, state of residence, education level, diabetes diagnosis, and drop out	Inverse probability weighting, log-binomial regression models, sensitivity analysis utilized Cox proportional hazards regression models IPW adjusted risk ratio of incident depression: Pesticide poisoning RR= 1.78 (95% CI: 0.76, 4.14) Ever mixed/applied permethrin (crops) RR= 1.44 (95% CI: 1.02, 2.03)

Table 1.3. Depression and exposure to pesticides (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Berk, 2014 Pop, heavy metal and the blues: Secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES national epidemiological survey	Adults who participated in one of the three waves (2005–2006, 2007–2008 and 2009–2010) of the NHANES	15140, Age 31-63 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Heavy metals in blood	Demographics and socioeconomic status (age, sex, poverty, family income, ethnicity and country of birth), cotinine levels and chronic medical illness, blood levels of cholesterol, glucose and creatinine	Binary Poisson regression with robust estimation of SE	Risk ratios for blood heavy metals and depression: Cadmium 1.48 (95% CI: 1.16,1.90) Lead 0.81 (95% CI: 0.64, 1.02), Mercury 0.62 (95% CI: 0.50, 0.78), frequency of fish consumption was associated with total circulating mercury (n=5500, r=0.366, p<0.001)
Beseler, 2006 Depression and pesticide exposures in female spouses of licensed pesticide applicators in the agricultural health study cohort	Participants enrolled in the Agricultural Health Study	29074 Female spouses age <30 to >60 years	Physician-diagnosed depression requiring medication, asked as part of questionnaire	Pesticides, asked if exposed in questionnaire	State, age, race, off-farm work, alcohol, cigarette smoking, physician visits, and solvent exposure	Logistic regression	Adjusted OR for depression for having a history of pesticide poisoning = 3.26 (95% CI: 1.72, 6.19)
Beseler, 2008 A cohort study of pesticide poisoning and depression in Colorado farm residents	Participants in the Colorado Farm Family Health and Hazard Surveillance (CFFHHS) project	653, majority age >30 years	Depressive symptoms via Center for Epidemiologic Studies-Depression (CES-D) scale	Pesticides, assessed via self-reported questionnaire at baseline	Gender, age, marital status, health status, income decline, and debt increase	Chi-square, Kruskal-Wallis test, generalized estimating equations	Adjusted OR for depression associated with pesticide poisoning: 2.00 (95% CI: 0.91, 4.39)

Table 1.3. Depression and exposure to pesticides (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Meyer, 2010 Mood Disorders Hospitalizations, Suicide Attempts, and Suicide Mortality Among Agricultural Workers and Residents in an Area With Intensive Use of Pesticides in Brazil	Agricultural workers and residents in Rio de Janeiro State from 1998 and 2007, in the Brazilian Hospital Information System	Exposed area: 3517 cases Control areas: 13,476(City) cases, 28,895(State) cases Ages 20-59	Hospitalization by Mood (Affective) Disorders of residents, ICD-10: F30–F39	Pesticides, estimated by expenditure of pesticide per agricultural worker, data from the Brazilian Institute for Geography and Statistics in 1996.	Sex and age	Stratification	Serrana Region (exposed) vs City of Rio de Janeiro (reference area) Overall Rate Ratio= 2.27 (2.19, 2.36) Men RR= 3.47 (3.26, 3.69) Women RR= 1.88 (1.79, 1.97) Serrana Region (exposed) vs Rio de Janeiro State (reference area) Overall Rate Ratio= 2.56 (2.47, 2.65) Men RR= 3.25 (3.07, 3.43) Women RR= 2.25 (2.16, 2.36)
Stallones, 2002 Pesticide Poisoning and Depressive Symptoms among Farm Residents	Farmers and spouses in northeastern Colorado from 1992–1997.	761, majority age >30 years	Depressive symptoms via Center for Epidemiologic Studies-Depression (CES-D) scale	Pesticides, assessed via self-reported questionnaire	Pesticide illness, sex, health status, income, age, marital status, education, see relative, number of drinks	Conditional logistic regression models	Adjusted OR for depression associated with pesticide related illness: 5.87 (95% CI: 2.56, 13.44)

Noise

We found ten studies of exposure to noise and depression. Four studies considered noise around airfields, two of which were related to the military. Miyakita et al. (2002) grouped residents living near U.S. military bases and airfields in Japan (and one control region) based on noise levels from measurements made by the prefectural government. About 7,000 people completed the Todai Health Index, a self-administered questionnaire that includes a depression scale. Higher noise levels were significantly associated with scoring high on the depression scale, driven in large part by the highest noise level (day-night average sound level over 70dB).

Three other studies considered noise around commercial airports. Tarnopolsky, Watkins, and Hand (1980) examined 5885 participants living around Heathrow airport in London, England. The Noise and Number Index that combines number of aircraft and average noise was used to determine noise contours around the airport and those living in high vs. low noise areas were compared on the General Health Questionnaire (GHQ). Depression score was found to be significantly worse in the low noise area. Hardoy et al. (2005) compared 71 people living near an airport in Sardinia to 284 age, sex, and employment status matched residents of other regions of Sardinia who had participated in a separate community survey. Depression was assessed with an Italian version of the CIDI. Lifetime prevalence of MDD was not different between the two groups. A similar study in Zahedan city, Iran considered a convenience sample of 100 people living near the airport and 100 living in the city (Tamini & Pak, 2016). They found no difference in depression measured with the data, depression, anxiety, and stress scale-21 (DASS-12). No adjustment for other factors were conducted.

Four additional articles addressed road traffic noise and depression. Sygna, Aasvang, Aamodt, Oftedal, and Krog (2014) examined participants in the Norwegian National Population

Register and measured aggregated anxiety and depression symptoms among 2898 participants with the Hopkins Symptom Checklist-25 (HSCL-25). Noise levels from road traffic were calculated at the most exposed façade of the home of each participant using the Nordic prediction method, which is based on sound measurements of passing cars and takes into account aspects like terrain, ground type, buildings and sound facades. Increasing road traffic noise was associated with a significant increase in HSCL-25 score. The second study followed 1725 of an original 2398 adult men 50-64 years old in Caerphilly, South Wales, for five years (Stansfeld, Gallacher, Babisch, & Shipley, 1996). Traffic noise maps were made from street level noise measurements, and participant depression symptoms assessed with the GHQ. After accounting for potential confounders including depression at baseline, there was no association between road traffic noise and depression scores. In a third study, noise levels were measured in the day and night in old Belgrade at three streets with heavy traffic and three with less traffic (Belojević, Jakovljević, & Aleksić, 1997). Self-report of feelings of depression, with four options for frequency, was compared between 253 residents of the noisy streets and 160 residents of the quieter streets. Feeling depressed was significantly more frequently reported among participants living in the noisy area than quiet area. Yoshida et al. (1997) measured equivalent sound levels (Leq) at the homes of 366 women living near a main road in Tokyo. The scale to measure depression was not provided, but differences in score across quintiles of sound levels was noted. It was not clear that there was an obvious increasing trend of depression with higher noise, although those in the highest quintile of noise (>70dBA) did report higher depression scores.

One study evaluated urban predictors of depression in surveys carried out among adults in India in 2003 and 2013 (Firdaus & Ahmad, 2014). The CES-D was used to assess depression, but the cutoff considered as depressed was not given. Indoor noise pollution and neighborhood

noise were significantly associated with depression in both years, while street noise was not. However, no details on how the noise was assessed were provided.

One study conducted randomized trials of ear plugs or sound cancelling headphones in a hospital in Germany with 72 patients randomized to three arms for each of the two trials (Czaplik et al., 2016). The Hospital Anxiety and Depression Scale (HADS) and the State-Trait Anxiety Scale were administered before and after the trial period, which went from 8PM to 6AM. No differences in depression scores were seen between any of the trial conditions for both ear plugs and sound cancelling headphones. Table 1.4 outlines the studies on depression and noise.

Table 1.4. Depression and exposure to noise

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Belojević, 1997 Subjective reactions to traffic noise with regard to some personality traits	Residents in central Belgrade with at least one-year residence period	413 Adults	Depression and other personality traits measured via the Eysenck Personality Questionnaire	Noise level measured via noise level analyzers, noise sensitivity measured by Weinstein Noise Sensitivity Scale	Non-parametric analyses	Mann-Whitney U or t-tests for non-parametric analysis, chi-square, Spearman rank correlations	Frequency of having feelings of depression: Noisy area: 1.7 ± 0.8 Control area: 1.4 ± 0.6 $p < 0.01$ Correlation between depression and subjective noise sensitivity: 0.27 $p < 0.001$
Czaplik 2016 Psychoacoustic analysis of noise and the application of earplugs in an ICU: A randomised controlled clinical trial	University hospital patients	144 patients in the ICU	Anxiety via State Trait Anxiety Inventory (STAI) score, Hospital Anxiety and Depression Scale (HADS) questionnaires administered at the beginning and end of the test period	Noise reduction via earplugs or noise cancelling using headphones	Randomized control trial, single blinded	Analysis of variance (ANOVA), two-tailed t-test (level of significance 0.05 or 0.017 for three groups according to the Bonferroni correction)	Mixed results: No significant differences of HADS Depression score for using earplugs or noise cancelling headphones vs. not.
Firdaus, 2014 Temporal variation in risk factors and prevalence rate of depression in urban population: Does the urban environment play a significant role?	People of Delhi, India, first survey February to April 2003, second survey January to March 2013	1326, Age ≥ 18 years	Depression measured by Centre for Epidemiologic Studies Depression Scale (CES-D)	Indoor noise pollution, street noise, neighborhood noise (no description given on measurement method)	Age, gender, marital status, employment and migratory status	Logistic regression	Indoor noise pollution 2003 Cohort Adjusted OR: 1.36 (95% CI: 1.09, 1.7) 2013 Cohort Adjusted OR: 3.04 (95% CI: 2.37, 3.91) Neighborhood noise 2003 Cohort Adjusted OR: 1.56 (95% CI: 1.28, 1.98) 2013 Cohort Adjusted OR: 1.62 (95% CI: 1.35, 1.94) Street noise 2003 Cohort Adjusted OR: 0.91 (95% CI: 0.73, 1.13) 2013 Cohort Adjusted OR: 0.57 (95% CI: 0.47, 0.70)

Table 1.4. Depression and exposure to noise (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Hardoy, 2005 Exposure to aircraft noise and risk of psychiatric disorders: the Elmas survey	Residents of the district of Gillaquas in the vicinity of Elmas airport	355 Adults	Depression measured by Composite International Diagnostic Interview (CIDI) Simplified	Aircraft noise, represented by those living about one mile from airport, controls were residents in the same region	Controls matched on sex, age and employment status	Chi-square test, odds ratios and confidence intervals calculated via the method of Miettinen	Major depressive disorder: OR= 0.7 (95% CI: 0.6, 1.2) Depression disorder Not otherwise specified: OR= 1.9 (95% CI: 0.8, 6.0)
Miyakita, 2002 Population-based questionnaire survey on health effects of aircraft noise on residents living around US airfields in the Ryukyus - Part 1: An analysis of 12 scale scores	Residents around U.S. airfields in Ryukyus	7095, Age 15-74 years	Depression measured by the Todai Health Index	Aircraft noise levels measured by prefectural government and municipalities around the airfields	Age, sex, occupation and the interaction of age and sex	Logistic regression, test of trend	Depression and level of noise exposure over 70 dB: Visual estimate of OR from figure (e) 1.75 (95% CI: 1.20, 2.75), p=0.01 Trend p=0.0379
Stansfeld, 1996 Road traffic noise and psychiatric disorder: prospective findings from the Caerphilly Study	Men in the Caerphilly study followed for 5 years	1725 Men age 50-64 years	30 item General Health Questionnaire (GHQ)	Road traffic noise measured by street measurements	Social class, employment status, marital status, physical illness, and baseline morbidity	Linear trend test	Adjusted mean depression score (SE) for levels of road traffic noise: 51-55 dBA: 1.19 (0.05) 56-60 dBA: 1.39 (0.13) 61-65 dBA: 1.32 (0.11) 66-70 dBA: 1.21 (0.16) Tests of heterogeneity p-value= 0.34

Table 1.4. Depression and exposure to noise (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Sygna, 2014 Road traffic noise, sleep and mental health	People in the Norwegian National Population Register who had addresses in the Norwegian Public Roads Administration and the City of Oslo database	2898, Age ≥ 18 years	Depression symptoms measured in aggregate with anxiety symptoms via Hopkins Symptom Checklist-25 Having poor mental health (Hopkins Symptom Checklist score ≥ 1.55)	Road traffic noise assessed at the most exposed façade of the home and calculated by the Nordic prediction method	Age, sex, education, employment, noise sensitivity, and somatic diseases.	Linear regression model, logistic regression model, multiple imputation	Change in Hopkins Symptom Checklist score per 10 dB increase in road traffic noise exposure among poor sleep quality: Beta=0.06 (95% CI: -0.02, 0.13) Having poor mental health per 10 dB increase in road traffic noise exposure among poor sleep quality: OR= 1.40 (95% CI: 0.99, 1.98)
Tamini, 2016 Comparative study of the effect of aircraft noise on emotional states between airport neighboring and city residents	Residents near airport of Zahedan, Iran	100 residents of Zahedan, 100 from neighboring airport	Depression, anxiety, and stress scale-21 (DASS-21)	Living near airport (airport neighboring) and locations with low to no exposure to aircraft noise (residents of Zahedan City)	Matched for sex in each exposure group (city, airport neighboring)	One-way between-groups multivariate analysis of variance (MANOVA)	No significant positive difference between the two groups regarding depression F=1.37 p=0.243 Significant positive differences regarding anxiety, stress and overall scores of DASS between airport neighboring and city residents in Zahedan city

Table 1.4. Depression and exposure to noise (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Tarnopolsky, 1980 Aircraft noise and mental health: I. Prevalence of individual symptoms	Residents around London Heathrow Airport	Approx. 5885, Age ≥ 16 years	Symptoms of depression measured by self-report, being bothered by aircraft noise assessed by interview	Aircraft noise levels measured by the Civil Aviation Authority	Age, sex, matched by occupation of head of household	Chi-square	Percentage acute onset(<2 weeks ago) of depression by level of noise exposure: Low= 8.9% High=10.7% $p>0.05$ Percentage chronic depression by level of noise exposure: Low= 20.2% High=16.6% $p<0.001$ Percentage depression by level of annoyance: Not bothered=27.7% Slightly bothered=26.5% Moderately bothered=25.8% Very bothered=31.7% $p<0.01$ Regardless of noise, most adverse health effects were reported more frequently among participants reporting high annoyance
Yoshida, 1997 Effects of road traffic noise on inhabitants of Tokyo	Residents near a main road in Tokyo	366 Adult Women, age 20-60 years	Depression measured via survey questions	Road traffic noise measured outside homes	Non-parametric analyses	Chi-square	Chi-square test of frequency of having depression comparing exposure to <70 dbA and ≥ 70 dbA: 5.7 $p<0.05$ Relative risk of having depression comparing exposure to <70 dbA and ≥ 70 dbA: 2.9 $p<0.05$

Secondhand Smoke

We found sixteen studies describing depression and exposure to secondhand smoke (SHS). One considered SHS indirectly by examining the association between depression and smoking policies both at home and work. Among 41,904 non-smoking adults in the Behavioral Risk Factor Surveillance System (BRFSS) data a higher odds of scoring high on the PHQ-9 was associated with less restrictive home and work smoking policies (Bandiera et al., 2010a). Two studies in Taiwan considered paternal smoking and maternal depression around pregnancy specifically; maternal smoking during pregnancy is illegal in Taiwan and so mothers were assumed to essentially all have not smoked during pregnancy. Alibekova, Huang, Lee, Au, and Chen (2016) assessed depression with the Edinburgh Postnatal Depression Scale (EPDS) among 533 couples and found that paternal smoking in the mother's presence during pregnancy, but not smoking when the mother was not present, was associated with significantly worse depression scores in mothers during pregnancy. Weng, Huang, Huang, Lee, and Chen (2016) assessed depression with the EPDS among 3,867 women who were pregnant or within 1 month postpartum and found an elevated odds ratio for depression (>13 on the EPDS) for women reporting always or usually having people smoke around them at home or work.

Eleven studies considered SHS exposure as adults and depression, and seven reported a positive association between SHS exposure and more depression. Kim, Kim, Lee, Lee, and Suh (2015) found a higher Beck Depression Inventory (BDI) score with self-reported exposure to environmental tobacco smoke (ETS) among 1,201 never-smoker women in the Korean Genome and Epidemiology Study (KoGES)-Kangwha. Bandiera et al. (2010b) found higher serum cotinine to be associated with worse PHQ-9 score among 2,965 nonsmokers in the 2005-2006 NHANES data. No associations between depression symptoms and SHS exposure were found

among former smokers. Kim, Choi, Kim, Shim, and Kim (2016) studied 123,665 2011 Korean Community Health Survey participants aged 19 years or above who were non-smokers and had no history of stroke, myocardial infarction, or days spent in bed from disability. SHS exposure and both depressive symptoms and history of depression diagnosis were assessed by self-report questionnaire. A higher number of reported hours per day of SHS exposure was associated with more depressive symptoms and higher odds of a depression diagnosis. Ye et al. (2015) studied 1,280 non-smoking middle-aged women age 40-60 years living in Guangzhou City, China, and found a positive association between self-reported exposure to SHS and depressive symptoms measured by CES-D. Three other studies focused on pregnant women. Tan et al. (2011) found an association between moderate to severe depressive symptoms (Beck Depression Inventory Fast Screen) and self-reported exposure to tobacco smoke in the home environment during pregnancy among 929 pregnant urban minority women. Mbah, Salihu, Dagne, Wilson, and Bruder (2013) found a positive association between exposures to environmental tobacco smoke, determined using salivary cortisol, and increased Edinburgh Perinatal Depression Scale (EPDS) scores among 129 pregnant non-smokers. Among 6,884 women from the North Carolina Pregnancy Risk Assessment and Monitoring System SHS exposure before pregnancy was associated with more self-reported post-partum depression (Khan, Arif, Laditka, & Racine, 2015).

In contrast, Asbridge, Ralph, and Stewart (2013) studied 49,701 non-smokers (former or never) from the 2010 Canadian Community Health Survey. SHS exposure was determined by self-reported exposure in the home or in a vehicle on a daily or near daily basis, and this was not associated with self-reported mood disorders. Bot et al. (2013) evaluated 1,088 non-smoking adults in the Netherlands Twins Register and 1,757 non-smoking adults in the Netherlands Study of Depression and Anxiety and found no association between increased plasma cotinine levels

and current depression measured with CIDI nor and depression severity measured with the Adult Self-Report (ASR) questionnaire. There was a positive association of SHS exposure with depression, measured by the Patient Health Questionnaire, among 162 participants free of chronic cardiovascular or lung disease in the Gutenberg Health Study (Michal et al., 2013). However, there was not an association found among the 19 participants with chronic cardiovascular or lung disease. Among 6,043 non-smoking adults who participated in the 2010-2012 Korean National Health and Nutrition Examination Survey there was an association between SHS and depression among those exposed at home but not overall (Gim, Yoo, Shin, & Goo, 2016); the specific questions used to define depressive symptoms were not indicated.

Two studies considered earlier life exposures to SHS and later life depression. Taha and Goodwin (2014) described adult onset depression, as assessed with the CIDI Short Form, among 2,053 enrollees in the Midlife Development in the United States Survey (MIDUS) in relation to self-report of smokers in the household during childhood or in adulthood. SHS exposure during childhood or adulthood alone was not associated with depression in adulthood, but SHS exposure in both childhood and adulthood was significantly associated with increased depression. However, this study did not control for potentially important confounders such as childhood socioeconomic status or parental depression. Among 176 participants in the New York Women's Birth Cohort (former child participants from the National Collaborative Perinatal Project) there were trends towards more depression measured with the CES-D among those who reported that their mother smoked during pregnancy or that someone smoked in their presence in childhood (Elmasry, Goodwin, Terry, & Tehranifar, 2014). However, these results did not reach significance and were only adjusted for current smoking rather than restricted to non-active smokers. Table 1.5 outlines the studies on depression and secondhand smoke.

Table 1.5. Depression and exposure to secondhand smoke

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Alibekova, 2016 Effects of smoking on perinatal depression and anxiety in mothers and fathers: A prospective cohort study	Couples from visits at the outpatient clinics of 5 selected hospitals in Taipei, Taiwan	533 couples (pregnant women and husbands)	Depressive symptoms via The Edinburgh Postnatal Depression Scale (EPDS)	Father's smoking	Age, marital status, education level, employment status, family monthly income, parity, other secondhand smoke exposure, marital adjustment, parental stress, history of depression, the couple's depression status, and paternal alcohol use for the "perinatal period" and "during pregnancy" models. For the "postpartum period" model, results were adjusted for all parameters mentioned, in addition to the infant's health status at up to 6 months after birth.	Generalized estimating equations	Paternal smoking in the mother's presence also increased maternal disturbances, especially for depression during pregnancy (1.2, 95% CI=0.1-2.3) and anxiety during the postpartum period (3.4, 95% CI=0.6-6.3). No significant association was found between paternal smoking but not in the mother's presence and maternal emotional disturbances. Paternal smoking but not in the mother's presence affected only paternal anxiety, especially in the postpartum period (regression coefficient 2.7, 95% CI 0.7-4.7) compared with nonsmokers.
Asbridge, 2013 Private space second-hand smoke exposure and the mental health of non-smokers: a cross-sectional analysis of Canadian adults	Non-smokers (former or never) from the 2010 Canadian Community Health Survey	49,701	Mental health indicators: self-reported diagnosed mood and anxiety disorders (lasting ≥ 6 months), and self-report measures of overall mental health and experiences of stress.	SHS exposure was determined by self-reported exposure in the home or in a vehicle on a daily or near daily basis	Stratified by smoking status, chronic disease status, and gender Adjusted logistic regression: sex, age, providence of residence, marital status, immigrant status, income, education, chronic disease, smoking status	Logistic regression	Adjusted regression models did not find significant association between SHS and mood disorders: OR 1.13 (z-statistic 1.32)

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bandiera, 2010a Secondhand smoke policy and the risk of depression	Participants of the 2006 Behavioral Risk Factor Surveillance System (BRFSS)	41904, Age 18 years and older	Depression measured by Patient Health Questionnaire (PHQ-8)	Potential for secondhand smoke (SHS) measured by SHS policy at home and work among non-smokers	Age, race/ethnicity, gender, education, general health, and alcohol consumption	Logistic regression	Risk of major depression, smoking allowed anywhere at home vs not allowed anywhere: OR 2.15 (1.24–3.71) Risk of major depression, smoking allowed anywhere at work areas vs not allowed anywhere: OR 2.40 (1.17–4.95)
Bandiera, 2010b Secondhand smoke exposure and depressive symptoms.	Participants of the 2005 to 2006 National Health and Nutrition Examination Survey (NHANES)	2962 Never smokers age $\geq$ 20 years	Depression measured by Patient Health Questionnaire (PHQ-9)	Secondhand smoke exposure measured via blood serum cotinine	Age, race/ethnicity, gender, education, cardiovascular disease, respiratory disease, diabetes mellitus, hypertension, thyroid disease, and cancers	Stratified analyses, zero-inflated Poisson regression	Adjusted beta for depression and SHS exposure among never-smokers: beta= 0.09 (SE: 0.03), p = 0.03 Adjusted (age, race/ethnicity, gender, and education only) beta for depression and SHS exposure among former smokers: beta= -0.01 (SE: 0.04), p= 0.68

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bot, 2013 Exposure to secondhand smoke and depression and anxiety: a report from two studies in the Netherlands	Netherlands Twins Register, Netherlands Study of Depression and Anxiety	2,845 non-smoking adults	Depression measured with Composite International Diagnostic Interview (CIDI) and depression severity measured with the Adult Self-Report (ASR) questionnaire	Plasma cotinine levels	Age, sex, education level, North-European ancestry, body mass index, physical activity, alcohol use, number of chronic diseases under treatment, and former smoker	Logistic regression, Linear regression	No association between increased plasma cotinine levels and current depression measured with CIDI nor and depression severity measured with the Adult Self-Report (ASR) questionnaire
Elmasry, 2014 Early Life Exposure to Cigarette Smoke and Depressive Symptoms Among Women in Midlife	Participants in the New York Women's Birth Cohort and former child participants from the National Collaborative Perinatal Project	172 Women age 38-44 years at follow-up	Center for Epidemiological Studies Depression Scale (CES-D)	Maternal smoking during pregnancy (MSP) and childhood secondhand smoke (SHS)	Age of mother when giving birth, maternal education, annual income at birth, occupation, race/ethnicity	Log-binomial regression	Risk of depressive symptoms among participants with MSP and childhood SHS exposure vs. those with no MSP and no childhood SHS exposure: Adjusted for maternal education RR= 2.40 (95% CI: 1.07, 5.41) Adjusted for maternal education, adult SHS, adult active smoking status, adult education RR= 1.69 (95% CI: 0.73, 3.93)

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Gim, 2016 Relationship between Secondhand Smoking with Depressive Symptom and Suicidal Ideation in Korean Non-Smoker Adults: The Korean National Health and Nutrition Examination Survey 2010-2012	Non-smoking adults who participated in the 2010-2012 Korean National Health and Nutrition Examination Survey (KNHANES)	6,043 adults	Self-reported measurements on depressive symptoms Individuals who reported depressive symptoms for at least 2 continuous weeks in the last year	Self-reported measurements on exposure to passive smoking Exposed group consisted of participants who reported that they were exposed to secondhand smoking for less than 1 hour or 1 hour or more.	Age, employment status, house income, education, health insurance, marital status, number of familial member, subjective body perception, subjective health status, number of chronic disease, cancer, sleeping hours, and alcohol use disorders	Logistic regression	No association between SHS and depression overall, OR 1.02 (95% CI, 0.866–1.299) Depression and SHS among those exposed at home, OR 1.62 1.298–2.017
Khan, 2015 Prenatal exposure to secondhand smoke may increase the risk of postpartum depressive symptoms	Participants in the North Carolina Pregnancy Risk Assessment and Monitoring System (PRAMS)	6884 women	Responding to the interview questions asking about post-partum depression.	Self-reported exposure to secondhand smoke	Maternal race, income, Medicaid recipient status, physical activity during pregnancy, pregnancy-induced hypertension and timing of entry into prenatal care.	Logistic regression	OR between SHS and PPDS: OR = 1.49, 95% CI: 1.23–1.80)

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Kim 2016a Secondhand smoke exposure and mental health problems in Korean adults	Participants in the 2011 Korean Community Health Survey	123665 (22,818 men and 100,847 women)	Depressive symptoms via asking "Have you felt little pleasure or hopeless continuously for over two weeks during the past year, and did this impact on your everyday life?" Presence of diagnosed depression via asking, "Have you ever been diagnosed with depression by a doctor?"	At home interviews asking about secondhand smoke exposure	Demographic factors, lifestyle, and chronic disease	ANOVA and a chi-square test, logistic regression	Adjusted OR for depression depressive symptoms with 1-<3 hr/d and ≥3 hr/d SHSE were 1.44 (95% CI, 1.14 to 1.82) and 1.59 (95% CI, 1.46 to 1.74), respectively. SHSE ≥3 hr/d had a higher OR of 1.37 (95% CI, 1.20 to 1.58) for diagnosed depression.
Kim, 2015a Association between environmental tobacco smoke and depression among Korean women	Women in the 2008-2011 Korean Genome and Epidemiology Study (KoGES)-Kangwha	1201 Women age 39-85 years	Depressive symptoms measured via the Beck Depression Inventory (BDI) questionnaire	Self-reported exposure to environmental tobacco smoke (ETS)	Age, BMI, menopause, household income, employment, alcohol intake, regular exercise, hypertension, diabetes, hypercholesterolaemia and psychosocial stress.	Linear and logistic regression	Depression for overall ETS exposure vs. no exposure: OR= 1.72 (95% CI: 1.25, 2.37) Occasional exposure vs. no exposure: OR= 1.56 (95% CI: 1.09, 2.24) Regular exposure vs. no exposure: OR= 2.19 (95% CI: 1.30, 3.69)

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Mbah, 2013 Exposure to environmental tobacco smoke and risk of antenatal depression: application of latent variable modeling	Pregnant women from the Tampa General Hospital Genesis Clinic, an obstetric clinic, in 2009 to 2011	236 Women age 18-44 years	Depression measured by the Edinburgh Perinatal Depression Scale (EPDS)	Self-reported passive smoke exposure with salivary cotinine confirmation	Marital status, smoking during pregnancy, race/ethnicity and obesity status	Latent variable modeling,	Depressive symptoms increased among all EPDS items for passive smoke exposure: Lowest adjusted OR among the 10 items: OR= 1.34 (95% CI: 1.28, 1.40)
Michal, 2013 Association of mental distress with smoking status in the community: Results from the Gutenberg Health Study	Participants free of chronic cardiovascular or lung disease in the Gutenberg Health Study	162	Depression measured by the Patient Health Questionnaire (PHQ-9)	Self-reported exposure to SHS via structured interview	Stratified by presence of chronic heart or lung disease Adjusted for age, sex, socioeconomic status, and partnership	Multinomial regression analysis	Association of SHS exposure with depression, measured by the Patient Health Questionnaire among those without chronic cardiovascular or lung disease, OR 1.62 (1.00–2.60), p=0.048 Association among the 19 participants with chronic cardiovascular or lung disease, OR 2.93(0.95–8.98), p=0.061

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Taha, 2014 Secondhand smoke exposure across the life course and the risk of adult-onset depression and anxiety disorder	Enrollees of the Midlife Development in the United States Survey (MIDUS)	2053 Adults	Depression measured by the Composite International Diagnostic Interview Short Form scales	Childhood and adult secondhand smoke exposure measured via asking if anyone who smoked lived with participant during childhood or currently lives with person	Age, gender, education level, and total household income from wages, pensions, social security, government assistance, lifetime daily smoking, physical abuse, and substance use	Logistic regression	Childhood SHS only and major depressive disorder (MDD): OR= 0.9 (95% CI: 0.6, 1.4) Adult SHS only and MDD: OR= 1.1 (95% CI: 0.7, 1.7) Both childhood and adult SHS exposure and MDD: OR= 1.8 (95% CI: 1.3, 2.6)
Tan, 2011 Relationships between self-reported smoking, household environmental tobacco smoke exposure and depressive symptoms in a pregnant minority population	Pregnant minority women residing in Washington, DC	929 Women age >18 years	Self-reporting smoke exposure and household environmental tobacco smoke exposure (HH-ETSE)	Beck Depression Inventory Fast Screen (depression is an exposure in this study to examine if it is a potential mediator)	Age, education, marital status, employment, and trimester of pregnancy (third vs. first/second)	Logistic regression	Prenatal HH-ETSE and moderate-to-severe depressive symptoms among non-smokers: OR= 2.5 (95% CI: 1.2, 5.2] Current smoking and moderate-to-severe depressive symptoms among smokers: OR= 1.9 (95% CI: 1.1, 3.5) Current smoking and mild depressive symptoms among smokers: OR= 1.8 (95% CI: 1.1, 3.1)

Table 1.5. Depression and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Weng, 2016 Effects of tobacco exposure on perinatal suicidal ideation, depression, and anxiety	Pregnant women and 1 month postpartum women in 5 hospitals in Taipei, Taiwan	3867	Depression measured via Edinburgh Postnatal Depression Scale (EPDS)	Self-assessed questionnaire asking about secondhand smoke exposure: "Does anyone smoke around you in your home or workplace?"	Perinatal period, marital status, monthly income, employment status, educational level, planned pregnancy, history of depression, and sleeping problems	Chi-square, multivariate logistic regression	Adjusted OR for depression among the women who had high secondhand smoke exposure: 1.55 (95 % CI = 1.20–2.01)
Ye, 2015 Dose-response relations between second-hand smoke exposure and depressive symptoms among middle-aged women	Middle-aged women in Guangzhou City	1280 non-smokers, middle-aged women	Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale	Self-reported exposure to secondhand smoke	Adjusted for: age, number of chronic diseases, marital status, employment, education, family monthly income, locality type, BMI, pressures in life, Kupperman menopausal index, social support, negative life events and history of depression.	Logistic regression	OR of depressive symptoms corresponding to SHS exposure in general (OR=2.04, 95% CI 1.48–2.79) using no exposure as reference.

Other Pollutants

There were eleven studies evaluating depression and other environmental pollutants. Four studies examined contaminants in biosamples collected from participants. The largest study was a cross sectional analysis by Berk et al. (2014) that included 15,140 adults who participated in one of three waves (2005–2006, 2007–2008 and 2009–2010) of the NHANES in which depression was assessed by the PHQ-9. In adjusted models many of the blood polyfluorinated compounds were significantly associated with less depression, as were urinary levels of the phenols benzophenone-3 and triclosan. However, no significant association was found between other urinary phenols or phthalates. In contrast, Shiue (2015) used urine biomarker data from NHANES from 2011-2012 and the same PHQ-9 depression assessment and found several phthalates to be associated with significantly increased depression. Other than the NHANES wave, the analysis and adjustments were similar between the Berk et al. (2014) and Shiue (2015) papers. Shiue (2015) also found most urinary polyaromatic hydrocarbons to be associated with significantly elevated OR for depression. Kim, Choi, Lim, and Hong (2016) used data from 2030 adults age 60 and older in the 2005-2012 NHANES waves to examine the association between 10 urinary phthalate metabolites and depression measured with the PHQ-9. Mono-(3-carboxypropyl) phthalate (MCPP), mono(carboxynonyl) phthalate (MCNP), and mono-n-butyl phthalate (MBP) were associated with depression. Most of the toxicants examined by Berk et al. (2014), Shiue (2015), and Kim, Choi, Lim, et al. (2016) have short half-lives and so one measure may not reflect longer term exposure well, which could add error to the estimation of exposures over relevant time periods and so contribute to differences in findings particularly in cross sectional studies such as NHANES. Polyfluorinated compounds, however, have half-lives on the order of several years and so are a somewhat better cumulative exposure estimate.

Polychlorinated biphenyls (PCBs) have even longer half-lives in blood than polyfluorinated compounds and so one blood measure is a good cumulative exposure estimate. Fitzgerald et al. (2008) studied the relationship between serum PCB concentrations and depression assessed with the BDI among 243 older adults in New York. A significant positive adjusted association existed between serum PCB concentrations and depressive symptoms (Fitzgerald et al., 2008).

Three studies used modeled or area estimates of toxicant exposures and depression. Yen et al. (2014) evaluated 1,621 residents of public buildings constructed using steel reinforcement bars contaminated with Cobalt-60. Exposure was estimated utilizing the Taiwan cumulative dose (TCD) exposure assessment system, which combines participant questionnaires detailing time spent in different rooms of contaminated housing during the contaminated period and measurements of exposures in the different rooms. A significant positive adjusted association was detected between depression assessed via the BDI and higher cumulative radiation exposure with the suggestion that exposure before age 12 mattered more (Yen et al., 2014). Reif et al. (2003) estimated exposure to trichloroethylene (TCE) in the Rocky Mountain Arsenal area using a hydraulic simulation modeling in conjunction with GIS to assign residential water levels. There was a trend towards worse depression scores assessed with the profile of mood states (POMS) and higher estimated residential TCE levels among the 143 participants although it did not reach statistical significance. However, a significant positive association was found with TCE levels among those who consumed at least one alcoholic drink per month. K. C. Lin, Guo, Tsai, Yang, and Guo (2008) conducted a study of the Yucheng cohort. They compared 162 subjects exposed to PCBs and polychlorinated dibenzofurans (PCDFs) from contaminated cooking oil and 151 unexposed subjects who were now over 60 years. No significant differences were found using the Geriatric Depression Scale-Short Form (GDS-S) to measure depressive symptoms.

Three studies considered electromagnetic fields (EMF). Abdel-Rassoul et al. (2007) compared 85 subjects living or working near a mobile phone base station antenna to 80 who worked more than 2km away. They found a significantly higher prevalence of depression symptoms measured by questionnaire among those living near the base station. While the hypothesis focused on exposure to radiofrequency radiation, the study design cannot exclude other factors related to living near a mobile phone base station including simple perception of being close to such an exposure. Beale, Pearce, Conroy, Henning, and Murrell (1997) conducted an investigation among 540 adults (participation of ~50% of households approached) living near high voltage power transmission lines in New Zealand and took multiple magnetic field measurements in rooms of each home where occupants stayed at least an hour per day to estimate exposures. Depression measured by the GHQ was significantly associated with magnetic field exposure (Beale et al., 1997). McMahan, Ericson, and Meyer (1994) evaluated depression among 152 women via the CES-D and found no significant differences in depression scores among those living adjacent to high-voltage transmission lines or one block away, even after stratifying by demographic variables.

Lastly, Farrow, Taylor, Northstone, and Golding (2003) conducted a large study focused specifically on post-partum depression—measured by the Edinburgh Postnatal Depression Score (EPDS) at eight months postpartum—among 10,976 women from the Avon Longitudinal Study of Parents. Measurement of indoor exposures to VOCs were done in 170 homes and models built to determine which products in the home correlated with total VOCs. The association between specific products and depression was then assessed. Air fresheners, aerosols, and carpet cleaners significantly predicted total VOCs, but few mothers used carpet cleaners so they were not considered further. Mothers who used air fresheners daily or most days had significantly worse

depression scores compared with never or once-a-week users. Using aerosols were not significantly associated with depression (Farrow et al., 2003). Table 1.6 outlines the studies on depression and other pollutants.

Table 1.6. Depression and exposure to other pollutants

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Abdel-Rassoul, 2007 Neurobehavioral effects among inhabitants around mobile phone base stations	Participants living near mobile phone base station antennas in in Shebin El-Kom City	165 Adults	Depression measured by the middle six questionnaire for assessment of psychological status and diagnosis of psychiatric disorders, from the El-Kasr El-Aini Hospital Psychiatric Department	Radiofrequency radiations (RFR) from mobile phone base station antennas, exposed defined as living under or 10 meters away from antennas, unexposed defined as living 2 kilometers from antennas	Matching control group on age, sex, occupation (employees and agriculture engineers), education level and mobile phone use	Chi-square, student t-tests and analysis of covariance (ANCOVA)	Depressive symptoms, exposed vs. unexposed: Chi-square= 4.03 (p<0.05) OR= 2.80 (95% CI: 1.02, 7.94)
Beale, 1997 Psychological effects of chronic exposure to 50 Hz magnetic fields in humans living near extra-high-voltage transmission lines	Participants having lived at least 6-months at residence in the Auckland Metropolitan area	540, Age 18-70 years	Major depression measured by the General Health Questionnaire-28 (GHQ)	Exposure to 50 Hz magnetic field by measuring 50 Hz magnetic field flux densities in rooms of homes	Age, gender, socioeconomic level, and life changes, self-rated health and perceived effect of power lines on personal health	Linear regression	Change in GHQ score for depression per unit change in time-integrated exposure to 50 Hz magnetic fields: beta= 0.0022 (95% CI: 0.00024, 0.0042), p= .029
Berk, 2014 Pop, heavy metal and the blues: Secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES national epidemiological survey	Participants in one of the three waves (2005–2006, 2007–2008 and 2009–2010) of the NHANES	15140, Age 31-63 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Persistent organic pollutants (POPs) in blood	Demographics and socioeconomic status (age, sex, poverty, family income, ethnicity and country of birth), cotinine levels and chronic medical illness, blood levels of cholesterol, glucose and creatinine	Prevalence ratios (PR) calculated via binary Poisson regression with robust estimation of SE	Blood POPs and depression: PR= 0.63 (95% CI: 0.44, 0.89) Perfluorooctanoic acid PR= 0.67 (95% CI: 0.49, 0.92) Perfluorohexane sulfonic acid PR= 0.62 (95% CI: 0.45, 0.86) Perfluorodecanoic acid PR= 0.63 (95% CI: 0.43, 0.92) Perfluorononanoic acid Urinary phenols and depression: PR= 0.55 (95% CI: 0.34, 0.88) Benzophenone-3 PR= 0.66 (95% CI: 0.47, 0.93) Triclosan

Table 1.6. Depression and exposure to other pollutants (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Farrow, 2003 Symptoms of mothers and infants related to total volatile organic compounds in household products	Women from the Avon Longitudinal Study of Parents	10119 Adults	Depression measured by the Edinburgh Perinatal Depression Scale (EPDS)	Indoor levels of total volatile organic compounds measured by air sampling	Age, highest education level of mother, housing tenure, number of children in the home, number of smokers in the home, mother's paid job status subsequent to the birth, dampness, condensation, or mold in the home, type of winter heating fuel, and month questionnaire was completed	Logistic regression	Maternal depression and daily use of air fresheners (n=3025) at 8 months postnatal: OR= 1.19 (95% CI: 1.05, 1.36) Maternal depression and daily use of aerosol (n=6134) at 8 months postnatal: OR= 1.03 (95% CI: 0.91, 1.17)
Fitzgerald, 2008 Polychlorinated biphenyl exposure and neuropsychological status among older residents of upper Hudson River communities	Participants living near upper portions of the Hudson River in New York, 2000-2002	243, Age 55-74 years	Depression assessed using the Beck Depression Inventory (BDI)	Polychlorinated biphenyls (PCBs) in blood serum	BMI, trait anxiety, employed, gout medications, antidepressants	Linear regression	Change of BDI total score per unit change in log transformed serum PCB: beta= 1.189 (SE: 0.438), p= 0.007 Test of linear trend for increasing mean total BDI score over quartiles of total serum PCBs p= 0.048

Table 1.6. Depression and exposure to other pollutants (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Kim, 2016 Urinary phthalate metabolites and depression in an elderly population: National Health and Nutrition Examination Survey 2005-2012	Participants in the 2005 to 2012 National Health and Nutrition Examination Survey	2030 participants aged 60 years or older	Depression measured by the Patient Health Questionnaire (PHQ-9)	Urinary phthalate metabolites	Adjusting for age, sex, race/ethnicity, education level, income-to-poverty ratio, smoking status, alcohol consumption, NHANES cycle, and urinary creatinine concentration	Logistic regression	Mono-(3-carboxypropyl) phthalate (MCPP), mono(carboxynonyl) phthalate (MCNP), and mono-n-butyl phthalate (MBP) were associated with depression
Lin, 2008 Neurocognitive changes among elderly exposed to PCBs/PCDFs in Taiwan	Participants from the 1979 Yucheng cohort in Taiwan	156, Age ≥ 60 years	Depression measured via the Geriatric Depression Scale-Short Form (GDS-S)	Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) from ingestion of contaminated cooking oil, measured by serum PCB levels	Matching control group on age, sex, and neighborhood Regression models adjusted for age and education	Linear regression, t-tests, Wilcoxon rank sum	Total GDS-S scores mean $\pm$ SD: Exposed males: 6.7 ± 2.2 Reference males: 6.6 ± 2.0 $p = 0.72$ Exposed females: 6.7 ± 2.1 Reference females: 6.7 ± 1.6 $p = 0.82$
McMahan, 1994 Depressive symptomatology in women and residential proximity to high-voltage transmission lines	Women living in Orange County, California	152 women	Center for Epidemiological Studies Depression scale (CES-D)	Living either adjacent to a transmission line or one block away. Magnetic field levels taken at front door of homes	Stratified by each risk factor: living on easement, ethnicity, age, tenure at residence, education, income	Stratified analysis	No significant differences in depression scores among those living adjacent to high-voltage transmission lines or one block away, even after stratifying by demographic variables

Table 1.6. Depression and exposure to other pollutants (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Reif, 2003 Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply	Residents of community with trichloroethylene (TCE) contaminated municipal water, 1981-1986	143 Adults	Depression measured by profile of mood states (POMS)	Trichloroethylene (TCE) and related chemicals from hazardous waste sites in residential water, measured via hydraulic simulation model and geographic information system (GIS)	Consumption of seafood once a week or more, years of education, current or previous smoking, and alcohol consumption	Multivariate analysis of variance via generalized linear model	Difference of mean POMS depression state scores between highest TCE category (>15 ppb) and lowest (<=5 ppb): +83% p=0.08 Difference of mean POMS depression state scores between highest TCE category (>15 ppb) and lowest (<=5 ppb) among those consuming alcohol: +204% p<0.01
Shiue, 2015 Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011-2012	Adults who participated in the 2011–2012 NHANES	5560, Age 20-80 years	Symptoms of depression via the Patient Health Questionnaire (PHQ-9)	Phthalates and polyaromatic hydrocarbons (PAHs) in urine	Age, sex, body mass index, education, ratio of family income to poverty, serum cotinine (smoking status), alcohol status, physical activity level, urinary creatinine	Survey-weighted logistic regression	Phthalates associated with depression: mono-2-ethyl-5-carboxypentyl, mono-n-butyl, mono-isobutyl, and mono-benzyl PAHs: 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

Table 1.6. Depression and exposure to other pollutants (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Yen, 2014 Risk factors of depression after prolonged low-dose rate environmental radiation exposure	Participants in the annual physical examinations of users of radiation-contaminated buildings between 2009 and 2009	1621, Age 18 years or older	Depressive symptoms measured via the Chinese version of the Beck depression inventory (BDI)-1A questionnaire	Radiation from steel reinforcement bars contaminated with cobalt 60, the cumulative excess radiation to which the participants were exposed by using the Taiwan cumulative dose (TCD) exposure assessment system	Age, sex, education, depression history	Logistic regression, generalized estimating equation	Risk of depression and >5 milli-Sievert (mSv) cumulative dose: OR= 1.46 (95% CI: 1.02, 2.07) Risk of depression and being male: OR= 1.80 (95% CI: 1.09, 2.96) Depression tendency among those <=12 years of age when informed of exposure (>=18 years as reference) and >5 mSv cumulative dose : OR= 1.86 (95% CI: 1.05, 3.30)

Anxiety

Metals

There were ten studies that examined exposure to metals and anxiety, and all but three considered depression and were described in the depression section above. Only the study by Mukherjee et al. (2014), described above, did not use biomarkers of exposure. They found significantly worse anxiety measured by the subjective symptoms questionnaire accompanying the World Health Organization Neurobehavioral Core Test Battery among the women in high endemic water arsenic areas.

Four studies described in the depression section above also considered anxiety in association with lead biomarkers. Bouchard et al. (2009) found blood lead to be associated with CIDI-defined panic disorder, but not generalized anxiety disorder in NHANES data. Rhodes et al. (2003), found patella bone lead to be associated with worse BSI anxiety score in the NAS, while both patella and tibia bone lead, and blood lead were significantly associated with a combined anxiety and depression score. Eum et al. (2012) found tibia bone lead to be associated with higher scores on the Crown-Crisp phobic anxiety scale among elderly women in the NHS. McFarlane et al. (2013) found a near significant positive association between early childhood blood lead levels and anxiety problems at ages 25-29 years assessed with the Adult Self-Report (ASR) (the adult version of the Child Behavior Checklist) only among females. They did not find an association between childhood blood lead levels and adult panic attacks as assessed with the CIDI.

Three studies described in the depression section above considered Mn exposure. The R. M. Bowler et al. (1999) study also found associations between blood Mn levels and anxiety

measured with the POMS and BSI. Among men less than 50 years of age, higher blood Mn was associated with significantly lower anxiety scores, while among men 50 years and older higher blood Mn levels were associated with significantly higher anxiety scores. As with depression, mentioned above, the subsequent study of the same population suggested that those at higher risk for alcohol use disorders showed a significant association between blood Mn and anxiety (Sassine et al., 2002). Unlike for depression in the study by (Rosemarie M. Bowler et al., 2012). Anxiety symptoms were assessed via the Symptom Checklist-90-Revised (SCL-90-R) and were significantly higher in the exposed town than the control, although the two groups had similar blood manganese levels (Rosemarie M. Bowler et al., 2012). Because blood Mn is under tight homeostatic control, it is possible that it is not as effective at identifying higher Mn exposures as is simply living in the area with higher air Mn concentrations. Other differences between the two areas cannot be ruled out as accounting for the differences in anxiety scores, but anxiety scores within the exposed town increased significantly with increasing estimated cumulative air Mn exposure based on a dispersion model average over a 5 year period.

Mercury was considered in the Bailer et al. (2001) study among 83 women mentioned above for depression. No associations between blood, urine, or saliva Hg concentrations and anxiety scores on the SCL-90-R were found. The study described in the depression section above of patients complaining of oral galvanism or mercury poisoning from dental amalgams and matched controls also considered anxiety and saw no association with Hg biomarkers, but suffered from the same problems described above (Bratel et al., 1997). Table 1.7 outlines the studies on anxiety and metals.

Table 1.7. Anxiety and exposure to metals

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bailer, 2001 Adverse health effects related to mercury exposure from dental amalgam fillings: Toxicological or psychological causes?	Women who had three or more amalgam fillings at time of examination (Jan 1997 to Dec 1998)	83, Women age 18-55 years	Anxiety symptoms measured via somatic symptoms (SOMS) in the SCL-90-R Somatization scale	Mercury in blood, urine, and saliva	Non-parametric analyses	Mann–Whitney U for non-parametric tests, chi-square for frequency comparisons, Pearson's correlations	Amalgam sensitive subjects had a self-concept of being weak and unable to tolerate stress, more cognitions of environmental threat, and increased habitual anxiety. Mean anxiety scale scores: Amalgam sensitive subjects, 53.3 (SD 12.2) Non-sensitive subjects, 47.7 (SD 11.2) ANCOVA F= 6.55 p>0.05
Bouchard, 2009 Blood lead levels and major depressive disorder, panic disorder, and generalized anxiety disorder in US young adults	Adults who participated in the 1999-2004 NHANES	1987, Age 20-39 years	Anxiety determined via the World Health Organization Composite International Diagnostic Interview (CIDI)	Lead in blood	Age, sex, race/ethnicity, education, poverty income ratio	Logistic regression	Increasing blood levels not associated with generalized anxiety disorder (p trend 0.75).
Bowler, 1999 Neuropsychiatric effects of manganese on mood	Residents who live in Southwest Québec downwind of point source, study results focused on men	273, Age 20-70	Anxiety measured via profile of mood states (POMS), Brief Symptom Inventory (BSI)	Manganese in blood	Age, education level, smoking status, alcohol intake, interaction of blood manganese and gender, interaction of blood manganese and age, fish consumption	T-tests, general linear model MANOVA	Blood manganese and age interaction found only among men. POMS: Men <50yrs and higher blood manganese (≥ 7.5 ug/L): significantly lower scores on Anxiety, no sig. difference for Depression Men ≥ 50 yrs and ≥ 7.5 ug/L: significantly higher scores on Depression and Anxiety BSI: Men <50yrs and higher blood manganese (≥ 7.5 ug/L): significantly lower scores on Anxiety, no sig. difference for Depression Men ≥ 50 yrs and ≥ 7.5 ug/L: significantly higher scores on Depression and Anxiety

Table 1.7. Anxiety and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bowler, 2012 Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure.	Randomly selected controls and residents of a community with elevated Mn-Air from industrial emissions	190 adults	Anxiety measured via Symptom Checklist-90-Revised (SCL-90-R)	Manganese levels in the air	Non-parametric analyses	t-tests, Mann–Whitney U test, ANCOVA, Cohen’s effect size, percentile of the mean generalized anxiety T score, regression models	The group means (SD) of MnB: Exposed= 9.65 µg/L (± 3.21) Comparison= 9.48 µg/L (± 3.16) p= 0.702 SCL-90-R generalized anxiety T-score: Exposed= 54.1 ± SD 9.0 Comparison= 51.6 ± SD 7.0 p= 0.035
Bratel, 1997 Potential side effects of dental amalgam restorations. (II). No relation between mercury levels in the body and mental disorders	50 patients from Department of Oral Diagnosis Göteborg University complaining of oral galvanism or mercury poisoning. 50 controls matched to age, sex, and postal zip code	50 exposed, 50 controls	ICD-9 for psychiatric outcomes Comprehensive psychopathological rating scale (CPRS), Zung scale, Karolinska scales of personality (KSP), mood adjective checklist (MACL), multidimensional health locus of control (MHLC) scales, illness behavior questionnaire (IBQ), and life event scale.	Mercury levels determined in whole blood, plasma, urine, and hair. Looked at mercury levels in a group of individuals who reported complaints with their amalgam restorations.	Matched on age, sex, postal zip code	Student paired t-test, Wilcoxon test, Pearson correlation	They found a higher incidence of psychiatric diagnosis in individuals with the amalgam restorations than in the control group. However, they found no difference in mercury levels and no correlation between mercury levels and severity of reported symptoms. Reported symptoms were thought to be part of a broad spectrum of mental disorders instead of mercury levels.

Table 1.7. Anxiety and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Eum, 2012 Relation of Cumulative Low-Level Lead Exposure to Depressive and Phobic Anxiety Symptom Scores in Middle-Age and Elderly Women	Nurses' Health Study	617 Women, Age 45-79 years	Anxiety measured via phobic anxiety scale of the Crown-Crisp Index (CCI) assessment	Tibia and patella bone lead measurements via K-shell X-ray fluorescence (KXRF)	Age at bone lead and at MHI-5 measurement, education, husband's education, alcohol consumption, pack-years of smoking, and employment status at MHI-5 measurement	Generalized linear mixed model	Anxiety symptoms and tibia lead among women who were either premenopausal or postmenopausal and consistently on hormone replacement therapy: Highest tertile of tibia lead (>11.5 ug/g) vs. Lowest tertile (<0.7 ug/g) OR= 2.79 (95% CI: 1.02, 7.59). Anxiety symptoms and patella lead among those either premenopausal or postmenopausal and consistently on hormone replacement therapy: Highest tertile of patella lead (>14.5 ug/g) vs. Lowest tertile (<8.5 ug/g) OR= 0.23 (95% CI: 0.07, 0.69)
McFarlane, 2013 Prospective associations between childhood low-level lead exposure and adult mental health problems: the Port Pirie cohort study	Port Pirie cohort	210, Mean age 26 years	Lifetime prevalence of DSM-IV disorder as an adult via Composite International Diagnostic Interview (WMH-CIDI 3.0), Adult Self-Report (ASR), the adult version of the Child Behaviour Checklist	Childhood (age 7 years) blood lead levels	For Females: HOME scores, Mothers' age at birth, paternal occupation, breastfeeding For Males: HOME scores, paternal education and maternal education for depressive problems	Logistic and linear regression	Anxiety problems linear regression: Females beta= 1.2 (SE 0.6) p=0.059 Males beta= -0.2 (SE 0.6) p>0.10

Table 1.7. Anxiety and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Mukherjee, 2014 Platelet hyperactivity, neurobehavioral symptoms and depression among Indian women chronically exposed to low level of arsenic	Women chronically exposed to low levels of arsenic in India	654, Women age 23-45 years	Anxiety measured by the subjective symptoms questionnaire accompanying the World Health Organization Neurobehavioral Core Test Battery [WHO-NCTB]	Arsenic in drinking water	Age, education, cooking years, menstrual length, adverse reproductive outcome experienced in past 1 year and family income	Chi-square test, Logistic regression	Prevalence of anxiety symptoms: Residing in endemic areas 43.3% vs. control areas 18.0% ($p < 0.001$) Arsenic in groundwater and anxiety in adjusted logistic regression model: OR = 1.49 (95% CI: 1.16, 3.46)
Rhodes, 2003 Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study	Veterans who participated in the Normative Aging Study	526, Men age 48-70 years	Symptoms of anxiety via the Brief Symptoms Inventory	Lead in blood and bone	Age, alcohol, education, and employment variables	Logistic regression	Anxiety Blood Pb OR= 1.024 (95% CI: 0.967, 1.085) Tibia Pb OR= 1.005 (95% CI: 0.986, 1.024) Patella Pb OR= 1.011 (95% CI: 0.999, 1.024) Phobic Anxiety Blood Pb OR= 1.056 (95% CI: 0.986, 1.130) Tibia Pb OR= 1.015 (95% CI: 0.994, 1.037) Patella Pb OR= 1.015 (95% CI: 1.000, 1.029)

Table 1.7. Anxiety and exposure to metals (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Sassine, 2002 Manganese accentuates adverse mental health effects associated with alcohol use disorders	Current drinkers of alcohol who live in Southwest Que'bec downwind of point source	253, Age 20-69 years	Alcoholism via CAGE, Anxiety measured via French Canadian version of the Brief Symptom Inventory (BSI)	Manganese in blood	None, utilized non-parametric analyses	Mann-Whitney U or t-tests for non-parametric analysis, chi-square, Spearman rank correlations, (ANOVA) or Kruskal-Wallis	Brief Symptom Inventory relative scores: Difference among all three risk levels for alcohol use disorders $p < 0.001$ High risk for alcohol use disorders had greatest BSI relative depression scores mean= 57.9 (SE 1.9). The differences in BSI relative score for anxiety were greatest among the three levels than the differences in the three levels in depression scores. Stratified by blood manganese levels, there was a significant difference ($p < 0.001$) in BSI relative score for anxiety and depression among the levels of risk for alcohol use disorders in the high blood manganese level group (≥ 7.5 ug/L), while the low blood manganese level group (< 7.5 ug/L) did not.

Air Pollution

There were three studies on air pollution and anxiety, two of which considered daily ambient air pollutant concentrations and hospital emergency department (ED) visits for anxiety. The Mieczyslaw Szyszkowicz (2007) paper described in the depression section above that used data from five hospitals in Edmonton, Canada, also considered associations with anxiety. They found no association between all measured ambient pollutants (NO₂, SO₂, O₃, PM₁₀, PM_{2.5}) in the study and the 23,178 ED visits for anxiety. Another paper by Cho et al. (2015) considered ED visits for panic attacks. They found a significant positive association between O₃ concentration on the same day or any of the prior three days (as well as averages of those) and risk of ED visits for panic attacks, but no association was found with the other pollutants in the study (NO₂, SO₂, CO, and PM₁₀).

The only study to explore individual level anxiety symptoms was by Power et al. (2015) who analyzed over 71,000 women in the Nurses' Health Study (NHS). The nurses completed the Crown-Crisp index phobic anxiety scale as part of their regular NHS questionnaires and exposure to particulate matter (PM) was estimated using well-validated spatiotemporal models of ambient exposure at the nurses' residences. They found a significant positive increase in the odds of having high anxiety symptoms with higher exposure to PM_{2.5}, but not PM₁₀. The association appeared driven by more recent exposures (prior weeks to months) rather than longer term past exposure (prior year or more). Table 1.8 outlines the studies on anxiety and air pollution.

Table 1.8. Anxiety and exposure to air pollution

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Cho, 2015 Ambient ozone concentration and emergency department visits for panic attacks	People visiting the emergency department in 2005–2009 in Seoul, Republic of Korea.	2320 emergency department visits for panic attacks, adults	Diagnosis of ‘panic disorder without agoraphobia’ (F41.0) measured via the International Classification of Diseases, 10th revision (ICD-10), defined “emergency department visit for panic attack” as an emergency case with F41.0.	CO, NO ₂ , O ₃ , SO ₂ , PM ₁₀ Monitoring data from Ministry of Environment	time-series study using a generalized additive model with a Poisson distribution	Time series, generalized additive model with Poisson distribution	The adjusted RR of panic attack-related emergency department visits: Same-day exposure to ozone: 1.051 (95% CI: 1.014, 1.090) Cumulative model for Lag 0-2 days: 1.068 (95% CI: 1.029, 1.107) Cumulative model for Lag 0-3 days: 1.074 (95% CI: 1.035, 1.114)
Power, 2015 The relation between past exposure to fine particulate air pollution and prevalent anxiety: observational cohort study	Women participating in the Nurses' Health Study	71271, Women age 57-85 years	Anxiety measured via the Crown-Crisp index phobic anxiety scale	Fine particulate air pollution measured via distance to a major road. Spatiotemporal prediction models yielding monthly estimates of exposure to particulate matter <10 µm (PM ₁₀) and <2.5 µm (PM _{2.5} or fine particulate matter)	Month of questionnaire return, nurse's education, husband's education, age, age squared, whether the nurse has a partner, employment status, physical activity, percent of residential census tract that is white, percent of residential census tract adults who lack a high school education, median home value of residential census tract, geographic region, residence within a metropolitan statistical area, and social support.	Logistic regression	Odds ratio of having high symptoms of anxiety per 10 µg/m ³ increase in PM _{2.5} exposure over multiple averaging periods: 1 month OR= 1.12 (1.06 to 1.19), p=0.0001 3 months OR= 1.13 (1.06 to 1.21), p=0.0004 6 months OR= 1.14 (1.05 to 1.23), p=0.002 12 months OR= 1.15 (1.06 to 1.25), p= 0.001 1988-2003 OR= 1.09 (1.01 to 1.18), p=0.03

Table 1.8. Anxiety and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Szyszkowicz, 2007 Air pollution and emergency department visits for depression in Edmonton, Canada.	People in Edmonton, Canada, served by five hospitals, years 1992 and 2002	23178 ED visits for anxiety	Diagnosis of anxiety measured via the International Classification for Diseases, 9th revision (ICD-9), rubric 300	CO, NO2, O3, SO2, PM10, PM2.5 Monitoring data from Environment Canada	Temperature and relative humidity	Generalized linear mixed models (Poisson), fixed slope, random intercept	All the results were negative; emergency department visits were not related to the ambient air pollutants in study (data not shown)

Pesticides

The review found no studies on pesticides and anxiety.

Noise

There were seven studies on noise and anxiety, four of which were described in the section above on depression. As noted in the depression section above, Sygna et al. (2014) found a significant positive association between road traffic noise level and an aggregated anxiety and depression symptoms measure (HSCL-25) in a Norwegian cohort. In the Stansfeld et al. (1996) study described in the depression section above, there were differences by road traffic noise exposure group in anxiety assessed with the GHQ, but not in a consistent pattern with increasing noise among men in the Caerphilly study. Hardoy et al. (2005) found higher prevalence of both generalized anxiety disorder and anxiety disorder not otherwise specified—measured with the CIDI—among the 71 living close to the commercial airport than among the 284 control residents in the same region. Tamini and Pak (2016) found higher anxiety among people living near the airport compared to in the city, although no adjustment for other factors was done.

Two much older studies took an experimental approach to assessing noise and anxiety. Edsell (1976) assessed state anxiety using the STAI before and after a social stress game played for an hour in the presence of low (51 dBA), medium (61 dBA) and high (75 dBA) noise. Among 48 students ages 18-26 randomized to exposure group the change in STAI state anxiety score was significantly greater with increasing noise level. Standing and Stace (1980) conducted a similar experiment among 45 students with a mean age of 19 randomized to the same noise levels as in the Edsel study, but without the social stress game. Instead, the subjects were given an intelligence test during the noise sessions, which were for only one half hour. Scores on both

the STAI state anxiety and Institute for Personality and Ability Testing (IPAT) anxiety scale were significantly higher in the highest noise group.

The Czaplik et al. (2016) clinical trial study described in the depression section above found no differences in anxiety scores in the ear plug trial, but did find differences for anxiety, although inconsistent ones. STAI anxiety was greater after the trial in the group with sound canceling headphones, although only significantly so for those without added sound masking, while HADS anxiety scores were lower in the group with sound canceling headphones, although only significantly so in the group with added sound masking. Table 1.9 outlines the studies on anxiety and noise.

Table 1.9. Anxiety and exposure to noise

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Czaplik 2016 Psychoacoustic analysis of noise and the application of earplugs in an ICU: A randomised controlled clinical trial	University hospital patients	144 patients in the ICU	Anxiety via State Trait Anxiety Inventory (STAI) score and Hospital Anxiety and Depression Scale (HADS) questionnaires administered at the beginning and end of the test period	Noise reduction via earplugs or noise cancelling using headphones	Randomized control trial, single blinded	analysis of variance (ANOVA), two-tailed t-test (level of significance 0.05 or 0.017 for three groups according to the Bonferroni correction)	Mixed results: STAI Anxiety score increased for those using noise reduction-activated ($p=0.01$) HADS Anxiety score decreased for those using noise reduction-activated ($p>=0.05$) and noise reduction with masking sound ($p=0.01$) No significant differences of HADS Depression score for using earplugs or noise cancelling headphones vs. not
Edsell, 1976 Anxiety as a function of environmental noise and social interaction	Students in a college Introduction to Psychology and a Human Engineering class	48, age 18-26 years	The State-Trait Anxiety Inventory (STAI), administered before and after playing the game, was used as a direct, subjective measure of anxiety. Eye blink test	Intermittent white noise at 61 dB(A) and 75 dB(A) was used for the Noisy and Very Noisy conditions, the ambient noise level of 51 dB(A) was used for Quiet. Three groups played the same game: quiet, noisy, and very noisy for one hour.	Non-parametric	Chi-square test	Median change in STAI scores between baseline and after the game: Quiet: -4.0 Noisy: -2.0 Very noisy: +3.0 Frequency of STAI scores above and below the combined group median among noise groups: Chi-square= 6.0, df=2, $p<0.05$
Hardoy, 2005 Exposure to aircraft noise and risk of psychiatric disorders: the Elmas survey	Residents of the district of Giliaquas in the vicinity of Elmas airport	355 Adults	Anxiety measured by Composite International Diagnostic Interview (CIDI) Simplified	Aircraft noise, represented by those living about one mile from airport, controls were residents in the same region	Controls matched on sex, age and employment status	Chi-square test, odds ratios and confidence intervals calculated via the method of Miettinen	Generalized Anxiety Disorder OR= 2.0 (95% CI: 1.0, 4.2), chi-square= 4.4, $p<0.05$ Anxiety Disorder Not Otherwise Specified OR= 2.9 (95% CI: 1.0, 4.1), chi-square= 4.1, $p<0.05$

Table 1.9. Anxiety and exposure to noise (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Standing, 1980 The effects of environmental noise on anxiety level	Students in a college Introduction to Psychology class	45, mean age 19 years	State-Trait Anxiety index (Qx) Institute for Personality and Ability Testing (IPAT) objective anxiety test	Low (43 dB), medium (61 dB), or high (75 dB) levels of ambient white noise for 30 minutes	Non-parametric	Chi-square test, analysis of variance, Cochran and Bartlett Box tests	Mean (SD) in STAI scores between baseline and after the game: Quiet: 36.29 (2.95) Noisy: 35.93 (7.43) Very noisy: 43.94 (5.52) Analysis of variance, F (2, 42)= 9.91, p<0.001 Frequency of STAI scores above and below the combined group median among noise groups: Chi-square= 22.0, df=2, p<0.001 IPAT scores (measuring anxiety as a trait) did not increase after noise exposure.
Stansfeld, 1996 Road traffic noise and psychiatric disorder: prospective findings from the Caerphilly Study	Men in the Caerphilly study followed for 5 years	1725 Men age 50-64 years	30 item General Health Questionnaire (GHQ)	Road traffic noise measured by street measurements	Social class, employment status, marital status, physical illness, and baseline morbidity	Linear trend test	Adjusted mean anxiety score (SE) for levels of road traffic noise: 51-55 dBA: 4.70 (0.07) 56-60 dBA: 5.20 (0.18) 61-65 dBA: 4.89 (0.15) 66-70 dBA: 5.02 (0.21) Tests of heterogeneity p-value= 0.03

Table 1.9. Anxiety and exposure to noise (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Sygna, 2014 Road traffic noise, sleep and mental health	People in the Norwegian National Population Register who had addresses in the Norwegian Public Roads Administration and the City of Oslo database	2898, Age ≥ 18 years	Depression symptoms measured in aggregate with anxiety symptoms via Hopkins Symptom Checklist-25	Road traffic noise assessed at the most exposed façade of the home and calculated by the Nordic prediction method	Age, sex, education, employment, noise sensitivity, and somatic diseases.	Linear regression model, logistic regression model, multiple imputation	Odds ratio for scoring ≥ 1.55 on the Hopkins Symptom Checklist-25 per 10dB increase in road traffic noise exposure, by sleep quality: Good: 0.94 (95% CI: 0.79, 1.13) Medium: 0.98 (95% CI: 0.73, 1.31) Poor: 1.40 (95%CI: 0.99, 1.98)
Tamini, 2016 Comparative study of the effect of aircraft noise on emotional states between airport neighboring and city residents	Residents near airport of Zahedan, Iran	100 residents of Zahedan, 100 from neighboring airport	Depression, anxiety, and stress scale-21 (DASS-21)	Living near airport (airport neighboring) and locations with low to no exposure to aircraft noise (residents of Zahedan City)	Matched for sex in each exposure group (city, airport neighboring)	One-way between-groups multivariate analysis of variance (MANOVA)	No significant positive difference between the two groups regarding depression $F=1.37$ $p=0.243$ Significant positive differences regarding anxiety, stress and overall scores of DASS between airport neighboring and city residents in Zahedan city

Secondhand Smoke

Six studies examined secondhand smoke (SHS) and anxiety. The study in the MIDUS cohort by Taha and Goodwin (2014) described in the depression section above also considered adult onset anxiety using the CIDI Short Form anxiety scales. SHS exposure during childhood or adulthood alone was not associated with general anxiety disorder in adulthood, but SHS exposure in childhood or adulthood were significantly associated with increased panic attack in adulthood, although not when adjusted for cigarette smoking. In the Asbridge et al. (2013) study described in the depression section above SHS was significantly positively associated with self-reported diagnosed anxiety disorders. In the Michal et al. (2013) paper described earlier no association was found between SHS and anxiety, measured by the Generalized Anxiety Disorder scale, among 162 participants free of chronic cardiovascular or lung disease. However, an association was found among the 19 participants with chronic cardiovascular or lung disease.

In the Alibekova et al. (2016) study described in the depression section above, paternal smoking in the presence of the mother, but not smoking when the mother was not present, was associated with significantly elevated odds of anxiety in the mother during the post-partum period. In the Weng et al. (2016) paper described above no association was found between SHS exposure and anxiety measured with the STAI during pregnancy or within 1 month postpartum. The Bot et al. (2013) study described in the depression section also found no association between increased plasma cotinine levels and current anxiety (CIDI) or anxiety severity (ASR). Table 1.10 outlines the studies on anxiety and secondhand smoke.

Table 1.10. Anxiety and exposure to secondhand smoke

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Alibekova, 2016 Effects of smoking on perinatal depression and anxiety in mothers and fathers: A prospective cohort study	Couples from visits at the outpatient clinics of 5 selected hospitals in Taipei, Taiwan	533 couples (pregnant women and husbands)	Anxiety symptoms via assessed using the State-Trait Anxiety Inventory (STAI) Anxiety symptoms measured by 5 self-reporting instruments from early pregnancy until 6 months postpartum.	Father's smoking	Age, marital status, education level, employment status, family monthly income, parity, other secondhand smoke exposure, marital adjustment, parental stress, history of depression, the couple's depression status, and paternal alcohol use for the "perinatal period" and "during pregnancy" models. For the "postpartum period" model, results were adjusted for all parameters mentioned, in addition to the infant's health status at up to 6 months after birth.	Generalized estimating equations	Paternal smoking in the mother's presence also increased maternal disturbances, especially for depression during pregnancy (1.2, 95% CI=0.1-2.3) and anxiety during the postpartum period (3.4, 95% CI=0.6-6.3). No significant association was found between paternal smoking but not in the mother's presence and maternal emotional disturbances. Paternal smoking but not in the mother's presence affected only paternal anxiety, especially in the postpartum period (regression coefficient 2.7, 95% CI 0.7-4.7) compared with nonsmokers.
Asbridge, 2013 Private space second-hand smoke exposure and the mental health of non-smokers: a cross-sectional analysis of Canadian adults	People in the 2010 Canadian Community Health Survey, a representative sample of 62,909 Canadians	49,701 non-smokers including former and never smokers, age ≥ 12 years	Anxiety measured by asking, "Do you have an anxiety disorder such as a phobia, obsessive compulsive disorder, or a panic disorder?"	Second hand smoke measured by questionnaire on if anyone smokes inside participants' homes or vehicles	Age, sex, province, immigrant, marital status, low income, highest education, one or more children <12 years in home, own dwelling, never smoker, and any chronic disease Stratified analyses on respondent's smoking status, physical health, and gender, self-report of presence of SHS and mental health	Logistic regression	Odds ratio (Z-statistic) of having an anxiety disorder and SHS exposure among never smokers: OR=1.61; $p < 0.05$ SHS and mood disorders among females: OR=1.34 (2.05); $p < 0.05$ SHS and anxiety disorders among females: OR=1.47 (2.33); $p < 0.05$ SHS and mood disorders among males: OR= 0.92 (0.47); $p > 0.05$ SHS and anxiety disorders among males: OR=1.02 (0.11); $p > 0.05$

Table 1.10. Anxiety and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bot, 2013 Exposure to secondhand smoke and depression and anxiety: a report from two studies in the Netherlands	Netherlands Twins Register, Netherlands Study of Depression and Anxiety	2,845 non-smoking adults	Anxiety measured with Composite International Diagnostic Interview (CIDI), severity of anxiety in the past week was measured in all participants with the 21-item Beck Anxiety Inventory (BAI)	plasma cotinine levels	Age, sex, education level, North-European ancestry, body mass index, physical activity, alcohol use, number of chronic diseases under treatment, and former smoker	Logistic regression, Linear regression	No association between increased plasma cotinine levels and current anxiety (CIDI) or anxiety severity (ASR).
Michal, 2013 Association of mental distress with smoking status in the community: Results from the Gutenberg Health Study	participants free of chronic cardiovascular or lung disease in the Gutenberg Health Study	162	Anxiety measured by the Generalized Anxiety Disorder scale	Self-reported exposure to SHS via structured interview	Stratified by presence of chronic heart or lung disease Adjusted for age, sex, socioeconomic status, and partnership	Multinomial regression analysis	No association of SHS exposure with depression, measured by the Patient Health Questionnaire, OR 0.83(0.41–1.68), p=0.61 However, an association was found among the 19 participants with chronic cardiovascular or lung disease. OR 3.54 (1.05–11.91), p=0.041

Table 1.10. Anxiety and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Taha, 2014 Secondhand smoke exposure across the life course and the risk of adult-onset depression and anxiety disorder	Enrollees of the Midlife Development in the United States Survey (MIDUS)	2053 Adults	Anxiety measured via the Composite International Diagnostic Interview Short Form scales	Childhood and adult secondhand smoke exposure measured via asking if anyone who smoked lived with participant during childhood or currently lives with person	Age, gender, education level, and total household income from wages, pensions, social security, government assistance, lifetime daily smoking, physical abuse, and substance use	Logistic regression	Childhood SHS only and generalized anxiety disorder (GAD): OR=0.8 (95% CI: 0.3, 1.7) Adult SHS only and GAD: OR= 1.0 (95% CI: 0.5, 2.5) Both childhood and adult SHS exposure and MDD: OR= 1.7 (95% CI: 0.9, 3.4)
Weng, 2016 Effects of tobacco exposure on perinatal suicidal ideation, depression, and anxiety	Pregnant women and 1 month postpartum women in 5 hospitals in Taipei, Taiwan	3867	Anxiety measured with the Chinese version of STAI during pregnancy or within 1 month postpartum	Self-assessed questionnaire asking about secondhand smoke exposure: "Does anyone smoke around you in your home or workplace?"	Perinatal period, marital status, monthly income, employment status, educational level, planned pregnancy, history of depression, and sleeping problems	Chi-square, multivariate logistic regression	OR anxiety among exposed to SHS, 0.882 (0.248-3.138), p>0.05

Other Pollutants

Three studies—all described in the depression section above—also examined anxiety as an outcome. In the Beale et al. (1997) study of exposure to magnetic fields, the authors reported a significant positive association between magnetic field exposure and anxiety measured by the GHQ, adjusting for potential confounders. Reif et al. (2003) found that anxiety score assessed with the POMS increased over increasing TCE exposure categories, but the highest category was not statistically higher than the lowest. The only study to use a biomarker of exposure found no association serum PCB concentration and either state or trait anxiety symptoms assessed with the STAI (Fitzgerald et al., 2008). Table 1.11 outlines the studies on anxiety and other pollutants.

Table 1.11. Anxiety and exposure to other pollutants

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Beale, 1997 Psychological effects of chronic exposure to 50 Hz magnetic fields in humans living near extra-high-voltage transmission lines	Participants having lived at least 6-months at residence in the Auckland Metropolitan area	540, Age 18-70 years	Anxiety measured by General Health Questionnaire-28 (GHQ)	Exposure to 50 Hz magnetic field by measuring 50 Hz magnetic field flux densities in rooms of homes	Age, gender, socioeconomic level, and life changes, self-rated health and perceived effect of power lines on personal health	Linear regression	Change in GHQ score for anxiety per unit change in time-integrated exposure to 50 Hz magnetic fields: beta= 0.0052 (95% CI: 0.0016, 0.0090) p= 0.0084
Fitzgerald, 2008 Polychlorinated biphenyl exposure and neuropsychological status among older residents of upper Hudson River communities	Participants living near upper portions of the Hudson River in New York, 2000-2002	243, Age 55-74 years	Anxiety measured via the State-Trait Anxiety Inventory (STAI)	Polychlorinated biphenyls (PCBs) in blood serum	State anxiety t-scores adjusted for: BMI, income, trait anxiety, activity level, sex hormones Trait anxiety t-scores adjusted for: Depression, state anxiety, employed, sex hormones	Linear regression	Linear regression beta =change in test score per unit change in log transformed lipid basis serum PCB Anxiety inventory state, t-scores: beta= -1.249 SE=1.037 p=0.230 Anxiety inventory trait, t-scores: beta= -0.380 SE=0.935 p=0.685
Reif, 2003 Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply	Residents of community with trichloroethylene (TCE) contaminated municipal water, 1981-1986	143 Adults	Anxiety measured by profile of mood states (POMS)	Trichloroethylene (TCE) and related chemicals from hazardous waste sites in residential water, measured via hydraulic simulation model and geographic information system (GIS)	Consumption of seafood once a week or more, years of education, current or previous smoking, and alcohol consumption	Multivariate analysis of variance via generalized linear model	Difference of mean POMS anxiety state scores between highest TCE category (>15 ppb) and lowest (<=5 ppb): +28%, p= 0.24 Difference of mean POMS depression state scores between highest TCE category (>15 ppb) and lowest (<=5 ppb) among those consuming alcohol: +71%, p=0.05

Suicide

Metals

Two studies examined metals exposure and suicide and both were ecological in design. Schrauzer and Shrestha (1990) examined the relation between lithium levels in municipal drinking water in 27 Texas counties over a 10 year period and rates of suicide by county identified from annual US vital statistics. They found a significant negative (protective) association between municipal drinking water lithium concentrations and suicide rates in models adjusted for population density. Rihmer et al. (2015) examined age-standardized suicide rates across 1639 Hungarian settlements in relation to 4 categories of measured arsenic levels in drinking water. The study found an increasing suicide rate by exposure category, although the increase was similar in the three higher groups all above 10µg/L. Only the second quartile was significantly different, which likely related to sample sizes in the groups. No adjustments other than the age standardization were done. Table 1.12 outlines the studies on suicide and metals.

Table 1.12. Suicide and exposure to metals

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Rihmer, 2015 Preliminary investigation of the possible association between arsenic levels in drinking water and suicide mortality	Residents in Hungarian settlements, 2005-2011	1639 settlements, children and adults	Raw data on numbers of annual suicide cases and population for all Hungarian settlements were provided by the Hungarian Central Statistical Office	Arsenic in drinking water, measured by annual water reports to the National Drinking Water Database	Ecologic study, could not adjust for important medical social-economic status factors related to suicidal behavior Questionable if study really is measuring effect of arsenic or pre-existing depression or determinants of poor SES	ANOVA, student's t-test	Significant difference between mean number of cases of suicide among exposure categories of arsenic in drinking water (low, intermediate, high, very high) with increasing mean number of cases of suicide with increasing category of exposure: ANOVA $F=16.83$; $p<0.001$; $df=3$.
Schrauzer, 1990 Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions	Residents in the 27 counties, 1978-1987	Estimated total population 10,074,000 All ages	County suicide mortalities from annual US vital statistics handbooks issued by the Department of Health and Human Services	Lithium levels in water, grouped 27 Texas counties into High, Medium, and Low lithium content in municipal water (specific source of data not given)	Ecologic study adjusted for population density	Student's t-test	Reported significantly lower suicide rates in counties with higher lithium

Air Pollution

We identified ten studies on suicide and air pollution. One study involved a nationwide study of the 16 administrative regions of the Republic of Korea from 2006 to 2011 (Kim, Myung, et al., 2015). Suicides were measured by International Classification of Diseases-10 (ICD-10) codes from death records, and air pollutant monitor data were obtained from the Korean Ministry of Environment. A significant positive association was found between suicide rates and both ozone concentrations and particulate matter pollution over the prior several weeks. Associations were not seen with NO₂, CO, and SO₂. In Taipei city, Taiwan, between 1991-2008 monthly air pollutant monitoring data was related to monthly completed suicide data from the department of health (Yang, Tsai, & Huang, 2011). In models adjusted for unemployment and other weather variables SO₂ and O₃ were significantly associated with an increased risk of suicide, while CO was negatively associated and PM₁₀ was not associated. Mieczyslaw Szyszkowicz, Willey, Grafstein, Rowe, and Colman (2010) examined the association between daily monitor air pollution data for NO₂, SO₂, O₃, CO, PM₁₀, and PM_{2.5} and daily ED visits for suicide attempts or suicide ideation from 1999-2003 (n=1,605) at St. Paul's Hospital in Vancouver, Canada. No significant associations were found overall, but positive significant associations were found between suicide attempts and CO, NO₂, SO₂, and PM₁₀ 0-2 days prior for different strata of sex and season, with more significant findings among men in the cold season. No statistically significant associations were reported for the warm months: April to September. Yackerson, Zilberman, Todder, and Kaplan (2014) considered 426 suicide attempts from the Beer-Sheva Mental Health Center in Israel and air monitor data on concentrations of solid air suspended particles. Significant positive correlations between air particle concentrations and number of suicide attempts was found with eastern winds (from the desert), but not with

western winds (from the sea). Biermann et al. (2009) investigated a population based register of 1008 suicides and 917 suicide attempts in Middle-Franconia, Germany. While O₃ was higher on days with 2 or more suicides than on days with fewer, they reported no association between O₃ and suicides overall, although there was no analytic consideration of other factors.

Five studies used a case-crossover design. C. Kim et al. (2010) evaluated the association between ambient air particulate matter and 4,341 completed suicides over a one-year period in the Republic of Korea. Air particulate matter monitoring data were examined over 0-3 days prior to the suicide and compared to the same days of the other weeks of the month in which the suicide occurred. There was a significant positive association between suicide and up to two days prior exposure to PM₁₀ and one day prior exposure to PM_{2.5}, with slightly stronger associations with cumulative lags. Bakian et al. (2015) utilized air pollution monitor data for NO₂, SO₂, PM_{2.5} and PM₁₀ in Salt Lake County, Utah, and 1,546 completed suicides between 2000-2010 from the Utah Department of Health's Office of the Medical Examiner in a case-crossover analysis. They found a significant positive association between suicide and exposure to NO₂ 2 and 3 days prior (as well as a 3-day cumulative lag) and exposure to PM_{2.5} two days prior. Results seemed driven by those in men and there was some variation by season. G. Z. Lin et al. (2016) studied the 1,550 registered suicide deaths in Guangzhou, China during 2003-2012 in relation to PM₁₀, NO₂, and SO₂ averaged from monitors around the city. They found a positive association between PM₁₀ and NO₂ two days before the suicide and with SO₂ the day before. As in the Bakian et al. (2015) study, the results in Guangzhou were stronger among males and there was some variation by season. C. F. S. Ng, Stickley, Konishi, and Watanabe (2016) assessed the association between daily exposures to PM_{2.5}, suspended particulate matter (SPM), SO₂ and NO₂, averaged across monitors in the region, and suicide in Japan between 2001 and

2011. No significant associations were seen with exposures on the same day or any of the three prior days, although some significant associations were found in stratified sub-analyses.

Finally, Greenburg, Field, Erhardt, Glasser, and Reed (1967) examined suicide deaths in New York City during a two week period in 1963 with very high SO₂ and coefficient of haze levels in comparison with deaths in the same weeks during the other years between 1961-1965. Although the overall number of deaths during the 1963 period was significantly greater than in other years, researchers found no significant difference of deaths due to suicide. Table 1.13 outlines the studies on suicide and air pollution.

Table 1.13. Suicide and exposure to air pollution

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Bakian, 2015 Acute air pollution exposure and risk of suicide completion	People with records in the Office of the Medical Examiner for Salt Lake County	1546, Age ≥ 35 years	Suicide data from the Utah Department of Health's Office of the Medical Examiner for Salt Lake County, Utah, between January 1, 2000, and December 31, 2010	Short-term exposure to nitrogen dioxide, particulate matter, and sulfur dioxide measured by the Environmental Protection Agency's AirData website, averaging data from all monitors	Case-crossover design Adjusted for average daily sunlight during the previous 3 days, daily mean temperature, daily mean temperature for the previous 3 days, mean dew point temperature, mean dew point temperature for the previous 3 days, daily mean air pressure, and daily mean air pressure for the previous 3 days	Time-stratified, conditional logistic regression analysis, single- or cumulative-lag model	Odds of suicide with interquartile increase: NO ₂ , average of the 3 days preceding suicide OR= 1.20 (95% CI: 1.04, 1.39) PM _{2.5} , two days before suicide OR= 1.05 (95% CI: 1.01, 1.10) NO ₂ , spring/fall transition period OR= 1.35 (95% CI: 1.09, 1.66) PM _{2.5} , average of the 3 days preceding suicide in the spring OR= 1.28 (95% CI: 1.01, 1.61)
Biermann, 2009 The hypothesis of an impact of ozone on the occurrence of completed and attempted suicides	Population based register of suicides in Middle Franconia (administrative district of Bavaria/Germany)	1008 suicides and 917 suicide attempts	Suicides measured by a register of suicides resulting from police action	Ozone levels data from the Institute of Chemical Analysis of the City of Nuremberg/Germany	Ecological study, non parametric	t-tests	Mean (SD) ozone levels: Days with one or no suicides observed: 79.8 lg/m ³ (36.3) Days with two or more suicides: 86.4 lg/m ³ (39.4) t-test value = 2.5; p = 0.014 No significant association between ozone levels and suicide attempts.

Table 1.13. Suicide and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Greenburg, 1967 Air pollution, influenza, and mortality in New York City; January-February 1963	Residents of New York City	809 deaths (<40 suicides), all ages	Suicides measured by ICD Codes for suicide E963, E970-979, from mortality data	SO ₂ and general particulate matter measured at Central Park	Control period selected a similar period in 1958 with similar temperature and epidemics of illnesses but having normal air pollution	Chi-square	No significant increase in accidental deaths, homicides, suicides, and deaths of early infancy (less than 28 days of age) was found during the critical period in 1963 compared to similar periods from 1961 to 1965.
Kim, 2010 Ambient particulate matter as a risk factor for suicide	Residents of 7 cities in Republic of Korea	4341 suicides, seven cities in the Republic of Korea, adults	Suicides measured by the Death Statistics Database of the National Statistical Office, and postmortem examination data from the National Police Agency	Ambient particulate matter concentrations measured by the Ministry of Environment and the Seoul Metropolitan Government	National holidays, mean hours of sunlight from the previous 2 days, cubic splines: temperature (df=6), the mean temperature of the 3 previous days (df=6), the dew point temperature (df=3), the mean dew point temperature of the previous 3 days (df=3), the air pressure (df=3), and the mean air pressure of the previous 3 days	Time-stratified, case crossover study, conditional logistic regression analysis, single- or cumulative-lag model	Change in suicide risk per interquartile range increase in PM₁₀ (average of 0 to 2 days prior to the day of suicide): 9.0% (95% CI: 2.4, 16.1) Change in suicide risk per interquartile range increase in PM_{2.5} (1 day prior to the day of suicide): 10.1% (95% CI: 2.0, 19.0) Among individuals with cardiovascular disease, change in suicide risk per interquartile range increase in PM₁₀ (average of 0 to 2 days prior to the day of suicide): 18.9% (95% CI: 3.2, 37.0)

Table 1.13. Suicide and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Kim, 2015b Association between air pollution and suicide in South Korea: A nationwide study	Residents of 16 administrative regions of the Republic of Korea, January 1 2006 to December 31 2011.	All ages of residents in the 16 regions	Daily number of completed suicide events in each of the 16 administrative regions of ROK over 6 years from January 1 2006 to December 31 2011, measured via the Korea National Statistical Office	Ozone, PM10, nitrogen dioxide, carbon monoxide and sulfur dioxide. Korean Ministry of Environment	Sunlight hours, temperature, consumer price index, unemployment rate, and stock index valuations, celebrity suicides, the regional weekly suicide rate per 10 million in the preceding week, average national monthly suicide number for the past 5 years	Linear regression, regional results were meta-analyzed with the DerSimonian-Laird random effect model	Percent of suicide increase relative to annual mean rate for an increase in ozone concentration from -1SD to +1SD for same week exposure= 7.8% (95% CI: 4.2%, 11.5%), corrected P < 0.0001 Percent of suicide increase relative to annual mean rate for an increase in particulate matter concentration from -1SD to +1SD for exposure of four weeks prior to suicide= 3.6% (95% CI: 1.5%, 5.7%), corrected P < 0.01
Lin, 2016 The impact of ambient air pollution on suicide mortality: a case-crossover study in Guangzhou, China	Suicides in Guangzhou, China during 2003-2012	1,550 registered suicide deaths	Suicides defined by International Classification of Diseases, tenth version (ICD-10)	PM10, NO2, and SO2 averaged from monitors around the city	Daily mean temperature, relative humidity, atmospheric pressure and sunshine duration. Further analyses were stratified by season, gender, age group, educational attainment and suicide type.	Conditional logistic regression analysis with a time-stratified case-crossover design	Positive association between PM10 and NO2 2 days before the suicide and with SO2 the day before A significant increase in suicide risk were associated with interquartile-range increases in the concentration of air pollutant, with an odds ratio of 1.13 (95 % confidence interval (CI): 1.01, 1.27) and 1.15 (95 % CI: 1.03, 1.28) for PM10 and NO2 at lag 02, and 1.12 (95 % CI: 1.02, 1.23) for SO2 at lag 01, respectively.

Table 1.13. Suicide and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Ng, 2016 Ambient air pollution and suicide in Tokyo, 2001-2011	Tokyo, Japan	29,939 suicide cases	Suicide deaths were ascertained based on the International Classification of Diseases, 10th Revision (ICD-10)	PM2.5, suspended particulate matter (SPM), SO2 and NO2, averaged across monitors in the region from the National Institute for Environmental Studies in Japan	public holidays, natural splines of daily mean temperature and relative humidity, both with 3 degrees of freedom Stratified by age, sex, marital status, season	Conditional logistic regression analysis with a time-stratified case-crossover design	No significant associations were seen with exposures on the same day or any of the three prior days, although some significant associations were found in stratified sub-analyses.
Szyszkowicz, 2010 Air pollution and emergency department visits for suicide attempts in Vancouver, Canada	People that visited the emergency department at hospital in Vancouver over 4 years and 2 month period, Jan 1999 - Feb 2003	1605 suicide attempt/ideation emergency department visits, ages <10 to >80 years	Emergency department visits for suicide attempts or suicide ideation Hospital Data from a Vancouver hospital, diagnosed ED visits identified by the standard and unique string ("SUICIDE ATTEMPT/IDEATION")	Ambient air pollution and weather measured by Environment Canada	Case-crossover design, included in the model temperature and relative humidity, stratified by sex	Time-series, generalized linear mixed models (Poisson mixed models)	Change in odds of suicide for cold period for 1-day lagged exposure to NO2: 23.9% (95% CI: 7.8, 42.4) Odds ratio for suicide for cold period for 1-day lagged exposure to NO2= 1.21 (95% CI: 1.03, 1.41) No statistically significant associations reported for the warm months: April to September.

Table 1.13. Suicide and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Yackerson, 2014 The influence of air-suspended particulate concentration on the incidence of suicide attempts and exacerbation of schizophrenia	People registered at the Beer-Sheva Mental Health Center, in Israel	426 suicide attempts, age 16-99 years	ICD codes for suicide attempts Cases registered at the Beer-Sheva Mental Health Center, in Israel	Total airborne particles, concentration of solid air suspended particles (SSP), 16-month period from 2001 to 2002, particles measured by instruments situated on the roof of the Ben-Gurion University building at a height of about 25 m above ground level	Stratified outcomes by wind speed and direction over time	Pearson and Spearman test correlations were used; the statistical significance was tested at $p < 0.1$.	Correlation between particle count and suicide attempts: Eastern wind: $p > 0.3$, $p < 0.05$ Western wind: $p < 0.2$, $p > 0.2$

Table 1.13. Suicide and exposure to air pollution (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Yang, 2011 Decomposing the association of completed suicide with air pollution, weather, and unemployment data at different time scales	Resident of Taipei City, July 1993 to December 2008.	4857 deaths by suicide in Taipei City, age ≥ 11 years	Suicides measured by the Department of Health, Taipei City Government, Taiwan	SO ₂ , NO _x , O ₃ , CO, PM ₁₀ , (and PM _{2.5} only after year 2005) Environmental Protection Administration, Taiwan	Age, gender, and means of suicide, temperature, barometric pressure, relative humidity, wind speed, sunshine duration, sunspot activity, unemployment	Stepwise linear regression to determine covariates Pearson's correlation for time series of suicide and environmental variables Applied Empirical mode decomposition (EMD) to investigate the temporal time scale association between suicide and its predictors	Found seasonal pattern of increased suicide occurring in early summer by increased air particulates and decreased barometric pressure, in which the latter was in accordance with increased temperature during the corresponding time. Gaseous air pollutants, such as sulfur dioxide and ozone, were found to increase the risk of suicide at longer time scales. Decreased sunshine duration and sunspot activity predicted the increased suicide. Environmental risks predicted 33.7% of variance in the suicide data, after controlling for the unemployment.

Pesticides

Five studies examined exposure to pesticides and suicide. One ecological study described in the depression section above found a higher hospitalization rate for suicide attempts in regions with greater pesticide expenditure per agricultural worker in a region of Brazil than comparison regions (Meyer et al., 2010). Blair et al. (2005) found no association between self-reported pesticide use and deaths due to suicide via linkage with the National Death Index among 32,345 spouses of participants in the Agricultural Health Study (AHS), adjusting for year of death, age, state, race, and gender. Zhang, Stewart, Phillips, Shi, and Prince (2009) investigated suicide ideation and exposure to pesticides among 9,159 residents in rural China on an individual level. Self-reported storage of pesticides at home was significantly associated with suicide ideation in the prior two years, although when stratified by rural regions, this result was found in the plains region, but not the mountain or coastal regions (Zhang et al., 2009). Beard et al. (2011) found no association between self-reported pesticide use and completed suicide identified via linkage with the National Death Index among 81,998 Agricultural Health Study (AHS) participants. This was also true in age and sex adjusted analyses of the 29,128 spouses only. In the Altinyazar et al. (2016) paper described in the depression section, AChE activity was lower among MDD patients who had attempted suicide (n=73), compared to controls or MDD patients who had not attempted suicide. Table 1.14 outlines the studies on suicide and pesticides.

Table 1.14. Suicide and exposure to pesticides

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Altinyazar, 2016 The Red Blood Cell Acetylcholinesterase Levels of Depressive Patients with Suicidal Behavior in an Agricultural Area	Patients suffering from depression and healthy controls in rural agriculture area in Turkey	149 patients diagnosed with major depressive disorder and had or did not have suicide attempts, 64 health controls who lived in the same rural district for at least 1 year	Red blood cell acetylcholine esterase (RBC-AChE) activity was examined as the basis of evaluating the degree of chronic environmental exposure to organophosphate pesticide residues, AChE activity determined from blood sample and cholorimetric method defined by Ellman et al	Diagnosis of depression via Beck's Depression Inventory [18] Anxiety via Beck's Anxiety Inventory	Occupations	Logistic regression	Adjusted for occupations: OR between AChE activity and suicide attempt was 0.394 (95% CI 0.214-0.727), $p=0.003$ A negative correlation was found between the number of suicide attempts of the patients in the past and their AChE activity levels ($r = -0.227$, $p = 0.001$). AChE activity and suicide attempts in the past correlation ($r=-0.227$, $p=0.001$) No correlation was found between patient group AChE activity levels and the Beck depression scale ($p = 0.189$), the Beck anxiety scale ($p = 0.767$) and the Impulsiveness scale ($p = 0.258$).
Beard, 2011 Suicide and Pesticide Use among Pesticide Applicators and Their Spouses in the Agricultural Health Study	Spouses of pesticide applicators in the Agricultural Health Study	81988 cohort members, of which 110 suicides, age ≥ 18 years	ICD-9 and ICD-10 codes in state mortality files and the National Death Index	Pesticide via AHS questionnaire	Age at enrollment, sex, number of children in family, frequency of alcohol consumption during the past 12 months, and smoking status	Cox proportional hazards regression models	No association found between prior pesticide use and suicide in applicators and their spouses, after adjustments. Results were the same for applicators and spouses together or for applicators alone and were consistent across several measures of pesticide use.

Table 1.14. Suicide and exposure to pesticides (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Blair, 2005 Mortality among participants in the agricultural health study	Spouses of participants in the Agricultural Health Study (AHS),	32,345 spouses	ICD-9 codes in state mortality files and the National Death Index	Pesticide via AHS questionnaire	SMRs adjusted for calendar year of death, age, state, race, and gender	Standardized mortality ratios (SMRs)	Found no association between self-reported pesticide use and deaths due to suicide
Meyer, 2010 Mood Disorders Hospitalizations, Suicide Attempts, and Suicide Mortality Among Agricultural Workers and Residents in an Area With Intensive Use of Pesticides in Brazil	Agricultural workers and residents in Rio de Janeiro State from 1981 to 2005 in the Brazilian National Mortality System	Suicides, Residents ages 20-59: Exposed area: 407 Reference areas: 1416 (City), 4164 (State) Suicide attempts, Residents ages 20-59: Exposed area: 709 Reference areas: 552 (City), 5100 (State)	Suicide, measured by Brazilian National Mortality System Suicide attempts, measured by Brazilian Hospital Information System (ICD-10: X60–X84)	Pesticides, estimated by expenditure of pesticide per agricultural worker, data from the Brazilian Institute for Geography and Statistics in 1996.	Sex and age	Stratification, Mortality Odds Ratio	Suicide attempts among residents age 20-59 in Serrana Region (exposed) vs City of Rio de Janeiro (reference area): Overall Rate Ratio= 11.17 (10.00–12.49) Men RR= 13.40 (11.62–15.45) Women RR= 8.03 (6.70–9.64) Suicide attempts among residents age 20-59 in Serrana Region (exposed) vs Rio de Janeiro State (reference area): Overall Rate Ratio= 2.92 (2.70–3.16) Men RR= 2.76 (2.51–3.03) Women RR= 3.26 (2.83–3.76)

Table 1.14. Suicide and exposure to pesticides (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Zhang, 2009 Pesticide exposure and suicidal ideation in rural communities in Zhejiang province, China	Adult residents of rural communities in Zhejiang province, China	9811 rural residents, mean age 44 years	Suicide ideation via interview	Pesticide storage at home and 12-item General Health Questionnaire (GHQ) via interview	Design effects, clustering, gender, age, education duration, annual income, rural stratum, marital status, physical health, family history or suicidal behavior, GHQ caseness, GHQ total score	Applied weighting for sample clustering, logistic regression	Storage of pesticides at home and suicide ideation: Overall OR= 1.63 (95% CI: 1.13, 2.35), p= 0.009 Mountain region OR= 1.07 (95% CI: 0.69, 1.65) Coastal region OR= 1.13 (95% CI: 0.32, 3.92) Plains rural region OR= 3.38 (95% CI: 1.49, 7.66)

Noise

No studies were found on noise exposure and suicide.

Secondhand Smoke

Four studies explored second hand smoke (SHS) and suicide. Chen et al. (2015) followed adolescents age 11 to 16 years at for three years and reported a significant positive association between living with a parent who was a current smoker and death from suicide identified in the Taiwan National Death Certification System. Mitrou et al. (2010) conducted a 14-year follow-up study of 2,736 children enrolled in the 1993 Western Australian Child Health Survey. Private or public hospital admission for deliberate self-harm (identified via ICD-9 or 10) was significantly associated with having a primary caregiver who smoked after adjustment for several SES factors. In the Korean National Health and Nutrition Examination study described in the depression section above (Gim et al., 2016), SHS was associated with an increased odds of reported suicidal ideation. In the Weng et al. (2016) study described in the depression section above, there was a significantly elevated odds ratio for responding “sometimes” or “quite often” to the question on thoughts of self-harm in the EPDS. Table 1.15 outlines the studies on suicide and secondhand smoke.

Table 1.15. Suicide and exposure to secondhand smoke

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Chen, 2015 Suicide and Other-Cause Mortality after Early Exposure to Smoking and Second Hand Smoking: A 12-Year Population-Based Follow-Up Study	Junior high students in southern Taiwan, 1995-2007	162682, age 11-16 years	Suicide data from the Taiwan National Death Certification System	Secondhand smoke (SHS) measured by structured questionnaire, SHS exposure was defined on the basis of at least one family member living with the student who was a regular smoker	Age, sex, parental highest education, asthma, allergic rhinitis and alcohol consumption.	Gehan's generalized Wilcoxon tests, Cox proportional hazards regression	Hazard ratios: 1.47 (95% CI 0.94-2.30) and 2.83 (95% CI 1.54-5.20), respectively for adolescents exposed to SHS of 1-20 cigarettes and >20 cigarettes/per day Sensitivity analysis adjusting for depression, the odds ratio between smoking and suicide was 4.80 (see S1 Text), comparable in strength to that derived from the main analyses.
Gim, 2016 Relationship between Secondhand Smoking with Depressive Symptom and Suicidal Ideation in Korean Non-Smoker Adults: The Korean National Health and Nutrition Examination Survey 2010-2012	Non-smoking adults who participated in the 2010-2012 Korean National Health and Nutrition Examination Survey (KNHANES)	6,043 adults	Self-reported measurements on suicide ideation Individuals who reported having suicidal ideas during the past year.	Self-reported measurements on exposure to passive smoking Exposed group consisted of participants who reported that they were exposed to secondhand smoking for less than 1 hour or 1 hour or more.	Age, employment status, household income, education level, health insurance, marital status, number of family members, subjective body perception, subjective health status, number of chronic diseases, cancer, hours of sleep, and alcohol use disorders	Logistic regression	Suicide ideation among those exposed to SHS overall, OR 1.43 (95% CI, 1.139–1.802) Suicidal ideation among those exposed to SHS at home, OR 1.72 1.379–2.145

Table 1.15. Suicide and exposure to secondhand smoke (Continued)

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Mitrou, 2010 Antecedents of hospital admission for deliberate self-harm from a 14-year follow-up study using data-linkage	Participants of the 1993 Western Australian Child Health Survey, followed-up in 2007	2736, age 18-31 at follow-up	Deliberate self-harm measured by ICD codes in hospital records in public and private hospitals in Western Australia Note: defining deliberate self-harm in this study also included suicides since prior to 1999 when suicide and self-inflicted injury were coded by same ICD-9, study excluded the 4 suicides 1999 to 2007 in analyses	Secondhand smoke (SHS) measured by interview questions on the smoking status of primary caregiver	Age at time of survey in 1993, sex, primary carer smoking status, family type, emotional problems, parenting style, maternal age at birth	Cox proportional hazards regression	Adjusted proportional hazard ratio for deliberate self-harm and smoking status of primary caregiver (smoker vs. nonsmoker)= 3.02 (95% CI: 1.53, 5.95), p<0.01
Weng, 2016 Effects of tobacco exposure on perinatal suicidal ideation, depression, and anxiety	Pregnant women and 1 month postpartum women in 5 hospitals in Taipei, Taiwan	3867	Suicide ideation measured via question 10 of the Edinburgh Postnatal Depression Scale (EPDS)	Self-assessed questionnaire asking about secondhand smoke exposure: "Does anyone smoke around you in your home or workplace?"	Perinatal period, age, marital status, monthly income, employment status, educational level, planned pregnancy, history of depression, and sleep quality	Chi-square, multivariate logistic regression	Suicidal ideation for the women who had high secondhand smoke exposure: OR 2.5 (95 % CI = 1.30–4.82) Women exposed to SHS had higher risk of suicide ideation during the second trimester: OR = 7.63; 3.25–17.93) and third trimester (OR = 4.03; 1.76–9.23).

Other Pollutants

Saadat, Bahaoddini, Mohabatkari, and Noemani (2004) examined the association between measured hydrogen sulfide (H₂S) from ambient natural gas and suicides in Masjid-i-Sulaiman, in southwestern Iran. Suicides and suicide attempts were determined from hospital medical records. The study found a seasonal fluctuation in suicides that correlated with seasonal mean levels of all reactive sulfur compounds. The study did not, however, consider any other factors that could possibly have also varied by season.

A study by Perry, Reichmanis, Marino, and Becker (1981) found a positive correlation between locations of suicides in West Midlands, England, and higher magnetic fields. At higher magnetic fields, the researchers found significantly more addresses where suicides occurred compared to control addresses. Authors collected data on suicides from coroner and police records. Authors measured magnetic field levels at the front door of residences. Table 1.16 outlines the studies on suicide and other pollutants.

Table 1.16. Suicide and exposure to other pollutants

First Author, Year, Title	Study Population	Sample	Outcome	Exposure	Matching or Adjustment Factors	Statistical Analysis	Results
Perry, 1981 Environmental power-frequency magnetic fields and suicide	County of Shropshire, the Mid-Staffordshire Health District, the Parish of Burntwood in Staffordshire and the Metropolitan Boroughs of Wolverhampton, Walsall and Dudley, United Kingdom	598 suicide cases of residents in study area (resided >14 days)	Coroners and police records of suicide cases	Magnetic field measurements were made at control and suicide addresses	Stratified by magnetic field levels, hours, days, and months, distance to nearest school, church, major road, open water, type of address	Two-tailed Mann-Whitney U-test, T-test, Chi-square test	Significant difference in measured magnetic field strength between control and suicide addresses, higher field strength at suicide addresses (Chi-square $p < 0.001$) No significant differences between the suicide and control addresses (Chi-square, $p > 0.05$) by months of the year, days of the week or hours of the day
Saadat, 2004 High incidence of suicide by burning in Masjid-i-Sulaiman (southwest of Iran), a polluted area with natural sour gas leakage	People with medical records in the Masjid-i-Sulaiman (MIS) "22nd Bahman" Hospital	561 suicide attempts (260 men and 301 women), completed suicide comprised of 19 men and 32 women, March 2000 to March 2002, age >15 years	Suicide and suicide attempts measured via medical records in the Masjid-i-Sulaiman (MIS) "22nd Bahman" Hospital including suicide and suicide attempts were reviewed.	Natural gas containing hydrogen sulfide (H ₂ S), reactive sulfur compounds measured at contaminated sites using lead peroxide, all reactive sulfur compounds were measured monthly	The study did not—and did not appear to have sufficient cases to—control for potential confounders either by further stratification of season by sex or apply regression models	Two-tailed Student's t-test, chi-square	Significant difference (Chi-square $p < 0.001$) in cases of self-burning and mean level of sulfur-compounds in ppm (SE) among seasons (Spring, Summer, Fall, Winter). Winter having the most cases and highest mean sulfur-compound levels followed by Spring, Summer, and Fall. Correlation between mean values of all reactive sulfur compounds and seasonal frequency of suicide: $r = 0.923$, $p = 0.038$

Discussion

We found the literature on environmental exposures and depression, anxiety or suicide to be rather limited, but many of the studies did find associations between exposures and worse mental health. However, the vast majority of studies have important limitations including small sample sizes, comparisons between crude proxies of exposure such as distinct communities, and designs that raise concern of reverse causation. Many of the studies were cross sectional in nature, for example studies based on NHANES data. Because mental health conditions affect behavior, this study design aspect makes it harder to conclude that the exposures are causally related to the mental health issues as opposed to the mental health issues affecting measured exposure levels. Nonetheless, several studies with stronger study designs still suggested associations between environmental exposures and worse mental health.

Studies of air pollution exposures more readily avoid reverse causation because the exposure estimates are not affected by personal behavior (Weisskopf & Webster, 2017). The largest group of any type of study examined associations between same day or prior few days' ambient pollutant concentrations and the number of hospital visits for depression or anxiety using a time series or case-crossover design (Cho et al., 2014; Mieczysław Szyszkowicz, 2007, 2011; Mieczysław Szyszkowicz et al., 2009; M. Szyszkowicz & Tremblay, 2011). Although there were some variations in specific air pollutants found to be associated or season in which the association was seen, the results generally suggested some aspects of air pollution are associated with depression, anxiety, and suicide. Studies of ambient air pollution and symptoms in individuals were less common. Two such studies of depression came to opposite conclusions, one finding associations and another not (Lim et al., 2012; Y. Wang et al., 2014). The only such

study of anxiety found associations with PM2.5 with the suggestion that more recent exposures were more relevant (Power et al., 2015).

Studies of metal exposures were mostly cross sectional, many using US NHANES data (Berk et al., 2014; Bouchard et al., 2009; Golub et al., 2010; T. H. H. Ng et al., 2013; Scinicariello & Buser, 2015; Shiue, 2015). While most of these did find associations with worse mental health, reverse causation is hard to rule out. However, several other studies with exposure assessments that more readily avoid reverse causation generally also found associations with more depression and anxiety, including several related to metals in drinking water (Mukherjee et al., 2014) while a protective association was seen between water selenium concentrations and depression (Johnson et al., 2013). Only three studies used biomarkers of exposure—in all cases biomarkers of lead—that more readily captured past exposure. One used child blood lead levels and found no association with young adult depression, but a nearly significant association with anxiety (McFarlane et al., 2013). Two others used bone lead in adults as a marker of cumulative exposure and did find associations with worse depression and anxiety (Eum et al., 2012; Rhodes et al., 2003).

Of work on pesticides and depression, the strongest studies were in the Agricultural Health Study cohort, although as exposures were based on self-report the analyses of prevalent depression could still suffer from reverse causation if reporting of past exposures was influenced by depression. Associations between pesticide exposures and both prevalent and incident depression among the spouses of pesticide applicators were found for history of pesticide poisoning, but not cumulative pesticide exposure (Beard et al., 2013; C. Beseler et al., 2006). It should be noted, though, that while these studies were not among workers, spouses of workers likely have different exposure routes and profiles than the general public. Also among spouses in

the Agricultural Health Study cohort, no association was seen with completed suicide (Beard et al., 2011), while self-reported storage of pesticides was associated with suicidal ideation in a Chinese study (Zhang et al., 2009). No studies were identified of pesticide exposures and anxiety

We found several studies of noise with exposure assessment generally done by extrapolating from some direct noise measurements and noise dispersion models. While some evidence for associations with both depression and anxiety were found, the literature was not completely consistent. Some study designs make it difficult to ascribe depression or anxiety differences specifically to noise exposure, as higher noise exposure would likely be almost completely co-linear with other aspects of living nearer noisy places such as airports. In addition, noise represents a tricky exposure for these types of studies as individuals are generally aware of these exposures, which is not the case with many other environmental contaminants. As a result, a participant's responses regarding depression and anxiety could be influenced by recognition of their exposure. At the same time, recognition of exposure could lead to annoyance and stress, which could then lead to biological effects resulting in worse mental health. This would nonetheless be a somewhat different causal path to worse mental health than would be postulated for most of the other environmental exposures considered here.

Secondhand smoke is an exposure that could conceivably suffer from some of the same issues outlined above for noise since people are generally aware of their exposure to secondhand smoke. Nonetheless, there are also more direct biological actions of secondhand smoke that could conceivably lead to worse mental health. Among studies of adult exposures, all but one did find associations between exposure to secondhand smoke and both depression and anxiety. A few studies also found associations between childhood secondhand smoke exposure, or the combination of childhood and adult exposure, and adult depression and anxiety. These studies

suffer less from the issue of annoyance or stress from the exposure driving the outcome, since the exposures were very removed in time.

Several other contaminants have also been explored, including some emerging chemicals like polyfluorinated compounds, phthalates, and triclosans, as well as older ones such as PCBs, TCE and different types of EMF. Often, although not always, significant associations with worse mental health were reported. However, many of these studies also suffered from the kinds of limitations discussed above. With these limitations in mind and caution given in interpretation, we provide a summary table of apparent associations and lack of associations between environmental contaminants and the mental health outcomes from our review (Table 1.17).

Table 1.17. Summary of associations between environmental contaminants and depression, anxiety, and suicide from review of the literature.

Outcome	Association	Environmental Pollutant
Depression	+	Lead, Cadmium, Manganese, Arsenic, Selenium, Tin, Indoor air pollution (PM10, PM2.5), Outdoor air pollution (CO, NO2, SO2, O3, PM10, PM2.5), Pesticides (poisoning history), SHS, Noise (airfield, road traffic), Phthalates, PAHs, PCBs, VOCs, TCEs, EMF, Gamma radiation
	0	Lead, Cadmium, Manganese, Mercury, Outdoor air pollution (CO, NO, NO2, SO2, O3, PM2.5, BC, UFP, Sulfates), Pesticides (cumulative exposure), Noise (airfield, road traffic, indoor hospital), SHS, PCBs, PCDFs, EMF
	-	Mercury, Selenium, Outdoor air pollution (O3), PFCs,
Anxiety	+	Lead, Cadmium, Arsenic, Zinc, Manganese, Outdoor air pollution (O3, PM2.5), Noise (airfield, road traffic, indoor hospital), SHS, PBDEs, TCEs, SHS, EMF, TCE
	0	Mercury, Outdoor air pollution (CO, NO2, SO2, O3, PM10, PM2.5), Noise (indoor hospital), SHS, PCBs, TCE
Suicide	+	Arsenic, Outdoor air pollution (CO, NO2, SO2, O3, PM10, PM2.5, H2S), Pesticides, SHS, EMF
	0	Pesticides, Outdoor air pollution (CO, NO2, SO2, O3, PM10, PM2.5)
	-	Lithium, Outdoor air pollution (CO)

The review did not find environmental pollutants that were negatively association with anxiety.

“+” = More exposure → Higher risk of outcome

“0” = Not suggestive of an association

“-” = More exposure → Lower risk of outcome

BC= black carbon

CO = carbon monoxide

EMF= electromagnetic fields

H2S= hydrogen sulfide

NO2 = nitrogen dioxide

O3 = ozone

PAHs= polyaromatic hydrocarbons

PBDEs = polybrominated diphenyl ethers

PCBs= polychlorinated biphenyls

PCDFs = polychlorinated dibenzofurans

PFCs= polyfluorinated compounds

PM10 = particulate matter with diameter ≤ 10 micrometers

PM2.5 = particulate matter with diameter ≤ 2.5 micrometers

SHS= secondhand smoke

SO2 = sulfur dioxide

TCE = trichloroethylene

UFP= ultrafine particles

VOCs= volatile organic compounds

Conclusion

Given the tremendous public health impact of adverse mental health conditions, understanding the contribution of environmental exposures—often modifiable—should be of paramount importance. The current literature, although limited, clearly suggests many kinds of environmental exposures may be risk factors for depression, anxiety, and suicide. Overall, the strongest studies appear to be of air pollution exposure. For other pollutants, while results are suggestive, important limitations exist with many of the studies. Gaps in the body of research include a need for more longitudinal studies, studies that can measure cumulative exposures as well as shorter-term ones, and studies that reduce the possibility of reverse causation.

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CHAPTER 2

Airline Pilot Mental Health and Suicidal Thoughts:

A Cross-sectional Descriptive Study via Anonymous Web-based Survey

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Airplane pilot mental health and suicidal thoughts: a cross-sectional descriptive study via anonymous web-based survey

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Abstract

Background: The Germanwings Flight 9525 crash has brought the sensitive subject of airline pilot mental health to the forefront in aviation. Globally, 350 million people suffer from depression—a common mental disorder. This study provides further information on this important topic regarding mental health especially among female airline pilots. This is the first study to describe airline pilot mental health—with a focus on depression and suicidal thoughts—outside of the information derived from aircraft accident investigations, regulated health examinations, or identifiable self-reports, which are records protected by civil aviation authorities and airline companies.

Methods: This is a descriptive cross-sectional study via an anonymous web-based survey administered between April and December 2015. Pilots were recruited from unions, airline companies, and airports via convenience sampling. Data analysis included calculating absolute number and prevalence of health characteristics and depression scores.

Results: One thousand eight hundred thirty seven (52.7%) of the 3485 surveyed pilots completed the survey, with 1866 (53.5%) completing at least half of the survey. 233 (12.6%) of 1848 airline pilots responding to the Patient Health Questionnaire 9 (PHQ-9), and 193 (13.5%) of 1430 pilots who reported working as an airline pilot in the last seven days at time of survey, met depression threshold—PHQ-9 total score ≥ 10 . Seventy-five participants (4.1%) reported having suicidal thoughts within the past two weeks. We found a significant trend in proportions of depression at higher levels of use of sleep-aid medication (trend test $z = 6.74$, $p < 0.001$) and among those experiencing sexual harassment ($z = 3.18$, $p = 0.001$) or verbal harassment ($z = 6.13$, $p < 0.001$).

Conclusion: Hundreds of pilots currently flying are managing depressive symptoms perhaps without the possibility of treatment due to the fear of negative career impacts. This study found 233 (12.6%) airline pilots meeting depression threshold and 75 (4.1%) pilots reporting having suicidal thoughts. Although results have limited generalizability, there are a significant number of active pilots suffering from depressive symptoms. We recommend airline organizations increase support for preventative mental health treatment. Future research will evaluate additional risk factors of depression such as sleep and circadian rhythm disturbances.

Keywords: Airline, Pilot, Mental health, Mental disorder, Depression, Suicidal

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Background

On March 24, 2015, Germanwings flight 4U 9525 crashed into the French Alps killing 150 people. Investigators of this tragic event report the 27-year-old co-pilot deliberately crashed the plane [1, 2]. Further examination of the co-pilot's history found evidence suggesting the co-pilot suffered from clinical depression [3]. Previous suicide attempts and having a history of mental disorders, particularly clinical depression, are risk factors of suicide [4].

Clinical depression, also referred to as major depressive disorder (MDD) – characterized by at least two weeks of depressed mood or loss of interest along with at least four additional symptoms of depression [5] – is the second leading cause of years of life lived with a disability (YLDs) [6] and third most important cause of disease burden worldwide and affects an estimated 350 million people [7, 8]. The United States (U.S.) leads the world in the percent of people (21%) who will have a mood disorder, including MDD, over their lifetime [9]. In the U.S., more females report having depression than males [8], 17% of people will have MDD over their lifetime [10], and 7% will have experienced an MDD in the past year [11]. MDD symptoms cause significant distress and social, occupational, and life activity impairment and may first appear at any age with most new cases occurring around 20 years of age in the U.S [5, 12]. Estimates of prevalence of diagnosed MDD or depressive symptoms related to MDD among high stress occupations include 12% among deployed and 13% among previously deployed U.S. military personnel [13], 7% among U.S. emergency medical technicians [14], and 10–17% among U.S. police officers [15].

There are an estimated 140,000 airline pilots internationally with about 70,000 in the U.S [16]. The majority of pilots are male: just over 4% of all pilots are female [17]. In the U.S., the Department of Transportation, Federal Aviation Administration (FAA) sets requirements for aeromedical examiners (AMEs) to evaluate fitness of pilots. Only through self-disclosure are mental disorders discussed and noted in pilot health records; AMEs do not diagnose mental health conditions (See Additional file 1 for more details). Underreporting of mental health symptoms and diagnoses is probable among airline pilots due to the public stigma of mental illness and fear among pilots of being “grounded” or not fit for duty [18, 19].

Studies of airline pilots have either not anonymously assessed mental health or had limitations in doing so. Prior studies have found a lower prevalence of depression among military pilots [19] and airline pilots [18, 20] compared to the general population. However, there is concern about underreporting of adverse health symptoms and incomplete medical information due to pilots protecting professional interests [18], and underreporting of the use of antidepressants in

aeromedical examinations has been found among a group of U.S. civilian pilots involved in fatal accidents [21]. Anonymous surveying could alleviate some of the issues with underreporting. Only one study of airline pilots has used anonymous reporting, but it did not specifically evaluate depression nor suicidal thoughts [18].

The objective of our study was to provide a more accurate description of mental health among commercial airline pilots underscoring symptoms related to clinical depression (hereafter also referred to as “depression”) using an anonymous survey to guard against fears of stigma and job discrimination. This study did not conduct clinical interviews of survey respondents to confirm diagnosis of depression, nor did it have access to medical records. This is the first study that we are aware of to describe mental health in a convenience sample of pilots outside of the information derived from aircraft accident investigations [22] or regulated health examinations, which are identifiable self-reports and physician interviews, and are records protected by civil aviation authorities and airline companies.

Methods

Study design

This is a cross-sectional descriptive study of commercial airline pilots who completed a web-based survey between April and December 2015. In order to protect pilots' ability to hold an FAA Medical Certificate the survey was completely anonymous and no internet protocol (IP) addresses were collected. The Institutional Review Board of the Harvard T.H. Chan School of Public Health reviewed and exempted the study.

Recruitment methods included targeted e-mail, newsletters, word-of-mouth, handing postcards to pilots, and aviation publication advertisements. Airline pilot populations that gave rise to the survey population included pilot unions (>5 unions), airline representatives (>65 airlines), pilot groups (>12 groups), and aviation safety organizations (>2 organizations). We targeted female pilots in recruiting because of the small percentage of female pilots among the general airline pilot population. We downloaded 3485 surveys on December 31, 2015.

The data analysis included all answered questions. We defined a completed survey as answering the final non-optional question. We assumed each participant was a pilot and only completed one survey. Several questions in the survey require knowledge that would only be readily available to pilots. An active pilot (co-author DDM) reviewed surveys for potential non-pilot participants. All surveys passed this screening. Finally, the survey instructed participants to leave the checkbox unmarked if they did not have a diagnosis of the listed disorder.

Survey description

The survey utilized standardized questions from the Job Content Questionnaire [23] and the Centers for Disease Control – National Center for Health Statistics (CDC-NCHS) National Health and Nutrition Examination Survey (NHANES) (CDC-NCHS 2011–2012) [24], which previous researchers applied to evaluate U.S. flight attendant health [25]. Participants were not likely to be biased to mental health outcomes since the survey covered other work and health topics. The survey took about 30 min for completion. We utilized Qualtrics software (Qualtrics, Provo, Utah) to disseminate surveys and collect responses.

Statistical analysis

We utilized STATA software (Version 13.1, StataCorp, College Station, Texas) for data analysis. We applied two-sided unequal variances t-test for continuous variables, Pearson's chi-squared test or Fisher's exact test ($n \leq 5$) for categorical variables, and nonparametric test for trend across ordered groups. Age was categorized into four groups using quartiles. We utilized the Kruskal-Wallis equality-of-populations rank test to compare scores among age categories. Significance was defined as p -value < 0.05 .

Outcome assessment

We evaluated depressive symptoms via the Patient Health Questionnaire (PHQ-9) depression module utilized in previous NHANES surveys (e.g., NHANES 2005–2006 and 2011–2012), which is well validated and used in clinical studies assessing depression [26, 27]. Briefly, the PHQ-9 depression module asks nine questions, which are the nine criteria for diagnosing depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Edition 4* (DSM-IV) [26]. Researchers record scores as frequency of depression symptoms over the past two weeks [26]. Response categories include “not at all,” “several days,” “more than half the days” and “nearly every day” and given a score ranging from 0 to 3, respectively. Total summed scores per participant range from 0 to 27. Studies evaluating validity of PHQ-9 report a total score of 10 or greater had an 88% sensitivity and 88% specificity for depression [26] with a kappa of 0.56 to 0.74 between PHQ-9 diagnosis and diagnosis by an independent mental health professional [28, 29]. Therefore, we refer to meeting the cut-off of having a PHQ-9 total score of 10 as depression.

Results

Of the 3485 participants, 1837 (52.7%) completed the survey and 1866 (53.5%) answered at least half of the survey. Completers initiated surveys from over 50 countries. Major locations included the United States (1586, 45.5%), Canada (438, 12.6%), and Australia (387, 11.1%).

Participants initiated surveys in Europe (406, 11.7%), Asia (413, 11.9%), South America (165, 4.7%), and South Africa (8, 0.2%). Locations with the most participants in Europe were Spain (134, 3.9%), United Kingdom (65, 1.9%), and Germany (32, 0.9%). For Asia the locations were United Arab Emirates (172, 4.9%), Hong Kong (147, 4.2%), and Thailand (13, 0.4%). For South America the locations were Colombia (74, 2.1%), Brazil (71, 2.0%), and Chile (8, 0.23%). Due to many missing responses among non-completers, comparisons between completers and non-completers were constrained to average tenure as a pilot (completers 18.0 years, 95% CI 17.5 to 18.4 vs. non-completers 16.9, 16.2 to 17.6, $p = 0.012$) and the proportion working one trip as an airline pilot in the past 30 days (completers 1417, 77.1% vs. non-completers 1099, 73.0%, $p = 0.006$). The response rate [30] among those who answered at least one question was 0.68. Of the 1826 who provided age, about half were middle aged with the median age for females and males at 42 (IQR 36–51) and 50 (IQR 41–60) years, respectively. Half of participants worked at least 16 years as a pilot and nearly four out of five worked one trip as an airline pilot in the past 30 days. The majority of respondents were non-smokers, married, and white. Over 60% earned a four-year college degree or had graduate education (Table 1).

Nearly all ages up to 80 years had pilots who met depression threshold–PHQ-9 total score ≥ 10 (Fig. 1). Among age categories, median total depression score decreased with increasing age quartile (Kruskal-Wallis rank test chi-square with ties = 157.63 with 3 d.f., $p < 0.001$) (Fig. 2). The number of pilots self-reporting having at least one day of poor mental health during the past month ranged from 94 (26.9%) among those over age 60 to 273 (56.5%) among 41 to 50 years (Table 2). Forty-seven (9.6%) respondents up to age 40 and 110 (11.9%) age 41 to 60 years reported having at least eight days of poor mental health during the past month (Table 2). Females had a greater proportion of having at least one day of poor mental health during the past month (females 139, 55.2% vs. males 697, 45.6%, $p = 0.005$) or having ever been diagnosed with depression (females 12, 4.7% vs. males 46, 2.9%, $p = 0.12$).

Median PHQ-9 total scores was lowest among those over 60 (Table 3) and were the same among sex with males (3, IQR(1–7), $n = 1591$) having a greater spread of total scores than females (3, (2–6), $n = 255$). The greatest differences in proportions between females and males experiencing at least one day of problems were among PHQ-9 items #1: Having little interest or pleasure in doing things (females 87, 34.1% vs. males 683, 43.1%, $p = 0.007$) and #5: Having poor appetite or overeating (140, 55.1% vs. 687, 43.5%, $p = 0.001$).

Among participants who answered the PHQ-9 questions, 233 (12.6%) met threshold associated with clinical levels of depression. Two-hundred-and-four (12.8%) males

Table 1 Characteristics of survey participants by age

	Age <41 n (%)	Age 41 to 50 n (%)	Age 51 to 60 n (%)	Age >60 n (%)	Total n (%)
Participants who indicated age	489 (26.8)	493 (27.0)	449 (24.6)	395 (21.6)	1826 (100%)
Gender (n = 1826) ^a					
Female	114 (23.3)	71 (14.4)	56 (12.5)	9 (2.3)	250 (13.7)
Male	375 (76.7)	422 (85.6)	393 (87.5)	386 (97.7)	1576 (86.3)
Tenure (n = 1826) ^a					
< 6 years	165 (33.7)	17 (3.5)	8 (1.8)	1 (0.3)	191 (10.5)
6–10 years	206 (42.1)	94 (19.1)	15 (3.3)	4 (1.0)	319 (17.5)
11–15 years	100 (20.5)	140 (28.4)	56 (12.5)	12 (3.0)	308 (16.9)
16–20 years	18 (3.7)	168 (34.1)	85 (18.9)	30 (7.6)	301 (16.5)
21–25 years	0 (0.0)	68 (13.8)	110 (24.5)	43 (10.9)	221 (12.1)
> 25 years	0 (0.0)	6 (1.2)	175 (39.0)	305 (77.2)	486 (26.6)
Recently Worked ^b (n = 1826) ^a					
No	20 (4.1)	31 (6.3)	53 (11.8)	308 (78.0)	412 (22.6)
Yes	469 (95.9)	462 (93.7)	396 (88.2)	87 (22.0)	1414 (77.4)
Education (n = 1817) ^a					
Less than high school diploma	2 (0.4)	1 (0.2)	3 (0.7)	2 (0.5)	8 (0.4)
High school or GED	60 (12.4)	72 (14.7)	49 (10.9)	38 (9.6)	219 (12.1)
Some college, no degree	85 (17.6)	82 (16.7)	53 (11.8)	81 (20.5)	301 (16.6)
Two-year college degree	62 (12.8)	47 (9.6)	27 (6.0)	26 (6.6)	162 (8.9)
Four-year college degree	217 (44.9)	221 (45.0)	226 (50.5)	148 (37.5)	812 (44.7)
Graduate education	57 (11.8)	68 (13.9)	90 (20.1)	100 (25.3)	315 (17.3)
Marital Status (n = 1817) ^a					
Married	274 (56.7)	395 (80.5)	356 (79.5)	325 (82.3)	1350 (74.3)
Widowed	1 (0.2)	0 (0.0)	3 (0.7)	14 (3.5)	18 (1.0)
Divorced	11 (2.3)	35 (7.1)	42 (9.4)	29 (7.3)	117 (6.4)
Separated	4 (0.8)	12 (2.4)	4 (0.9)	8 (2.0)	28 (1.5)
Never Married	106 (22.0)	23 (4.7)	20 (4.5)	8 (2.0)	157 (8.6)
Living with partner	87 (18.0)	26 (5.3)	23 (5.1)	11 (2.8)	147 (8.1)

^aTwo-sided Fisher's exact test *p*-value <0.01^bRecently worked means worked one trip as an airline pilot in past 30 days

and 29 (11.4%) females (χ^2 $p = 0.52$) met depression threshold. One-hundred and ninety-two (13.6%) of the 1413 pilots who reported working as an airline pilot in the last 30 days met depression threshold (Table 4).

Among screening questions concerning psychological symptoms (PHQ-9 questions 1,2,6,7,9), a greater proportion of males than females reported “nearly every day” experiences in loss of interest (males 59, 3.7% vs. females 2, 0.8%, $p = 0.01$), feeling depressed (27, 1.7% vs. 4, 1.6%, $p = 1.00$), feeling like a failure (34, 2.2% vs. 3, 1.2%, $p = 0.47$), trouble concentrating (34, 2.2% vs. 5, 2.0%, $p = 1.00$), and thinking they would be better off dead or having thoughts of self-harm (10, 0.6% vs. 0, 0.0%, $p = 0.37$). Seventy-five participants (4.1%) reported having thoughts of being better off dead or self-harm within the past two

weeks (pilots working within the past month 49, 3.5% vs. not 26, 6.4%, $p = 0.008$). A higher percentage of males (23, 1.5%) vs. females (1, 0.4%, $p = 0.24$) felt that the problems they reported on the PHQ-9 made it very or extremely difficult for them to work, take care of home matters, or engage in healthy relationships with people.

Among those who answered the PHQ-9 questions and indicated their location of initiating the survey, 232 (12.6%) met threshold associated with clinical levels of depression. We stratified location of survey initiation into countries exhibiting more western cultural influence (i.e., countries in North and South America, Europe, or Australia) and those exhibiting less (i.e., countries in Asia). There were 1576 (85.5%) participants initiating surveys in more culturally western countries and 267 (14.5%) in less

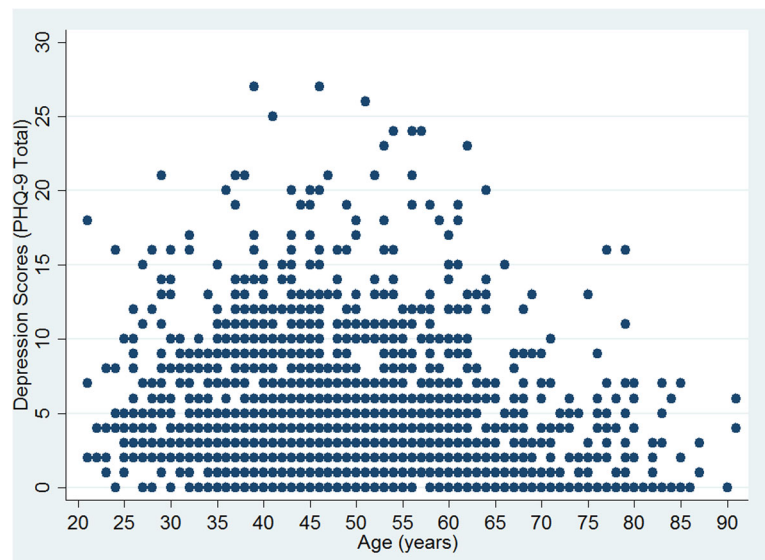


Fig. 1 Total Depression Scores by Age ($n = 1848$). Each dot represents one participant. Some dots overlap

culturally western countries. Countries with more western cultural influence had a lower percentage of pilots meeting depression threshold than others (172, 10.9% vs. 60, 22.5%, $p < 0.001$). Examining this further by sex reveals the prevalence of meeting threshold is similar among females (more western 27, 11.3% vs. less 2, 13.3%, $p = 0.68$). This was not the case among males with more western having a prevalence lower than less western (145, 10.9% vs. 58, 23.0%, $p < 0.001$). Furthermore, 61 participants (3.9%) initiating surveys in more culturally western countries compared to 14 (5.3%) in less western countries

reported having thoughts of being better off dead or self-harm within the past two weeks. This difference was not statistically significant ($p = 0.31$). Grouped by sex, there was no significant difference among females (more western 7, 2.9% vs. less 0, 0.0%, $p = 1.00$) or males (more western 54, 4.1% vs. less 14, 5.6%, $p = 0.31$).

The proportion meeting depression threshold among pilots working in the past month was higher as the frequency of taking sleep aid medicines in the past month increased (Table 5). The survey found 19 (16.2%) working pilots met depression threshold among those consuming

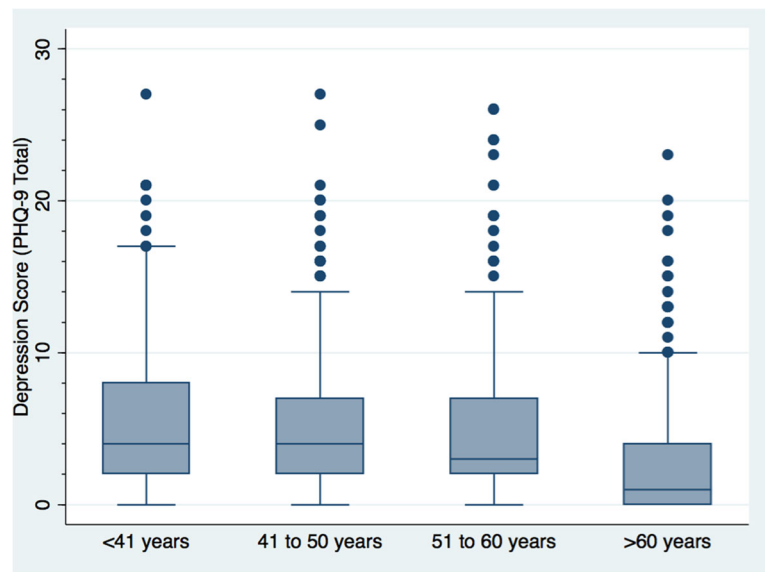


Fig. 2 Total Depression Scores by Age Quartiles (years) ($n = 1848$). Each dot represents an outlier. Maximum possible depression score (PHQ-9 Total) is 27

Table 2 Mental health characteristics of survey participants

	Age <41 n (%)	Age 41 to 50 n (%)	Age 51 to 60 n (%)	Age >60 n (%)	Total n (%)
Mental Health not Good (Days/Past month) (<i>n</i> = 1759) ^a					
0 days	230 (47.4)	210 (43.5)	236 (53.5)	256 (73.1)	932 (53.0)
1–7 days	208 (42.9)	215 (44.5)	153 (34.7)	66 (18.9)	642 (36.5)
8–14 days	19 (3.9)	24 (5.0)	20 (4.5)	11 (3.1)	74 (4.2)
15–21 days	20 (4.1)	23 (4.8)	10 (2.3)	4 (1.1)	57 (3.2)
22–28 days	3 (0.6)	3 (0.6)	4 (0.9)	4 (1.1)	14 (0.8)
> 28 days	5 (1.0)	8 (1.7)	18 (4.1)	9 (2.6)	40 (2.3)
Ever diagnosed with sleep disorder (<i>n</i> = 1826) ^{ab}	15 (3.1)	40 (8.1)	54 (12.0)	51 (12.9)	160 (8.8)
Ever diagnosed with depression (<i>n</i> = 1826) ^b	11 (2.3)	15 (3.0)	11 (2.5)	20 (5.1)	57 (3.1)
In the past 7 days, how many days did you experience the following symptoms?					
Fatigue, Everyday (<i>n</i> = 1826)	15 (3.1)	26 (5.3)	30 (6.7)	17 (4.3)	88 (4.8)
Depression, Everyday (<i>n</i> = 1826)	4 (0.8)	5 (1.0)	7 (1.6)	3 (0.8)	19 (1.0)

^aTwo-sided Chi-square or Fisher's Exact Test *p*-value < 0.05^bIncluding unknown number of participants that did not answer

more than one drink of alcohol per day. The proportion of pilots meeting the same threshold was higher among those experiencing sexual harassment (36.4% among those experiencing harassment 4 or more times in the past week) or verbal harassment (42.9% among those experiencing harassment 4 or more times in the past week) in the last 12 months at work.

Discussion

The Germanwings crash in March of 2015 has brought a sensitive subject to the forefront in aviation; pilot mental health. To date, this is the first study providing a description from anonymous reporting of mental health among commercial airline pilots with an emphasis on depression and suicidal thoughts. Our study also oversampled female pilots (13.7% of our study population) to better describe this minority population (about 4%) among commercial airline pilots [17]. We utilized an anonymous web-based survey to collect responses and a clinically validated questionnaire, PHQ-9, to determine depression (PHQ-9 total score ≥ 10).

In the context of reporting depression, female pilots reported more days with poor mental health and having more diagnosed depression than male pilots, which mirrors reporting among the general population. The prevalence of depression (12.6%) among pilots from our study is much higher than some studies utilizing identifiable surveys and medical records [19, 20] and possibly lower than another study [31]. One study utilizing anonymous case reporting among commercial airline pilots between years 1996 and 1999 found the prevalence of psychiatric disease around 7.5% [18]. However, this study did not report information on depression or suicidal thoughts and its authors

acknowledged the inability to identify an exact reference population [18]. In addition, a study utilizing the medical record database of U.S. Air Force pilots estimated a prevalence of depression of 0.06% during years 2001–2006 [19]. Researchers evaluating airline pilots in the New Zealand Health Survey found a prevalence of depression of 1.9% during years 2009–2010 [20]. A report on Air Canada pilots with long term disability found a prevalence of mental disorders at 15.8% [31]. These studies did not evaluate prevalence of pilots having suicidal thoughts. Furthermore, estimates of prevalence of depression or depressive symptoms among other high stress occupations include 12% among deployed and 13% among previously deployed U.S. military personnel [13], 7% among U.S. emergency medical technicians [14], and 10–17% among U.S. police officers [15]. From these studies of mental illness in pilots and similar high stress occupations, the prevalence of depression in our results seem probable. Moreover, the higher prevalence of depression among victims of frequent sexual or verbal harassment in our study provides further evidence of its existence among airline pilots, deep negative effects on its victims, and the urgent need to eliminate this form of harassment and help this subpopulation of workers.

Our study found 75 pilots (4.1%) reported having thoughts of being better off dead or self-harm within the past two weeks. To our knowledge, this is the most current measure of the prevalence of suicidal thoughts among airline pilots. One study estimated an aircraft assisted suicide rate of 0.33% over a 20 year period in the U.S. following analysis of aircraft accidents from 1956 to 2012 [32]. However, this study measured completed suicides, not prevalence of suicidal thoughts.

Table 3 Patient Health Questionnaire Depression Module (PHQ-9) by Age Category

Over the last 2 weeks, how often have you been bothered by the following problems:	Age <41 n (%)	Age 41 to 50 n (%)	Age 51 to 60 n (%)	Age >60 n (%)	Total n (%)
1) Little interest or pleasure in doing things? (<i>n</i> = 1812) ^{ab}					
Not at all	247 (50.6)	258 (52.6)	265 (59.4)	282 (72.9)	1052 (58.1)
Several days	189 (38.7)	184 (37.5)	138 (30.9)	80 (20.7)	591 (32.6)
More than half the days	39 (8.0)	33 (6.7)	21 (4.7)	17 (4.4)	110 (6.1)
Nearly everyday	13 (2.7)	16 (3.3)	22 (4.9)	8 (2.1)	59 (3.3)
2) Feeling down, depressed, or hopeless? (<i>n</i> = 1800) ^{ab}					
Not at all	344 (70.8)	349 (71.1)	341 (76.8)	323 (85.2)	1357 (75.4)
Several days	113 (23.3)	111 (22.6)	75 (16.9)	44 (11.6)	343 (19.1)
More than half the days	22 (4.5)	24 (4.9)	17 (3.8)	7 (1.9)	70 (3.9)
Nearly everyday	7 (1.4)	7 (1.4)	11 (2.5)	5 (1.3)	30 (1.7)
3) Trouble falling or staying asleep, or sleeping too much? (<i>n</i> = 1809) ^{ab}					
Not at all	100 (20.6)	109 (22.3)	122 (27.3)	219 (56.6)	550 (30.4)
Several days	241 (49.6)	245 (50.1)	192 (43.0)	106 (27.4)	784 (43.3)
More than half the days	95 (19.6)	85 (17.4)	83 (18.6)	34 (8.8)	297 (16.4)
Nearly everyday	50 (10.3)	50 (10.2)	50 (11.2)	28 (7.2)	178 (9.8)
4) Feeling tired or having little energy? (<i>n</i> = 1806) ^{ab}					
Not at all	79 (16.2)	77 (15.8)	107 (23.9)	195 (51.2)	458 (25.4)
Several days	267 (54.7)	261 (53.4)	231 (51.6)	141 (37.0)	900 (49.8)
More than half the days	101 (20.7)	104 (21.3)	74 (16.5)	28 (7.4)	307 (17.0)
Nearly everyday	41 (8.4)	47 (9.6)	36 (8.0)	17 (4.5)	141 (7.8)
5) Poor appetite or overeating? (<i>n</i> = 1805) ^{ab}					
Not at all	223 (46.0)	229 (46.9)	247 (55.3)	290 (75.3)	989 (54.8)
Several days	158 (32.6)	163 (33.4)	137 (30.7)	69 (17.9)	527 (29.2)
More than half the days	73 (15.1)	72 (14.8)	42 (9.4)	16 (4.2)	203 (11.3)
Nearly everyday	31 (6.4)	24 (4.9)	21 (4.7)	10 (2.6)	86 (4.8)
6) Feeling bad about yourself – or that you are a failure or have let yourself or your family down? (<i>n</i> = 1811) ^{ab}					
Not at all	345 (70.7)	353 (72.0)	345 (77.4)	326 (84.2)	1369 (75.6)
Several days	106 (21.7)	103 (21.0)	72 (16.1)	50 (12.9)	331 (18.3)
More than half the days	30 (6.2)	23 (4.7)	16 (3.6)	6 (1.6)	75 (4.1)
Nearly everyday	7 (1.4)	11 (2.2)	13 (2.9)	5 (1.3)	36 (2.0)
7) Trouble concentrating on things, such as reading the newspaper or watching TV? (<i>n</i> = 1803) ^{ab}					
Not at all	305 (62.5)	287 (58.5)	304 (68.3)	305 (80.5)	1201 (66.6)
Several days	149 (30.5)	167 (34.0)	107 (24.0)	62 (16.4)	485 (26.9)
More than half the days	24 (4.9)	29 (5.9)	18 (4.0)	7 (1.9)	78 (4.3)
Nearly everyday	10 (2.1)	8 (1.6)	16 (3.6)	5 (1.3)	39 (2.2)
8) Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual? (<i>n</i> = 1810) ^{ab}					
Not at all	414 (84.8)	407 (83.1)	390 (87.8)	357 (92.0)	1568 (86.6)
Several days	56 (11.5)	66 (13.5)	33 (7.4)	23 (5.9)	178 (9.8)
More than half the days	14 (2.9)	13 (2.7)	12 (2.7)	7 (1.8)	46 (2.5)
Nearly everyday	4 (0.8)	4 (0.8)	9 (2.0)	1 (0.3)	18 (1.0)
9) Thoughts that you would be better off dead or of hurting yourself in some way? (<i>n</i> = 1798)					
Not at all	469 (96.1)	468 (95.7)	426 (96.0)	360 (95.5)	1723 (95.8)
Several days	13 (2.7)	16 (3.3)	13 (2.9)	14 (3.7)	56 (3.1)

Table 3 Patient Health Questionnaire Depression Module (PHQ-9) by Age Category (Continued)

More than half the days	4 (0.8)	3 (0.6)	1 (0.2)	1 (0.3)	9 (0.5)
Nearly everyday	2 (0.4)	2 (0.4)	4 (0.9)	2 (0.5)	10 (0.6)
Median PHQ-9 total score (IQR) n	4 (2–8) 489	4 (2–7) 491	3 (2–7) 449	1 (0–4) 389	3 (2–7) 1848
How difficult have these problems made it for you to do your work, take care of things at home, or get along with people? (n = 1812) ^{ab}					
Not at all	269 (55.1)	262 (53.5)	282 (62.8)	306 (79.5)	1119 (61.8)
Somewhat	199 (40.8)	207 (42.2)	139 (31.0)	70 (18.2)	615 (33.9)
Very	17 (3.5)	16 (3.3)	17 (3.8)	5 (1.3)	55 (3.0)
Extremely	3 (0.6)	5 (1.0)	11 (2.5)	4 (1.0)	23 (1.3)

^aTwo-sided Chi-square or Fisher's Exact Test *p*-value < 0.05^bNon-parametric test for trend of item scores across age groups, *p*-value < 0.05

We hypothesize two possible explanations for the lower prevalence of meeting depression threshold in pilots who initiated the survey in more western culture countries compared to others. One reason is the type of culture the pilots identify themselves with and country of survey initiation is not an accurate match. If true more western culture pilots were flying longer trips (such as from western to eastern culture countries) compared to true less western culture pilots, then these more western culture pilots may be more likely to initiate surveys in less western culture countries because of more downtime between flights. This could result in the misclassification of less western culture pilots appearing to have higher prevalence of meeting threshold for depression. Underlying factors could stem from longer trips increasing the risk of experiencing greater circadian rhythm disruption and longer exposure to other possible occupational factors related to mental illness. This misclassification also could occur the other way with healthier true less western culture pilots flying to more western culture countries and initiating surveys. Thus making western pilots appear healthier.

Another explanation for this result is that type of culture the pilots identify themselves with and country of survey initiation is an accurate match and that pilots from more western culture countries in our study have a lower prevalence of meeting depression threshold. We were unable to validate what culture pilots identify with due to lack of data. Nevertheless, even if the country of survey initiation accurately matches with pilots' culture

identification, our study has limited data on pilots surveyed outside western culture countries.

The prevalence of having suicidal thoughts between more western and less western culture countries of survey initiation was not significantly different at the 0.05 level. That said, the slightly higher prevalence of suicidal thoughts among less western culture countries may be due to the reasons given for the difference in prevalence of depression.

Additionally, the results of the comparison of more against less western culture countries in our study do not align with patterns in survey results of mental disorders around the world [33]. These surveys find more western culture countries generally having a higher 12-month prevalence of mood disorders [33]. However, researchers note that differences in mood disorder prevalence between high and low prevalence countries are likely smaller than the surveys show [33]. This is likely due to more underestimation of prevalence in low prevalence countries [33]. Consequently, this provides further evidence that the type of culture the pilots identify with in our study and country of survey initiation is not an accurate match.

Moving more generally, the topic of mental illness among airline pilots is not new, but identifying and assisting pilots with mental illness remains a present day challenge. Although the results of this study do not gauge pilots' level of access to mental health treatment, it stimulates dialogue of treatment options available to assist pilots. More importantly, the subpopulations of

Table 4 Depression among survey participants by age group

Worked as an airline pilot in past 7 days (n = 1199)					
Elevated Depression Symptoms ^a	Age <41	Age 41 to 50	Age 51 to 60	Age >60	Total
No, n (%)	350 (85.2)	339 (85.4)	281 (87.5)	63 (90.0)	1033 (86.2)
Yes, n (%)	61 (14.8)	58 (14.6)	40 (12.5)	7 (10.0)	166 (13.8)
Worked one trip as an airline pilot in past 30 days (n = 1413)					
Elevated Depression Symptoms ^a	Age <41	Age 41 to 50	Age 51 to 60	Age >60	Total
No, n (%)	401 (85.5)	392 (85.0)	350 (88.4)	78 (89.7)	1221 (86.4)
Yes, n (%)	68 (14.5)	69 (15.0)	46 (11.6)	9 (10.3)	192 (13.6)

^aElevated Depression Symptoms means PHQ-9 total score ≥ 10

Table 5 Sleep aid medicine use, alcohol consumption, sexual harassment, verbal harassment and depression among working airline pilots

Taken medicine (prescribed or "over the counter") to help with sleep among those worked in past 30 days (<i>n</i> = 1425) ^a					
Elevated Depression Symptoms ^b	Not during past month	< Once a week	Once or twice a week	Three or more times a week	Total
No, <i>n</i> (%)	875 (89.6)	170 (86.7)	118 (79.7)	70 (66.7)	1233 (86.5)
Yes, <i>n</i> (%)	101 (10.4)	26 (13.3)	30 (20.3)	35 (33.3)	192 (13.5)
Alcohol Consumption among those worked in past 30 days (<i>n</i> = 1417)					
Elevated Depression Symptoms ^b	Never or < 1 Drink per month	>1 Drink per month to 1 Drink per week	> 1 Drink per week to 1 Drink per day	>1 Drink per day	Total
No, <i>n</i> (%)	119 (83.8)	341 (87.0)	666 (87.0)	98 (83.8)	1224 (86.4)
Yes, <i>n</i> (%)	23 (16.2)	51 (13.0)	100 (13.1)	19 (16.2)	193 (13.6)
Frequency of sexual harassment in last 12 months among those worked in past 30 days (<i>n</i> = 1414) ^a					
Elevated Depression Symptoms ^b	Never	1 time	2–3 times	4 or more times	Total
No, <i>n</i> (%)	1129 (87.0)	62 (88.6)	24 (68.6)	7 (63.6)	1222 (86.4)
Yes, <i>n</i> (%)	169 (13.0)	8 (11.4)	11 (31.4)	4 (36.4)	192 (13.6)
Frequency of verbal harassment in last 12 months among those worked in past 30 days (<i>n</i> = 1398) ^a					
Elevated Depression Symptoms ^b	Never	1 time	2–3 times	4 or more times	Total
No, <i>n</i> (%)	973 (88.7)	148 (83.6)	74 (71.8)	12 (57.1)	1207 (86.3)
Yes, <i>n</i> (%)	124 (11.3)	29 (16.4)	29 (28.2)	9 (42.9)	191 (13.7)

^aFisher's exact test (two-sided) and trend test *p*-value < 0.05^bElevated Depression Symptoms means PHQ-9 total score ≥ 10

victims of sexual or verbal harassment need even more urgent assistance. That said, barriers to seeking treatment for mental health issues among high stress occupations such as military personnel deployed in combat operations, emergency situation first responders, and firefighters and police officers are documented in the literature [34–36]. Although different in degree and severity of stressors, commercial airline pilots may experience similar occupational and individual barriers to seeking treatment [37]. These include shift-work, long and continuous hours, and increased stigma towards admitting one has mental health problems resulting from work.

Long and continuous work-hours make scheduling treatment difficult [38]. In addition, researchers attribute stigma among workers in high stress public safety protection occupations, which we argue includes piloting commercial aircraft, to the emphasis on being resilient and independent; thus, admitting having a mental health problem is extremely difficult [39, 40]. Other barriers to seeking treatment include increased social withdrawal among those experiencing symptoms of mental health problems such as depression [41] and concerns toward treatment (e.g., not trusting mental health professionals) [41, 42] and self-reporting (e.g., belief admitting will cause harm to career) [43], and social norms (e.g., weak support of those getting treatment) [34].

Since mental health problems are prevalent among our participants and maybe exacerbated in high stress work situations, we agree with the argument that organizations are responsible for ensuring employees who develop

mental health problems receive timely mental health treatment [40]. Houdmont, Leka, and Sinclair [34] discuss three ways to increase treatment seeking among employees: (1) normalizing the receipt of needed mental health treatment (e.g., getting leadership endorsement), (2) emphasizing getting mental health treatment will prevent more severe problems from affecting employee performance, and (3) tailoring treatment to the occupational context. There are a number of deliverable solutions currently in place, which incorporate elements of these three recommendations.

Specifically, applying traditional cognitive behavioral treatment (CBT) while integrating work experiences shows promise in faster return to work among those on leave for mental health issues [44]. Furthermore, research supports the efficacy of internet-based treatments (e.g., CBT delivered online) as a viable option [45] for mild to moderate depression [46]. Reviews of internet-based psychological treatments for depression such as Internet-based CBT (ICBT) find it an effective alternative to face-to-face psychological treatments with the caveat that guided ICBT is more effective than unguided [47]. Findings also support therapist contact before and/or after ICBT have further efficacious effect of treatment [47]. Concerns toward ICBT include a meta-analysis published in 2013 of effectiveness of computerized CBT on adult depression showing the lack of significant effect of long-term treatment outcomes compared to short-term treatment duration and significantly high participant drop-out [48].

Despite the disadvantages, we believe the above studies give good reason for increased attention to commercial airlines considering work-experience tailored interventions such as ICBT for treating mental health problems, specifically depression, among pilots. Such initiatives could run parallel with leadership endorsement of professional face-to-face contact throughout the guided recovery process. We acknowledge our study does not evaluate how to increase access to treatment and cannot rate or recommend a specific treatment. However, ICBT is one example of a possible intervention found in the literature.

We acknowledge the inability to draw causal inferences due to the study design. However, the numbers raise concern regarding mental health among pilots. Limitations of this study include potential underestimation of frequencies of adverse mental health outcomes due to less participation among participants with more severe depression compared to those with less severe or without depression. This would lead to downward bias of the true estimate of depression prevalence over the survey period. Conversely, upward bias could occur if participants with underlying mental illness are more likely to participate and complete a survey than those without illness due to participant familiarity with the purpose of the study. We believe upward bias is minimized since participants are less likely to know the focus of our study because the survey covers many topics other than depression or suicidal thoughts. In addition, the survey was not described to participants as a mental health study but as a pilot health study.

Furthermore, completers worked as a pilot significantly longer on average than non-completers by over a year and more of them worked in the past 30 days than non-completers. Because of this, completers may exhibit better general health than non-completers and report lower frequency of depressive symptoms. We could not assess this due to non-responses.

Another source of underestimation is the length of the online survey. After implementation, we received feedback regarding the survey being too lengthy. Thus, if survey completers are different in characteristics from non-completers and if this difference influences depression scores, we posit the length of the survey may discourage more depressed participants from completing the survey. This also would result in downward bias.

This study did not conduct clinical interviews of survey respondents to confirm diagnosis of depression, nor did it have access to medical records. We felt the strength of participant anonymity out-weighed the ability to gather this information, and the medical literature provides evidence for good sensitivity and specificity of the PHQ-9 diagnosis compared with diagnosis from structured interviews [26, 28, 29].

Another limitation of this study is reduced generalizability to the general population of airline pilots. This is due

to non-random sampling, incomplete participation, and the inability to determine an exact reference population due to anonymous participation. That said, aviation health researchers have utilized anonymous surveying before and published results while acknowledging these same limitations [18]. Furthermore, the only way to achieve responses from airline pilots was to make the survey completely anonymous. Nevertheless, the key findings remain surprising—hundreds of pilots currently flying are managing depression, and even suicidal thoughts, without the possibility of treatment due to the fear of negative career impacts.

Conclusion

This study fills an important gap of knowledge by providing a current glimpse of mental health among commercial airline pilots, which to date had not been available. Our study found 233 (12.6%) of the 1848 airline pilots responding to the PHQ-9 met criteria for likely depression. Of the 1430 pilots who reported working as an airline pilot in the last seven days at time of survey, 193 (13.5%) met these criteria. Seventy-five participants (4.1%) reported having thoughts of better being off dead or self-harm within the past two weeks. We found a significant trend in proportions of depression at higher levels of use of sleep-aid medication (trend test $z = 6.74$, $p < 0.001$) and among those experiencing sexual harassment ($z = 3.18$, $p = 0.001$) or verbal harassment ($z = 6.13$, $p < 0.001$). Although the results have limited generalizability, there are a significant number of active pilots suffering from depressive symptoms. Future studies will evaluate additional predictors such as sleep and circadian rhythm disturbances.

Poor mental health is an enormous burden to public health worldwide. The tragedy of Germanwings flight 4U 9525 should motivate further research into assessing the issue of pilot mental health. Although current policies aim to improve mental health screening, evaluation, and record keeping, airlines and aviation organizations should increase support for preventative treatment.

Additional file

Additional file 1: Airline Pilot Mental Health Screening. (DOCX 24 kb)

Abbreviations

AMEs: Aeromedical examiners; CBT: Cognitive behavioral treatment; CDC-NCHS: U.S. Centers for Disease Control – National Center for Health Statistics; d.f.: Degrees of freedom; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Edition 4; FAA: U.S. Department of Transportation, Federal Aviation Administration; ICBT: Internet-based CBT; IP: Internet protocol; IQR: Interquartile range; IRB: Institutional Review Board; MDD: Major depressive disorder; NHANES: U.S. National Health and Nutrition Examination Survey; PHQ-9: Patient Health Questionnaire 9; U.S.: United States; YLDs: Years of life lived with a disability

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Availability of data and material

The dataset supporting the conclusions of this article is available by contacting Dr. Joseph G. Allen.

Authors' contributions

ACW (first author) interpreted the data, performed statistical analysis, and drafted the manuscript. DDM participated in study design, disseminated surveys, and helped to draft the manuscript. MGW participated in interpretation of data and helped to draft the manuscript. EM participated in interpretation of data and helped to draft the manuscript. TSB participated in interpretation of data and helped draft the manuscript. JGA conceived and designed the study, as well as participated in interpretation of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Institutional Review Board (IRB) of the Harvard T.H. Chan School of Public Health determined that IRB14-4504 (study protocol number) meets the criteria for exemption per the regulations found at 45 CFR 46.101(b)(2). Participants voluntarily gave consent to participate at the beginning of the web-survey.

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Appendix: Chapter 2, Supplemental

Airline pilot mental health screening

Psychological diagnoses, including depression, and prescription of psychiatric medication can precipitate a pilot losing the FAA Medical Certificate and subsequent loss of license to operate an airplane, which is permanent or temporary depending on diagnosis. Fear of this scenario is a likely reason pilots underreport mental health problems and underutilize professional medical help (Aviation Medicine Advisory Service, 2016; Aviation Today's Daily Brief, 2010; Lollis, Marsh, Sowin, & Thompson, 2009; Parker, Stepp, & Snyder, 2001). Airlines perform initial standard screening during the interview process, including self-reporting questions mentioned earlier. Standardized written tests constitute the evaluation. No follow-up screening or testing occurs after employment; only the required FAA First or Second Class medical examinations, which do not screen for mental health (only self-disclosure by pilots). The hiring process at most airlines has the applicant submit an employment application, complete one or several interviews, a written evaluation, complete a simulator proficiency flight, and pass a general physical examination (D. Donnelly-McLay, personal communication, Dec 3, 2015). Once the applicant has accepted employment at an airline, there are no further reviews or screenings by the airline. The only requirement is for the pilots to pass their annual or bi-annual FAA Medical Examination and complete and pass the airline's annual or semi-annual simulator training.

In the United States, all airline pilots are required to undergo an annual or bi-annual FAA Medical Examination. There is no mental health screening requirement or psychological testing during these exams. Pilots complete the FAA Form 8500-8 Medical Certificate, a self-report. Mandatory response questions include:

“Have you ever in your life been diagnosed with, had, or presently have any of the following: Mental disorders of any sort, depression, anxiety, etc.; Suicide attempt; Alcohol dependency or abuse; Substance dependence or a failed drug test ever; or substance abuse or use of illegal substance in the last two years?”

(Federal Aviation Administration, 2017).

Current requirements for these exams performed by an Aeromedical Examiner (AME) prohibit, “diagnosis of psychosis, bipolar disorder, or severe personality disorder” (Federal Aviation Administration, 2015a). Any mental health issue is only identified by self-report. In the case of a pilot who self-reports having depression, the AME would report the pilot as unfit to fly unless the AME, “...considers the applicant’s condition as unlikely to interfere with the safe exercise of the applicant’s licence and rating privileges” (9.1.3 Annex 1, 6.3.2.2.1) (International Civil Aviation Organization, 2012).

Europe and other worldwide regions follow International Civil Aviation Organization (ICAO) guidelines from the *ICAO Manual of Civil Aviation Medicine*, which identify mental health concerns but leaves out specifics of verifying diagnoses (International Civil Aviation Organization, 2012). A medical examiner cannot issue a passing medical exam if the pilot admits to having any type of diagnosed mental disorder. The manual recommends a pilot is unfit to fly if diagnosed with depression and is currently using anti-depressant medication. Since 2012, the ICAO notes mental health issues merit increased attention. ICAO proposes the requirement to implement a health education system for holders of pilot licenses. If approved by the ICAO Air

Navigation Commission, this is one step forward in addressing pilot mental health (International Civil Aviation Organization, 2015).

Self-reported medical conditions that chronically interfere with sleep such as insomnia, sleep apnea, or depression/anxiety disqualify a pilot for aviation duties (Federal Aviation Administration, 2015a). The FAA permits “occasional or limited use” of sleep aids and prohibits “daily/nightly use” (Federal Aviation Administration, 2015a). A list of acceptable sleep aids and minimum required wait time prior to flying indicate at least 24 hours to 72 hours (Federal Aviation Administration, 2015b).

Aviation Medical Examiner

The role of the Aviation Medical Examiner is to “examine applicants and determine whether or not they meet the medical standards for the issuance of the airman medical certificate...The medical standards are found in Title 14 of the Code of Federal Regulations, Part 67” (Federal Aviation Administration, 2015a). The regulations pertaining to the medical standards of mental health are:

I. Code of Federal Regulations All Classes: 14 CFR 67.107(a)(b)(c), 67.207(a)(b)(c), and 67.307(a)(b)(c) (a) No established medical history or clinical diagnosis of any of the following: (1) A personality disorder that is severe enough to have repeatedly manifested itself by overt acts. (2) A psychosis. As used in this section, "psychosis" refers to a mental disorder in which: (i) The individual has manifested delusions, hallucinations, grossly bizarre or disorganized behavior, or other commonly accepted symptoms of this

condition; or (ii) The individual may reasonably be expected to manifest delusions, hallucinations, grossly bizarre or disorganized behavior, or other commonly accepted symptoms of this condition. (3) A bipolar disorder.

(U.S. Government Publishing Office, 2012).

Additional Pilot Testing

Airline pilots are also subject to random drug and alcohol testing throughout their careers, although this testing is not part of the annual FAA Medical examinations. This Testing is required by the Omnibus Transportation Employees Testing Act of 1991 and by DOT and FAA regulations (49 CFR part 40 and 14 CFR part 120) (Federal Aviation Administration, 2015c).

Appendix Bibliography

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CHAPTER 3

Correlation Over Time of Toenail Metals Among Participants in the VA Normative Aging Study from 1992 to 2014

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Abstract

Background

Scientists use biomarkers to evaluate metal exposures. One biomarker, toenails, is easily obtained and minimally invasive, but less commonly used as a biomarker of exposure. Their utility will depend on understanding characteristics of their variation in a population over time. The objective of our study is to describe the correlation of toenail metal levels many years apart among participants in the VA Normative Aging Study (NAS).

Methods

Toenail clippings from 825 participants of the NAS from year 1992 to 2014 were analyzed for lead (Pb), Arsenic (As), Cadmium (Cd), Manganese (Mn), and Mercury (Hg). We utilized linear mixed models to assess correlation between toenail metal concentrations in multiple toenail samples from the same subject collected years apart and identified the optimal covariance pattern by likelihood ratio tests and Akaike's information criterion (AIC). Correlations among different metals were described using Spearman correlations.

Results

The average number of times toenail samples were collected from each subject ranged from 1.63 (Hg) to 2.04 (As). The average number of years between toenails collected per subject ranged from 4.73 (SD=2.44) (Mn) to 5.35 (SD=2.69) (Hg). Metal concentrations had slightly different correlation patterns over time, although for all metals correlations decreased with increasing time

between samples. Estimated correlations over a 3-year span were highest for toenail Pb (0.68) and Hg (0.67), while As, Cd, and Mn had lower correlations of 0.49, 0.44, and 0.47, respectively. Even across a six-year span, the lowest correlation was 0.35 (Cd).

Conclusion

Our results suggest that Pb, As, Cd, Mn, and Hg levels from toenail clippings can reasonably reflect exposures over several years in elderly men in the NAS. Even across six years, toenail metal levels were generally well correlated among NAS participants. As such, they may be useful as biomarkers of exposure in epidemiological studies of similar populations.

Introduction

Researchers have utilized human blood, bone, hair, and urine to assess people's exposures to contaminants from the environment. One biomarker of exposure that is less frequently used but could potentially be useful in epidemiology studies is toenails. Toenails are easily obtained, minimally invasive, and more easily stored than urine and blood making them potentially advantageous in many studies. In addition, toenails from people wearing shoes are likely to have less external contamination, or have less contamination from hygiene products such as selenium containing shampoos, than hair (Garland et al., 1993; LeBlanc, Dumas, & Lefebvre, 1999). Disadvantages of utilizing other biomarkers such as urine and blood include the requirement of sterile collection containers and specific training (e.g., phlebotomy). In addition, blood metals may only reflect recent exposure and hence are not good biomarkers for longer-term exposures. Toenails likely capture a somewhat longer exposure window.

Some epidemiological studies utilizing toenails include selenium in toenails from the general population reflecting selenium intake from dietary supplements and meals (Hunter et al., 1990; Longnecker et al., 1996; Ovaskainen et al., 1993; Swanson et al., 1990). In addition, general population studies evaluating arsenic in toenails show positive correlation with drinking water and soil arsenic concentrations (Hinwood et al., 2003; Karagas et al., 2001; Karagas et al., 2000). Toenails grow at a rate of roughly 1.00-1.50mm/month (0.05 mm/day), so the direct exposure window estimated from a sample of clippings from all ten toenails covers several weeks to months about 6-12 months prior to clipping (Grashow et al., 2014; Laohaudomchok et al., 2011; Levit & Scher, 2001; Longnecker et al., 1996; Sakamoto et al., 2015; Slotnick & Nriagu, 2006; Steven Morris, Stampfer, & Willett, 1983; Weller, Hunter, & Mann, 2014).

Toenail metal concentrations measured at one time point have been used to evaluate the relationship between exposures to metals and many health outcomes including blood pressure (Mordukhovich et al., 2012) and cancer (Hunter et al., 1990; Maasland, Schouten, Kremer, & van den Brandt, 2016). However, few studies evaluating metal concentrations in toenails have multiple toenail samples per subject over many years, and have not estimated how correlations change over many years. Thus, how well one toenail sample reflects exposures outside the 6-12 months prior to clipping is less clear. One study found wide variability in Pb concentrations in toenail samples collected 4 months apart (Gulson, 1996). A study evaluating trace elements in toenails among women in the U.S. found a correlation between two measurements of As and Hg taken six-years apart to be 0.54 and 0.56, respectively (Garland et al., 1993). This study did not evaluate Pb, Cd, or Mn. Hinnert et al. (2012) found toenails collected at three different occasions over the span of one year had toenail Hg correlations ranging from 0.75 (1st and 3rd visits) to 0.92 (1st and 2nd visits).

Despite the prior work using toenails as biomarkers of exposure, there has been only limited exploration of the correlation of toenail metal concentrations over longer periods. Understanding how metal levels in toenails change over many years for an individual in the general population is important to know to understand the time-period of exposure reflected by the toenail measures when using them as exposure biomarkers in epidemiological studies. Our study utilizes toenail data from an ongoing longitudinal study, the VA Normative Aging Study (NAS), to understand how toenail metal concentrations change over time for an individual. We utilized multiple toenail samples per participant collected over many years to examine the correlations of metals in toenails over time.

Methods

Study Population

The NAS is an ongoing longitudinal study of men in the greater Boston metropolitan area with no known chronic medical conditions at the time of recruitment (Bell, Rose, & Damon, 1972). Participants were World War II and Korean War veterans and non-veterans living the Boston area. The NAS started in 1961 and enrolled 2 280 healthy men who were evaluated at clinical visits every 3-5 years. Between 1992 and 2014, 825 of 1 286 still active NAS participants provided toenail clippings at several different clinical visits (maximum of 9 visits per subject among the 1 286 active participants from 1992 to 2014). If possible, toenails were collected from all toes and placed in small paper envelopes. Samples were stored in locked facilities at room temperature. All participants gave written informed consent. The Institutional Review Boards of the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and the Boston VA Medical Center approved this research.

Metals Analysis

We analyzed lead (Pb), arsenic (As), cadmium (Cd), manganese (Mn), and mercury (Hg) in the toenails. Toenail clippings from all ten toes were collected and pre-cleaned by sonicating for 15 minutes in approximately 10 milliliters (mL) of 1% Triton X-100 solution to remove extraneous contaminants. The samples were rinsed with distilled deionized water and dried at 60°C for 24 hours in a drying oven. Samples were weighed. If the weight of the whole toenail sample was greater than 0.1 grams (g), a portion of the toenail sample was used for mercury analysis. The rest of the sample was dissolved in HNO₃ acid for 48 hours and diluted to 5 mL with deionized water. Samples that weighed less than 0.1 g were acid-digested for Pb, As, Cd, and Mn only.

Lead, arsenic, cadmium, and manganese. Samples dissolved in HNO₃ acid were analyzed by inductive coupled plasma-mass spectrometry (ICP-MS). Analysis of the most recent 300 toenail samples (years range 1998 to 2014) utilized the Agilent 8800 ICP-MS Triple Quad (Agilent technologies, Inc., Delaware, USA). The other samples were analyzed using Perkin Elmer Elan DRC II ICP-MS (PerkinElmer, Inc., Connecticut, USA). We used exactly the same sample preparation method for all samples presented in this paper. Machines used to analyze samples were checked for comparability and accuracy by comparing the results of measuring the certified reference materials in one machine against the other. We found no adjustments were needed for between instrument variability.

For Pb, Cd, Mn, and As analysis, quality control (QC) measures included analysis of the National Institute of Standard and Technology Standard Reference Material 1643e (trace elements in water, Gaithersburg, MD) and a 1.0 nanogram per milliliter (ng/mL) mixed element standard solution of Pb, Cd, Mn and As solution as initial calibration verification standard, continuous calibration standards, and procedural blank. Certified reference material GBW 07601 (human hair; Institute of Geophysical and Geochemical Exploration, Langfang, Hebei Province, People's Republic of China) was used as the QC sample. We used a large preparation of GBW 07601 (2.0 grams per liter (g/L)) and a preparation of pooled toenail sample to monitor inter-day and intra-day variations. Certified reference material NIES CRM-13 (Analysis of National Institute for Environmental Studies certified reference material 13 (human hair; Ibaraki, Japan)) was used as the QC standard.

Recovery of the QC from the in-house preparation of the solution of pooled toenail sample digested in acid was 90%-110% with 95% precision for the four metals. Recovery of

NIES CRM-13 was 90-110% for Pb, As, and Cd. Recovery of GBW 07601 was 99% for Mn. The between-assay coefficient of variation between days was 2.94% for the four metals.

Limit of detection (LOD) for the QC blanks with analytical solution for the four metals (micrograms per milliliter ($\mu\text{g/mL}$)): Pb 0.00001, As 0.00001, Cd 0.000001, Mn 0.00002. The LOD for the sample itself varied according to sample weight, and equaled the LOD for the analytical solution multiplied by the dilution factor. Since sample weight varied from 0.009 g to 0.760 g, the LOD ranged from 0.000001 $\mu\text{g/g}$ (Cd) to 0.00253 $\mu\text{g/g}$ (Mn). The average LOD among the four metals was 0.000126 $\mu\text{g/g}$.

Mercury. Mercury analysis occurred only if there was sufficient sample left after analyzing for the other metals. Mercury assays utilized the Direct Mercury Analyzer 80 (Milestone Inc., Monroe, CT, USA), and samples were analyzed using a matrix-matched calibration curve derived from different weights of certified reference material GBW 07601. Recovery of the NIES CRM-13 was 99%. Quality control included daily calibration verification of high and low ends of the calibration curve, procedural blank, and analysis of NIES CRM-13. Mercury recovery was 90-110%, with >90% precision. The average (lowest, highest) LOD for Hg was 0.00607 $\mu\text{g/g}$ (0.00171, 0.0355 $\mu\text{g/g}$). Similar to the previous metals, the range of LOD was due to different sample weights.

Blood lead. Blood samples collected from 1992 to 2008 were analyzed for lead. Whole blood samples were collected in lead-free tubes containing edentate calcium disodium (EDTA) and analyzed at ESA Laboratories, Inc., Chelmsford, Massachusetts. After digestion with nitric acid and centrifuge, the laboratory analyzed the supernatant with Zeeman background-corrected

graphite furnace atomic absorption, which was calibrated with national Bureau of Standards blood lead standards materials. All glassware were soaked overnight in 20% nitric acid and rinsed with distilled water to prevent lead contamination.

Diet. Dietary data, including supplement use, were obtained via a semi-quantitative food frequency questionnaire administered at each study visit (Willett et al., 1985). For example, consumption of whole grains (combining wheat, rice, oats, and corn) was grams consumed per day at time of survey.

Statistical Methods

Because toenail metal concentrations were right skewed, we log(10)-transformed them for analyses. For the small number of samples that had negative (less than LOD) measured Pb, As, and Mn levels, we substituted the LOD for that measurement divided by the square root of two. There were no negative toenail Hg measurements, while toenail Pb had one negative measurement, As had two, and Mn had one. We took the same substitution approach with Cd despite a larger number of negative Cd values (106, 5.8%). One of these negative Cd measurements did not have an LOD reported so we substituted with the lowest positive toenail Cd measurement in the data set. Toenail Cd levels had many more negative values than other metals due to many more very low Cd levels measured in the toenails.

We evaluated different methods for handling the 106 negative toenail Cd measurements. These included adding the absolute value of the most negative measurement to all toenail Cd measurements (Kurtosis=86.824) or adding the absolute value of the most negative measurement plus one (Kurtosis=112.665). Both of these methods resulted in log toenail Cd distributions that

were less-normal compared to log values of the LOD divided by the square root of 2 substitution method (Kurtosis=2.880). Other transformations such as taking the square, square root, cube, cube root, and the inverse of these for toenail Cd values also resulted in inferior normal distributions.

We applied linear mixed models to assess correlation between metal concentrations across multiple toenail samples per subject collected years apart. Because NAS study visits are not always equally spaced, and because toenails are not always collected, the intervals between individuals' toenail samples vary. The distribution of years between repeated toenail samples from the same subject is shown in Figure 3.1. The linear mixed model statistical approach considers all the pairwise correlations between the many toenail samples from all NAS subjects, and the varying time intervals between them, and determines the optimal covariance pattern to describe the overall function of change in correlation over time for each metal separately; either using likelihood ratio tests for nested covariance pattern models or Akaike's information criterion (AIC). A hybrid covariance structure combining an exponential and a compound symmetry structure—describing a decreasing correlation among toenails collected further apart superimposed on a baseline non-zero correlation and previously described by Fitzmaurice (2004)—provided the best overall fit for each metal. This hybrid covariance structure is then used to predict the correlation between toenail concentrations of a given metal at any time interval regardless of the actual interval between two toenail samples for any individual.

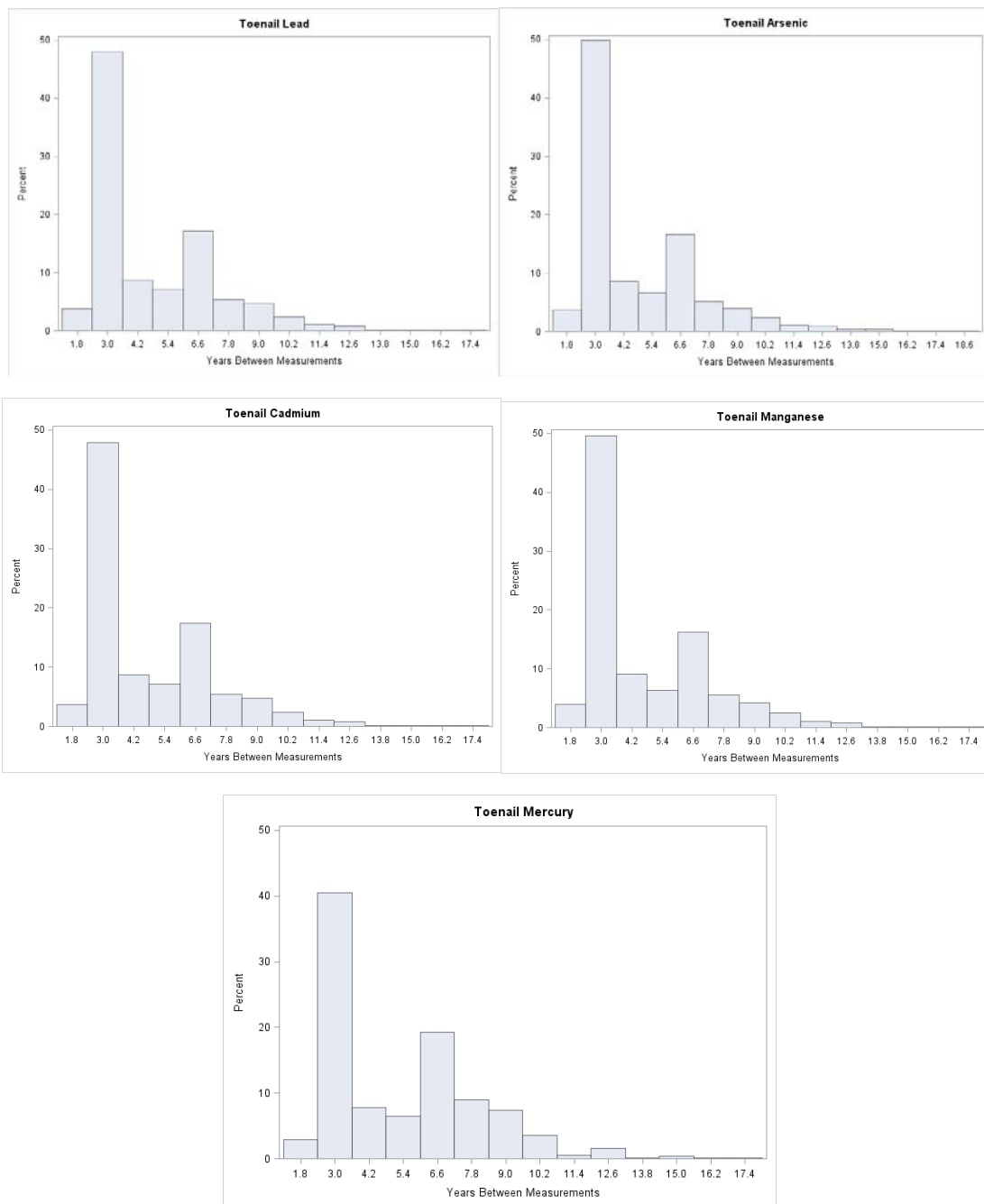


Figure 3.1. Distribution of years between measurements for toenail metals among NAS participants, 1992 to 2014

For variables that are strong predictors of some of the metals, we considered correlations between subjects' multiple toenail samples separately among those who never reported the strong predictor and those who did at least once. The strong predictors considered were use of Mn supplements, consuming whole grains, and eating canned tuna more than once per week. In addition, we applied Spearman correlations to evaluate correlation between metal levels at first visit with donated toenails (e.g., correlation of toenail Pb and As). Student's t-test were used to compare difference in means. Significance was defined as an alpha level of <0.05 .

Code availability

We utilized SAS software (Version 9.4, SAS Institute Inc., Cary, North Carolina) for data analysis. Code for analyses is available via contacting the corresponding author.

Results

Demographics

At the first visit where toenail clippings were donated, participants were on average 70 years old, almost all white, and just under 4 out of 5 were overweight or obese (Table 3.1). Nearly all subjects were never or former smokers, with 95% of smokers quitting by 1990. About 9 out of 10 of those who reported consumption of canned tuna did so up to once per week. Clinical visits were fewest during the winter.

Table 3.1. Characteristics of participants at their first visit with donated toenails, 1992 to 2014.

Characteristic	n	Mean	S.D.
Age (years)	825	70.7	± 7.0
Smoking (pack-years)	824	21.6	± 26.5
Years of education	803	14.9	± 3.0
Alcohol intake (g/day)	112	11.7	± 15.9
Year of visit	825	1998.6	± 3.9
Manganese from food (mg)	732	4.5	± 2.4
Whole grain amount in diet (g)	347	26.0	± 21.5
Blood Lead (µg/dL)	759	4.5	± 2.6
BMI (kg/m ²)	n	%	
	<25	174	21.1
	25-29	439	53.2
	≥30	212	25.7
Smoking Status			
	Never Smoker	255	31.0
	Former Smoker	530	64.4
	Current Smoker	38	4.6
Race/ethnicity			
	Non-Hispanic white	806	97.9
	Non-Hispanic black	12	1.5
	Hispanic white	4	0.5
	Hispanic black	1	0.1
Season of first clinical visit			
	Spring	209	25.4
	Summer	233	28.3
	Fall	242	29.4
	Winter	139	16.9
Canned tuna consumption			
	never,<1/month	182	23.7
	1-3/month	277	36.1
	1/week	215	28.0
	>1/week	93	12.1

Metal Measurement Occasions

Individual participants provided toenail clippings on up to six separate study visits. Each subject on average had about two samples analyzed for each toenail metal (Table 3.2). The distribution of years between toenail samples (Figure 3.1) had an average number of years between samples per subject that ranged from 4.73 (SD=2.44) years for Mn to 5.35 (SD=2.69) for Hg. The average years between the first and last sample per subject ranged from 8.21 (SD=4.15) for Hg to 10.08 (SD=4.82) for Pb. Overall, around 46% of measurements were taken roughly three years apart and about 18% taken roughly 6.5 years apart corresponding to typical intervals between NAS study visits. The distribution of years between measurements among the five toenail metals were similar except for Hg (Figure 3.1), which showed the frequency of years between measurements to occur less around 3 and more around 6.5 years compared with the other metals.

Table 3.2. Toenail metal measurements among NAS participants, 1992 to 2014

	People	# of samples	Mean # of samples per subject	Mean years btw. samples	S.D.	Median years btw. samples	Mean years btw. 1st and last sample	S.D.	Median years btw. 1st and last sample
Lead	790	1818	2.03	4.81	2.45	3.48	10.08	4.82	10.41
Arsenic	804	1866	2.04	4.79	2.57	3.34	9.96	4.81	10.43
Cadmium	789	1812	2.03	4.82	2.46	3.49	10.06	4.79	10.41
Manganese	766	1757	2.02	4.73	2.44	3.35	9.82	4.63	10.46
Mercury	711	1266	1.63	5.35	2.69	4.20	8.21	4.15	8.46

Metal Concentrations

The correlations between the toenail metal concentrations at first visit with donated toenail clippings are shown in Supplemental Table S1.2 along with correlations with blood Pb. At the first sample, toenail Pb had the widest range of concentration levels (min 0.007, max 32.52 µg/g) and toenail As had the narrowest range (min 0.0004, max 1.70 µg/g). Toenail Pb had

the highest interquartile range (IQR) of concentration levels while toenail Cd had the lowest (Table 3.3).

Table 3.3. Number of participants (n), median, and inter-quartile range (IQR) of metal concentrations at first donated toenail sample.

	Lead	Arsenic	Cadmium	Manganese	Mercury
n	790	804	789	766	711
Median, (µg/g)	0.323	0.071	0.018	0.270	0.252
IQR	0.541	0.063	0.033	0.398	0.339

Participants reporting consumption of Mn supplements had a higher first donated sample mean toenail Mn level than not taking supplements (p-value= 0.04) (Supplemental, Table S1.1). A significant difference was found between those reporting consumption of whole grains having a higher first donated sample mean toenail Mn level (p-value=0.0002) and higher mean toenail As level (p-value=0.0009). In addition, those that reported consuming canned tuna more than once per week had a significantly higher first donated sample mean toenail Hg level (p-value<0.0001).

Over 95% of toenail metal measurements came from former or never smokers (Supplemental Table S1.4 to S1.8). By 1991, over 95% of NAS participants who smoked had quit, leaving 30 to 35 current smokers (depending on metal) with at least one visit with donated toenails (toenail collection began in 1992). Among these, only 18 had more than one visit. Therefore, we did not describe correlations of subjects' toenail metals stratified by smoking status, but presented median levels of metals by order of donated toenail samples. At the first donated sample, former smokers had slightly higher median metal levels than never smokers, except for Cd, which was the same. At first donated sample, current smokers had the lowest median metal levels for Pb, Cd, and Hg but had the highest median level for Mn.

Over 92% of blood Pb, came from former or never smokers (Supplemental Table S1.9, Supplemental). At first donated toenail sample with blood Pb data, never and current smokers had the same median blood Pb levels. Current smokers had a higher median blood Pb than never and former smokers.

Correlations between Metals

Correlations between metal levels at first visit with donated toenail clippings were significant between most pairs of toenail metal comparisons (Supplemental Table S1.2) except for Pb-Hg, Cd-Hg, Mn-Hg, Mn-Blood Pb, and Hg-Blood Pb. Correlations were highest for Pb-Cd (0.55), As-Mn (0.54), and Pb-Mn (0.46). The lowest correlations were Hg-Cd (0.02), Hg-Pb (-0.03), and Hg-Blood Pb (-0.03). Correlations between toenail Pb and blood Pb for subjects with both measures at visits was 0.30 (n=729, $p<0.0001$).

Correlations of Toenail Metal Measurements over Time

The estimated within person correlation patterns of toenail metal concentrations over time from the hybrid covariance model were slightly different for the different metals, although for all metals correlations decreased with increasing time between samples (Figure 3.2).

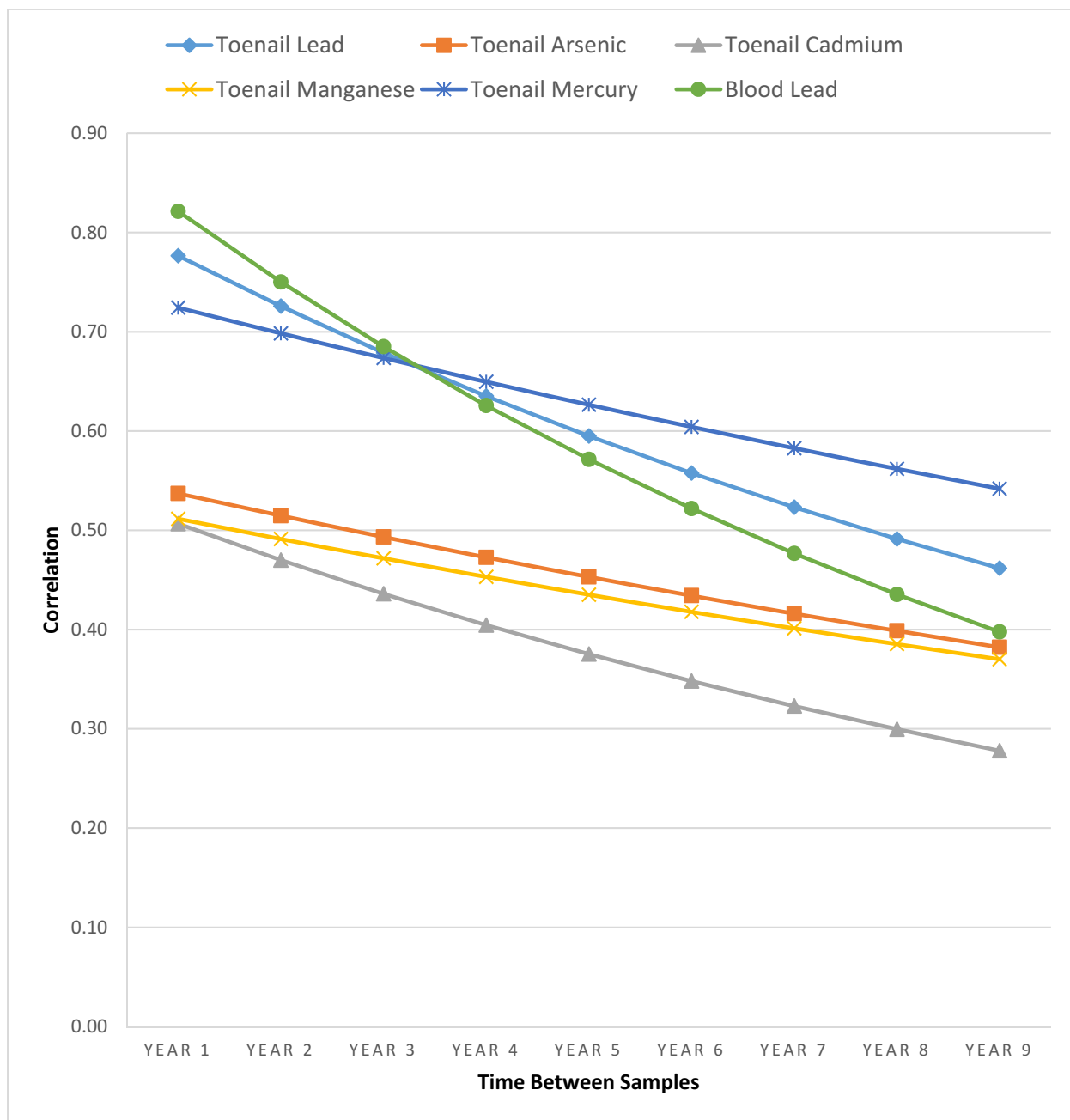


Figure 3.2. Estimated correlations of toenail metal levels by years between measurement occasions via hybrid covariance structure, 1992 to 2014. (Blood lead shown for comparison)

Correlations over time were virtually the same for toenail As and Mn. Toenail Cd correlations started just slightly lower than As and Mn at the 1-year interval, but the correlation dropped off slightly more steeply over time. The decline in correlation over time for Hg was similar to Cd, but started at a much higher correlation at the 1-year interval. Toenail Pb had a similar correlation at the 3-year interval as Hg, but the correlation dropped off more steeply over time. Interestingly, blood Pb (3463 samples, median 4.00, IQR 3.00, min 0.29, max 35.00 µg/dL) collected during the same study period had a higher correlation than toenail Pb at the 1-year interval, similar correlation at the 3 year interval, and a lower correlation and steeper drop-off after the 3-year interval (Figure 3.2).

When we considered known high levels of exposure to metals—taking supplements with Mn, consuming whole grains (Mn, As), or eating canned tuna more than once per week (Hg)—we found that the correlation of those metals across multiple samples collected over time was higher at shorter intervals, but then decreased to either the same or lower correlation of those not taking supplements, not consuming whole grains or eating canned tuna less frequently at the seven-year interval (Table 3.4, Figure 3.3).

Table 3.4. Estimated correlation of measures of toenail manganese (Mn), arsenic (As), and mercury (Hg) at hypothetical sample collection intervals 1 to 7 years apart stratified by Mn in supplements, consumption of whole grains, and frequency of consumption of canned tuna.

				Correlation						
	Toenail Metal	n	Visits	1 Year Apart	2 Years	3 years	4 years	5 years	6 years	7 years
No Mn supplements	Mn	565	1196	0.50	0.48	0.46	0.44	0.43	0.41	0.40
Taking Mn supplements	Mn	201	561	0.75	0.60	0.50	0.44	0.40	0.38	0.36
Reported no consumption of whole grains	Mn	211	258	0.40	0.40	0.40	0.40	0.40	0.40	0.40
Reported consumption of whole grains	Mn	555	1499	0.54	0.51	0.49	0.46	0.44	0.42	0.40
Reported no consumption of whole grains	As	247	316	0.60	0.49	0.46	0.45	0.45	0.45	0.45
Reported consumption of whole grains	As	577	1550	0.54	0.52	0.50	0.47	0.45	0.43	0.42
Canned tuna consumption 1/week or less	Hg	525	917	0.73	0.70	0.68	0.66	0.65	0.63	0.61
Canned tuna consumption >1/week	Hg	186	349	0.83	0.72	0.64	0.57	0.51	0.47	0.44

n= participants: Having at least one visit with taking supplements, consumption of whole grains, or consuming more than 1 can of tuna per week comprised the “taking Mn supplements”, “reported consumption of whole grains”, or “canned tuna consumption >1/week” groups. Those that never took supplements, consumed whole grains, or consumed more than 1 can of tuna per week comprised the “no mn supplements”, “reported no consumption of whole grains”, or “canned tuna consumption 1/week or less groups”.

Visits= visits with toenail metal

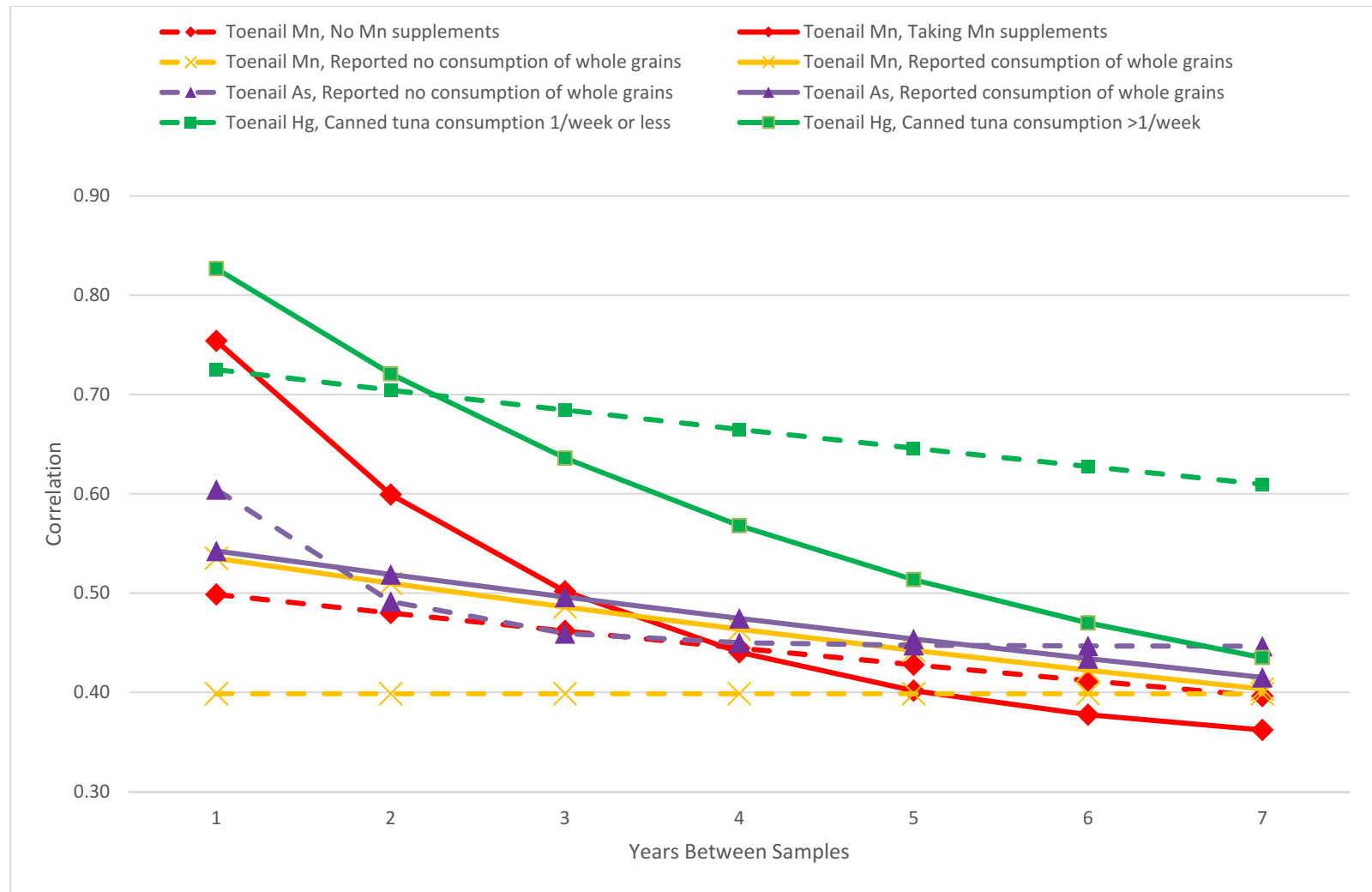


Figure 3.3. Estimated correlation of repeated measures of toenail manganese (Mn), arsenic (As), and mercury (Hg) taken 1 to 7 years apart stratified by Mn in supplements, consumption of whole grains, and frequency of consumption of canned tuna. (The correlation for measurements taken one year apart was estimated by the hybrid covariance structure since no actual measurements were taken 1-year apart.)

Discussion

The objective of our study was to describe the correlations of metal concentrations among multiple toenail samples per participant collected over time in the NAS. We found the correlation of metals ranged from 0.44 (Cd) to 0.68 (Pb) for toenail samples collected three-years apart (the most common duration between visits) (Figure 3.2). These correlations steadily decreased with increasing time intervals between samples. Importantly, for toenail Pb and Hg, the correlations remained above 0.5 out to 7 years, while for Mn and Cd, correlations fell to that level after a year, and for As, by 3 years. Hence, toenail Pb and Hg measurements capture longer windows of exposure.

Our study of 825 participants and 1,818 toenail samples analyzed for Pb found Pb to have the highest within-person correlation across a three-year period. One study of toenails with subjects' samples collected 4 months apart found wide variability in Pb concentrations (Gulson, 1996). A study evaluating trace elements in toenails among women in the U.S. found a correlation between two measurements of As and Hg taken six-years apart to be 0.54 and 0.56, respectively (Garland et al., 1993). This study did not evaluate Pb, Cd, or Mn. Hinnert et al. (2012) found toenails collected at three different occasions over the span of one year had toenail Hg correlations ranging from 0.75 (1st and 3rd visits) to 0.92 (1st and 2nd visits). Our study found the estimated correlations at a six-years interval for As and Hg to be 0.43 and 0.59, respectively, which are similar to correlations of Garland et al. (1993). Our toenail Hg correlation for a 1-year interval was 0.72, which is similar to Hinnert et al. (2012).

We included blood Pb in our study because it is the standard for, and a well-studied biomarker of, exposure to Pb when investigating Pb exposure and health outcomes (Barbosa, Tanus-Santos, Gerlach, & Parsons, 2005; Bouchard et al., 2009; Cheng et al., 2001; Pirkle et al.,

1994; Rhodes, Spiro, Aro, & Hu, 2003; Schwartz et al., 1991). The geometric mean (GM) of blood Pb levels of our study cohort at the first visit (3.9 ug/dL, [95% CI 3.7-4.0], calculated from Table 1 blood Pb data) was similar to the U.S. general population living in cities with ≥ 1 million people from 1988-1991 (GM 3.9 ug/dL [95% CI 3.6-4.3]) (Pirkle et al., 1994).

Our results found a high correlation across multiple samples per subject for both blood Pb and toenail Pb (Figure 3.2). In addition, there was a significant, but modest positive correlation between blood Pb and toenail Pb levels at first visit with toenail sample (Supplemental Table S1.2). Toenail Pb had higher correlation across multiple samples per subject than blood Pb when samples were taken >3 years apart (Figure 3.2), which suggests that a single toenail sample may capture long term exposures better than blood. This finding is supported by studies reporting toenail Pb reflecting longer exposure durations than blood Pb (Grashow et al., 2014; Levit & Scher, 2001; Slotnick & Nriagu, 2006; Steven Morris et al., 1983; Weller et al., 2014).

Our findings of higher toenail Mn levels among those taking Mn supplements compared to those not taking supplements seems intuitive. A study examining 49 toenail samples from welders found that those with higher dietary intake of Mn did have higher toenail Mn levels (Laohaudomchok et al., 2011). A study of welders in Thailand found higher levels of toenail Mn among those with higher levels of blood Mn compared to those with lower blood Mn levels (Wongwit, Kaewkungwal, Chantachum, & Visessamee, 2004).

Our results of significantly higher average toenail Mn levels among those reporting consumption of whole grains compared to those not reporting consumption are consistent with research indicating whole grains as a source of Mn exposure (CDC, 2012; Linus Pauling Institute, 2014). A search in PubMed and Web of Science did not find studies evaluating how whole grain consumption affects toenail Mn concentration correlations over time.

Strong evidence exists for consumption of fish such as tuna and other saltwater fish as a primary source of Hg exposure (CDC, 1999; NRC, 2000). A study conducted among 579 males from the Health Professionals Follow-up Study found the primary exposure route for Hg, measured via toenails, was consumption of tuna and saltwater fish, with a correlation of 0.31 ($p < 0.05$) between toenail Hg and tuna consumption (Joshi et al., 2003). We found a higher correlation across toenails collected less than 2 years apart among those who consumed more tuna, although the correlation dropped to lower than that of non-consumers over greater intervals (Table 3.4 and Figure 3.3).

A dominant, consistent single exposure source should reduce variation in toenail concentrations over time and so increase the correlation because that source would dominate the contribution to biomarker concentrations even in the face of fluctuations in other lower level exposures. However, if that dominant exposure source does not remain constant over time, then the correlation in biomarker concentrations would likely drop steeply since there would be very large differences in biomarker concentration between samples collected when the dominant source was present vs. absent. The strong predictors of some of our metals that we considered are dietary. Diet is generally found to be relatively stable (Dekker et al., 2013; Jankovic et al., 2014), but as the interval between assessments lengthens dietary habits have been found to be more likely to vary (Movassagh, Baxter-Jones, Kontulainen, Whiting, & Vatanparast, 2017; Weismayer, Anderson, & Wolk, 2006). These dietary patterns are consistent with the higher level of correlation between toenail metal concentrations over shorter intervals, but then the same or lower correlations over longer intervals, among those ever reporting the dominant exposure sources we explored compared with those that did not report these sources.

Our results suggest that toenails could be utilized in addition to other well-studied biomarkers such as hair, blood, and urine in assessing exposure to metals, specifically Pb, As, Cd, Mn, and Hg. Toenails in general are less prone to contamination among people wearing shoes than hair and fingernails from external sources such as dirt and soaps (Garland et al., 1993; LeBlanc et al., 1999). In addition, toenails are more isolated than blood and urine from other metabolic activities in the body, and represent longer exposure periods than blood or urine (Barbosa et al., 2005; Garland et al., 1993; Hopps, 1977; Willett, 1987). The exposure window estimated from toenail clipping covers several weeks to months with time of exposure at about 6-12 months before clipping (Grashow et al., 2014; Levit & Scher, 2001; Slotnick & Nriagu, 2006; Steven Morris et al., 1983; Weller et al., 2014). Furthermore, collecting toenail clippings is painless, less invasive than drawing blood samples, and more convenient to store (Garland et al., 1993). Therefore, utilizing toenails may be more convenient and less expensive to collect, store, and transport compared to blood (Davis et al., 2017).

Limitations to our study include low Cd levels that resulted in almost 6% negative readings. Our statistical approach requires a normal distribution necessitating log-transformation and thus some substitution of the negative values. Setting all negative values to zero would have falsely increased correlations as it would have reduced the variability in those measurements. Because each measurement had a separate LOD, our substitution approach maintained some variability, although our estimates still could have been slightly over-estimated because of this.

There are limits to the generalizability of our findings because correlations over time will depend on external exposures in the specific population being examined. To the extent that other populations have different exposure patterns than the NAS, the correlations could be different.

However, our findings were similar to other studies when similar intervals were considered (Garland et al., 1993; Hinnners et al., 2012).

Another limitation is our study population only evaluated males residing in the Boston metropolitan area. Nevertheless, studies among females support our results regarding correlations of toenail Hg among multiple toenail samples per person. As described earlier, Hinnners et al. (2012) reported correlations ranging from 0.75 (1st and 3rd visits) to 0.92 (1st and 2nd visits). A search in PubMed for correlations of toenail Pb, As, Cd, Mn, and Hg across multiple toenail samples among women did not reveal additional published articles.

Conclusion

Our results suggest that Pb, As, Cd, Mn, and Hg levels from toenail clippings can reasonably reflect exposures over several years in the NAS population—a population of elderly men residing in the Boston metropolitan area. Specifically, toenail metal levels provide good estimates up to 5 years (Cd had lowest correlation of 0.38 at measures 5 years apart). Understanding the drop off in correlation over time for the different metals can be used with statistical approaches to account for error in estimating prior exposures in epidemiologic studies of health outcomes (Rosner, Spiegelman, & Willett, 1992).

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Appendix: Chapter 3 Supplemental

Summary: The following tables describe toenail metal levels stratified by sources from consumption, correlation between different metal levels (e.g., Pb-As), or toenail metal levels stratified by smoking status.

Table S1.1. Average toenail Mn and Hg levels (log values) from first visit with toenail metal data stratified by Mn in supplements, consumption of whole grains, and frequency of consumption of canned tuna.

	Toenail Metal	n	Mean	SD	Median	IQR
No Mn supplements	Mn	759	-0.549	0.442	-0.573	0.575
Taking Mn supplements¹	Mn	97	-0.467	0.357	-0.458	0.457
Reported no consumption of whole grains	Mn	724	-0.559	0.444	-0.583	0.576
Reported consumption of whole grains²	Mn	347	-0.454	0.420	-0.476	0.577
Reported no consumption of whole grains	As	765	-1.108	0.316	-1.150	0.361
Reported consumption of whole grains³	As	347	-1.048	0.261	-1.068	0.331
Canned tuna consumption 1/week or less	Hg	670	-0.631	0.407	-0.630	0.558
Canned tuna consumption >1/week⁴	Hg	98	-0.467	0.300	-0.449	0.432

n= first visits with toenail metal data and consumption status. The first visit an individual reported not having Mn supplements and having toenail Mn data is counted as one out of the 759. The first visit an individual reported having Mn supplements and having toenail Mn data is counted as one out of the 97. Some individuals contributed to both consumption groups.

SD= standard deviation

IQR= interquartile range

Student's t-test of means of toenail metal between consumption groups, two-sided, p-values:

¹p=0.04

²p<0.001

³p<0.001

⁴p<0.001

Table S1.2. Correlations between metal measurements at first visit with donated toenails, 1992 to 2014 (top: Spearman's rho, middle: p-value, bottom: number of participants)

	Pb	As	Cd	Mn	Hg	Blood Pb
Pb	1	0.40	0.55	0.46	-0.03	0.31
		<.0001	<.0001	<.0001	0.395	<.0001
	813	791	812	792	678	749
As		1	0.27	0.54	0.08	0.10
			<.0001	<.0001	0.045	0.0056
		815	790	791	656	751
Cd			1	0.39	0.02	0.17
				<.0001	0.653	<.0001
			812	791	678	749
Mn				1	-0.05	0.04
					0.186	0.263
				792	657	728
Hg					1	-0.03
						0.398
					678	632

Table S1.3. Number of participants and median (IQR) metal concentration by order of donated toenail sample¹, 1992 to 2014.

	1	2	3	4	5	6
Lead, n	790	490	302	170	55	11
%	100.0	62.0	38.2	21.5	7.0	1.4
Median, µg/g	0.323	0.261	0.242	0.192	0.184	0.116
IQR	0.541	0.475	0.406	0.414	0.301	0.171
Arsenic, n	804	511	304	176	58	13
%	100.0	63.6	37.8	21.9	7.2	1.6
Median, µg/g	0.071	0.077	0.075	0.071	0.069	0.054
IQR	0.063	0.060	0.052	0.060	0.051	0.019
Cadmium, n	789	490	302	169	52	10
%	100.0	62.1	38.3	21.4	6.6	1.3
Median, µg/g	0.018	0.014	0.012	0.012	0.011	0.010
IQR	0.033	0.021	0.019	0.019	0.015	0.024
Manganese, n	766	478	290	167	47	9
%	100.0	62.4	37.9	21.8	6.1	1.2
Median, µg/g	0.270	0.283	0.281	0.248	0.257	0.205
IQR	0.398	0.398	0.324	0.397	0.423	0.089
Mercury, n	711	362	145	42	5	1
%	100.0	50.9	20.4	5.9	0.7	0.1
Median, µg/g	0.252	0.192	0.161	0.155	0.156	0.165
IQR	0.339	0.252	0.191	0.123	0.068	0.000

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.4. Number of subjects and median toenail lead levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2014

	1	2	3	4	5	6
All (n)	790	490	302	170	55	11
%	100	62.0	38.2	21.5	7.0	1.4
Median (ug/g)	0.323	0.261	0.242	0.192	0.184	0.116
Never Smokers (n)	244	157	95	56	13	5
%	100	64.3	38.9	23.0	5.3	2.0
Median (ug/g)	0.318	0.262	0.296	0.276	0.232	0.060
Former Smokers (n)	509	316	193	106	39	6
%	100	62.1	37.9	20.8	7.7	1.2
Median (ug/g)	0.341	0.262	0.216	0.180	0.159	0.141
Current Smokers (n)	35	17	13	8	3	0
%	100	48.6	37.1	22.9	8.6	0.0
Median (ug/g)	0.300	0.223	0.231	0.070	0.073	—

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.5. Number of subjects and median toenail arsenic levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2014

	1	2	3	4	5	6
All (n)	804	511	304	176	58	13
%	100.0	63.6	37.8	21.9	7.2	1.6
Median (ug/g)	0.071	0.077	0.075	0.071	0.069	0.054
Never Smokers (n)	251	158	98	60	16	6
%	100.0	62.9	39.0	23.9	6.4	2.4
Median (ug/g)	0.067	0.074	0.076	0.070	0.081	0.056
Former Smokers (n)	518	335	191	107	39	7
%	100.0	64.7	36.9	20.7	7.5	1.4
Median (ug/g)	0.072	0.080	0.075	0.070	0.069	0.053
Current Smokers (n)	33	18	14	9	3	0
%	100.0	54.5	42.4	27.3	9.1	0.0
Median (ug/g)	0.068	0.070	0.097	0.078	0.067	—

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.6. Number of subjects and median toenail cadmium ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2014

	1	2	3	4	5	6
All (n)	789	490	302	169	52	10
%	100.0	62.1	38.3	21.4	6.6	1.3
Median (ug/g)	0.018	0.014	0.012	0.012	0.011	0.010
Never Smokers (n)	244	157	95	55	12	4
%	100.0	64.3	38.9	22.5	4.9	1.6
Median (ug/g)	0.018	0.013	0.013	0.011	0.016	0.022
Former Smokers (n)	509	316	193	106	37	6
%	100.0	62.1	37.9	20.8	7.3	1.2
Median (ug/g)	0.018	0.014	0.011	0.012	0.011	0.008
Current Smokers (n)	35	17	13	8	3	0
%	100.0	48.6	37.1	22.9	8.6	0.0
Median (ug/g)	0.016	0.017	0.015	0.015	0.023	—

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.7. Number of subjects and median toenail manganese levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2014

	1	2	3	4	5	6
All (n)	766	478	290	167	47	9
%	100.0	62.4	37.9	21.8	6.1	1.2
Median (ug/g)	0.270	0.283	0.281	0.248	0.257	0.205
Never Smokers (n)	239	153	92	55	13	4
%	100.0	64.0	38.5	23.0	5.4	1.7
Median (ug/g)	0.244	0.281	0.276	0.320	0.342	0.278
Former Smokers (n)	495	308	184	104	32	5
%	100.0	62.2	37.2	21.0	6.5	1.0
Median (ug/g)	0.280	0.290	0.280	0.233	0.226	0.169
Current Smokers (n)	30	17	13	8	2	0
%	100.0	56.7	43.3	26.7	6.7	0.0
Median (ug/g)	0.374	0.278	0.335	0.307	1.266	—

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.8. Number of subjects and median toenail mercury levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2014

	1	2	3	4	5	6
All (n)	711	362	145	42	5	1
%	100.0	50.9	20.4	5.9	0.7	0.1
Median (ug/g)	0.252	0.192	0.161	0.155	0.156	0.165
Never Smokers (n)	218	109	49	10	2	0
%	100.0	50.0	22.5	4.6	0.9	0.0
Median (ug/g)	0.214	0.163	0.146	0.120	0.401	—
Former Smokers (n)	459	239	88	29	2	1
%	100.0	52.1	19.2	6.3	0.4	0.2
Median (ug/g)	0.285	0.203	0.177	0.161	0.185	0.165
Current Smokers (n)	34	13	8	3	1	0
%	100.0	38.2	23.5	8.8	2.9	0.0
Median (ug/g)	0.189	0.103	0.134	0.146	0.147	—

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S1.9. Number of subjects and median blood lead levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2008

	1	2	3	4	5
All (n)	1256	1012	728	389	78
%	100.0	80.6	58.0	31.0	6.2
Median (ug/dL)	5.00	4.00	4.00	3.00	3.00
Never Smokers (n)	377	301	227	121	32
%	100.0	79.8	60.2	32.1	8.5
Median (ug/dL)	5.00	4.00	3.00	3.00	3.00
Former Smokers (n)	779	650	468	253	42
%	100.0	83.4	60.1	32.5	5.4
Median (ug/dL)	5.00	4.00	4.00	3.00	3.00
Current Smokers (n)	100	61	33	15	4
%	100.0	61.0	33.0	15.0	4.0
Median (ug/dL)	6.00	5.00	5.00	3.00	3.00

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

CHAPTER 4

Association between Lead, Arsenic, Cadmium, Manganese, and Mercury in Toenails and Symptoms of Depression and Anxiety in the VA Normative Aging Study

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Abstract

Background

Mental health disorders are a tremendous burden worldwide. The biological relevance of metals exposures, particularly lead, on psychiatric outcomes is documented. Scientists have utilized biomarkers to evaluate metal exposures. One biomarker, toenails, is easily obtained and minimally invasive. However, it is less commonly used as a biomarker of exposure and has not been evaluated on its relationship with psychiatric outcomes. The main objective of our study is to investigate the relationship between metal levels from multiple toenail samples per participant and symptoms of depression and anxiety among participants in the VA Normative Aging Study (NAS).

Methods

Toenail clippings from 825 participants of the NAS from year 1992 to 2014 were analyzed for lead (Pb), Arsenic (As), Cadmium (Cd), Manganese (Mn), and Mercury (Hg). We utilized multivariate linear and logistic mixed models to assess the association with these five metals and symptoms of depression, anxiety, and global indices for general psychopathologic status measured by the Brief Symptom Index (BSI). We also evaluated the relationship between cumulative average toenail metals and outcomes. Secondary analyses included evaluating the association between bone and blood lead with the same outcomes. We reviewed cumulative average blood lead and most recent visit with BSI as well as first visit with bone lead with most recent visit with BSI.

Results

There were 1862 visits that had both toenail and BSI data among 806 subjects (average of 2.31 visits per subject). The average years between visits with both types of data was 3.23 (SD= 0.97 years). After adjusting for covariates and multiple toenail metals per subject, toenail Mn showed a trend of increasing risk of higher anxiety symptoms, and toenail Hg displayed a decreasing risk of higher total symptoms. Adjusted regression models for cumulative average toenail Pb, Cd, Mn, and Hg found positive associations with various outcomes. Secondary analysis found a trend toward higher depression and anxiety scores with higher patella Pb levels. An increase in tibia Pb was associated with an increasing trend in all outcomes except for total symptoms. No associations were found between blood Pb and any outcomes among linear mixed models and cumulative average linear regression models.

Conclusion

Our study tentatively suggests that toenails from NAS participants may be an important biomarker to measure the association between metals and symptoms of depression or anxiety measured via the BSI. That said, toenails are an adequate biomarker for some global indices for general psychopathologic status such as high PST and high PSDI among NAS subjects. Collection of toenail clippings are minimally invasive compared to blood and urine, and toenails are much cheaper to store and transport. We suggest that due to these reasons researchers should still consider collecting toenails in addition to other biomarkers from NAS participants and similar populations.

Introduction

The burden of mental disorders on public health is tremendous. An estimated 905 million cases of mental disorders occurred worldwide in 2015 (G. B. D. Disease Injury, 2016).

Depression is the third most important cause of disease burden worldwide and affects about 300 million people globally (CDC, 2016; Mathers, Fat, Boerma, & World Health, 2008; WHO, 2017). In 2010, depression accounted for the most disability-adjusted life years (DALYs) among mental and substance use disorders—accounting for approximately 74.5 million disability adjusted life years worldwide (Whiteford et al., 2013). In the US, 17% of people will have Major Depressive Disorder (MDD) over their lifetime (Kessler, Berglund, et al., 2005) and 7% will have experienced an MDD in the past year (Kessler, Chiu, Demler, & Walters, 2005).

There are many potential risk factors for MDD: Women are at higher risk than men (Whiteford et al., 2013). Those age 30 to 59 years have higher risk than other age groups (Kessler, Berglund, et al., 2005). Lower education attainment, unemployment, and adverse childhood experiences place people at higher risk (Blazer, Kessler, McGonagle, & Swartz, 1994; Chapman et al., 2004). Experiencing one episode of MDD puts an individual at 50% risk of experiencing another, and the subsequent risk increases with additional episodes (NIMH, 1985).

Improved understanding of the role of modifiable risk factors for symptoms of MDD could have great health, and associated financial, benefits. Financial costs from MDD to employers in the US in 2000 measured \$83 billion, with the majority (62% or \$52 billion) due to lost workplace productivity (Greenberg et al., 2003). Employers spent over \$44 billion annually in lost productivity due to MDD with 81% due to poorer on-the-job performance (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003). Others estimate that employers lose 27 workdays per worker per year due to MDD; two-thirds of which is due to “presenteeism”—workers are present but are

less productive (Kessler et al., 2006). Furthermore, the cost of MDD to employers in lost work days is as great or greater than the cost of many other common medical conditions, including heart disease, diabetes, or back problems (Druss, Rosenheck, & Sledge, 2000). The personal costs from MDD include significant clinical morbidity, increased mortality from suicide, and loss of quality of life (Wang, Simon, & Kessler, 2003).

Anxiety disorders are the most common types of psychiatric disorder in the general population and affect around 270 million people worldwide (G. B. D. Disease Injury, 2016; Kessler, Berglund, et al., 2005). Anxiety disorders are characterized by disruptive fear, worry, and related behavioral disturbances such as avoidance or physical sensations of hyperarousal (Mathers et al., 2008). Approximately 29% of people have an anxiety disorder in their lifetime and 18% have experienced an anxiety disorder in the past year (Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005). Anxiety disorders are associated with reduced productivity and increased psychiatric and non-psychiatric medical care, absenteeism, and risk of suicide (Lépine, 2002). The monetary cost of anxiety disorders is also substantial; in the US, the annual direct cost of anxiety disorders in the 1990s has been estimated to be \$42.3 billion (P. Greenberg et al., 1999).

Women have a higher prevalence of anxiety disorders than men (McLean, Asnaani, Litz, & Hofmann, 2011) and the onset for most anxiety disorders is commonly in adolescence or young adulthood. However, the incidence of anxiety disorders remains substantial in midlife, and new cases continue to arise into later life, especially in the case of generalized anxiety disorder (Kessler, Berglund, et al., 2005). Although numerous pharmacologic and non-pharmacologic therapies are available, remission is not always possible. Many patients have persistent symptoms despite use of first line treatments (Lanouette & Stein, 2010).

Anxiety and MDD are somewhat lower in the elderly (each occur in an estimated 5% of persons over 65 (CDC, 2015, 2016) but much higher percentages of older people suffer from clinically relevant depressive (10-30%) or anxiety (~20%) symptoms that do not meet full diagnostic criteria (Druss et al., 2000; Kessler et al., 2006; Lépine, 2002; Wang et al., 2003). These symptoms are associated with excess morbidity and significant functional impairment (American Psychiatric & American Psychiatric Association, 2013; CDC, 2014, 2015; P. Greenberg et al., 1999; Mathers et al., 2008) and greater risk of subsequent depression and anxiety clinical diagnoses (Hasin, Fenton, & Weissman, 2011; Kessler et al., 2009; Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005; Whiteford et al., 2013). Furthermore, depression and anxiety increase the risk for suicide and all-cause mortality; substantially detrimentally affect physical, mental, and social functioning; are associated with worse cognitive functioning; and lead to greater healthcare service use and costs (Blazer et al., 1994; Druss et al., 2000; Greenberg et al., 2003; Kessler et al., 2006; Stewart et al., 2003; Wang et al., 2003).

Metal Neurotoxics

Trace metals such as lead and mercury are well known neurotoxics that are widely found in air, soil, dust and water. Mercury, particularly organic mercury, is a neurotoxicant and can cause birth defects (Casarett, Doull, & Klaassen, 2008). Arsenic, particularly inorganic arsenic, causes neuropathy and is associated with hearing loss and decreased intelligence quotient (IQ) in children (ATSDR, 2007). Cadmium is modestly associated with decreased attention, psychomotor speed, and memory (ATSDR, 2012a). Manganese, although an essential nutrient, can have adverse effects on the nervous system. Chronic exposures have been linked to loss of coordination and increase in anxiety, insomnia, and forgetfulness (ATSDR, 2012b).

Research into the neurotoxic effects of such metals has focused largely on the negative effect on the central nervous system with regard to cognitive function, such as reaction time, memory and motor function (Camerino, Cassitto, & Gilioli, 1993; Shih, Hu, Weisskopf, & Schwartz, 2007). Studies have investigated the association between exposures to these metals at low levels and neuropsychological function in adults in addition to occupational studies suggesting an association may exist (Baker et al., 1984; Baker et al., 1985; Barbosa, Tanus-Santos, Gerlach, & Parsons, 2005; Lilis et al., 1977; Maizlish, Parra, & Feo, 1995; Parkinson, Ryan, Bromet, & Connell, 1986; Schwartz et al., 2005). Other studies found associations between low-level exposure to lead and psychological disorders and symptoms among adults (Bouchard et al., 2009; Eum et al., 2012; Rhodes, Spiro, Aro, & Hu, 2003). Other metals such as arsenic and cadmium have been associated with neurological and renal damage, respectively (ATSDR, 2004). A study found neurological damage from binary mixtures and observed a greater than additive effect of lead on arsenic (low-moderate confidence), arsenic on lead (moderate confidence), cadmium on lead (low confidence), and chromium(VI) on arsenic (low confidence), and less than additive for the effect of arsenic on chromium(VI) (ATSDR, 2004). Animal studies of exposures to metals have shown different binary metal mixtures appear to collect in different organs and cause different tissue damage (Elsenhans, Schmolke, Kolb, Stokes, & Forth, 1987) as well as affect different levels of neurotransmitter in different regions of the brain (Mejía, Díaz-Barriga, Calderón, Ríos, & Jiménez-Capdeville, 1997).

There is good evidence that lead affects biological systems that are relevant for psychiatric outcomes. Lead is a known neurotoxicant and influences processes implicated in depression and anxiety, such as monoaminergic signaling and the hypothalamic-pituitary-adrenal (HPA) axis (Bressler, Kim, Chakraborti, & Goldstein, 1999; Cory-Slechta et al., 2008; Kala &

Jadhav, 1995; Lasley, Greenland, Minnema, & Michaelson, 1984; Virgolini, Chen, Weston, Bauter, & Cory-Slechta, 2005). Lead influences nearly every neurotransmitter system in the brain including glutamatergic, dopaminergic, and cholinergic systems. Lead exposure stimulates protein kinase C, which can result in changes to blood-brain barrier and inhibition of cholinergic modulation of glutamate-related synaptic transmissions (Casarett et al., 2008). Furthermore, exposure to lead is a risk factor for many cardiovascular endpoints, which are associated with adverse psychological outcomes (Alexopoulos et al., 1997; Eum et al., 2011; Navas-Acien, Guallar, Silbergeld, & Rothenberg, 2007; Vink, Aartsen, & Schoevers, 2008; Weisskopf et al., 2009).

Toenails

The main reason for utilizing toenails in this study is that toenails are easily obtained, minimally invasive, and more easily stored than urine and blood making them potentially advantageous in many studies. In addition, toenails from people wearing shoes are likely to have less external contamination, or have less contamination from hygiene products such as selenium containing shampoos, than hair (Garland et al., 1993b; LeBlanc, Dumas, & Lefebvre, 1999). Toenails are more isolated than blood and urine from other metabolic activities in the body, and represent longer exposure periods than blood or urine (Barbosa et al., 2005; Garland et al., 1993b; Hopps, 1977; Willett, 1987).

Toenails grow at a rate of roughly 1.00-1.50mm/month (0.05 mm/day), so the direct exposure window estimated from a sample of clippings from all ten toenails covers several weeks to months about 6-12 months prior to clipping (Grashow et al., 2014; Laohaudomchok et al., 2011; Levit & Scher, 2001; Longnecker et al., 1996; Sakamoto et al., 2015; Melissa J.

Slotnick & Jerome O. Nriagu, 2006; Steven Morris, Stampfer, & Willett, 1983; Weller, Hunter, & Mann, 2014). Toenail metal concentrations measured at one time point have been used to evaluate the relationship between exposures to metals and many health outcomes including blood pressure (Irina Mordukhovich et al., 2012) and cancer (Hunter et al., 1990; Maasland, Schouten, Kremer, & van den Brandt, 2016).

Some epidemiological studies utilizing toenails include selenium in toenails from the general population reflecting selenium intake from dietary supplements and meals (Hunter et al., 1990; Longnecker et al., 1996; Ovaskainen et al., 1993; Swanson et al., 1990). In addition, general population studies evaluating arsenic in toenails show positive correlation with drinking water and soil arsenic concentrations (Hinwood et al., 2003; Margaret R. Karagas et al., 2001; Karagas et al., 2000). Studies among welders found toenail metals were positively correlated with exposures to welding fumes up to 6-12 months prior to clipping (Grashow et al., 2014; Laohaudomchok et al., 2011).

Methods

Study Population

The NAS is an ongoing longitudinal study of men in the greater Boston area with no known chronic medical conditions at the time of recruitment (Bell, Rose, & Damon, 1972). These conditions included heart disease, cancer, recurrent asthma, sinusitis, bronchitis, diabetes, gout, peptic ulcer, and systolic blood pressure greater than 140 millimeters of mercury (mm Hg) or diastolic pressure greater than 90 mm Hg. Since its inception with 2280 healthy men in 1961, participants are evaluated every 3-5 years. The overall attrition rate has been less than 1% annually, and response rate to mailed questionnaires that supplement onsite examinations has

been greater than 80%. Between 1992 and 2014, 825 of 1286 still active NAS participants provided toenail clippings at least one of several different study visits. All participants gave written informed consent. The Institutional Review Boards of the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and the Boston VA Medical Center approved this research.

Metals Analysis

We analyzed lead (Pb), arsenic (As), cadmium (Cd), manganese (Mn), and mercury (Hg) in the toenails. Toenail clippings from all ten toes were collected and pre-cleaned by sonicating for 15 minutes in approximately 10 milliliters (mL) of 1% Triton X-100 solution to remove extraneous contaminants. The samples were rinsed with distilled deionized water and dried at 60°C for 24 hours in a drying oven. Samples were weighed. If the weight of the whole toenail sample was greater than 0.1 grams (g), a portion of the toenail sample was used for mercury analysis. The rest of the sample was dissolved in HNO₃ acid for 48 hours and diluted to 5 mL with deionized water. Samples that weighed less than 0.1 g were acid-digested for Pb, As, Cd, and Mn only.

Lead, arsenic, cadmium, and manganese. Samples dissolved in HNO₃ acid were analyzed by inductive coupled plasma-mass spectrometry (ICP-MS). Analysis of the most recent 300 toenail samples (years range 1998 to 2014) utilized the Agilent 8800 ICP-MS Triple Quad (Agilent technologies, Inc., Delaware, USA). The other samples were analyzed using Perkin Elmer Elan DRC II ICP-MS (PerkinElmer, Inc., Connecticut, USA). We used exactly the same sample

preparation method for all samples presented in this paper. Comparability and accuracy of both methods were validated using certified reference materials. We found no adjustments were needed for between instrument variability.

For Pb, Cd, Mn, and As analysis, quality control (QC) measures included analysis of the National Institute of Standard and Technology Standard Reference Material 1643e (trace elements in water, Gaithersburg, MD) and a 1.0 nanogram per milliliter (ng/mL) mixed element standard solution of Pb, Cd, Mn and As solution as initial calibration verification standard, continuous calibration standards, and procedural blank. Certified reference material GBW 07601 (human hair; Institute of Geophysical and Geochemical Exploration, Langfang, Hebei Province, People's Republic of China) was used as the QC sample. We used a large preparation of GBW 07601 (2.0 grams per liter (g/L)) and a preparation of pooled toenail sample to monitor inter-day and intra-day variations. Certified reference material NIES CRM-13 (Analysis of National Institute for Environmental Studies certified reference material 13 (human hair; Ibaraki, Japan)) was used as the QC standard.

Recovery of the QC from the in-house preparation of the solution of pooled toenail sample digested in acid was 90%-110% with 95% precision for the four metals. Recovery of NIES CRM-13 was 90-110% for Pb, As, and Cd. Recovery of GBW 07601 was 99% for Mn. The between-assay coefficient of variation between days was 3% for the four metals.

Limit of detection (LOD) for the QC blanks with analytical solution for the four metals (micrograms per milliliter ($\mu\text{g/mL}$)): Pb 0.00001, As 0.00001, Cd 0.000001, Mn 0.00002. The LOD for the sample itself varied according to sample weight, and equaled the LOD for the analytical solution multiplied by the dilution factor. Since sample weight varied from 0.009 g to

0.760 g, the LOD ranged from 0.000001 µg/g (Cd) to 0.00253 µg/g (Mn). The average LOD among the four metals was 0.000126 µg/g.

Mercury. Mercury analysis occurred only if there was sufficient sample left after analyzing for the other metals. Mercury assays utilized the Direct Mercury Analyzer 80 (Milestone Inc., Monroe, CT, USA), and samples were analyzed using a matrix-matched calibration curve derived from different weights of certified reference material GBW 07601. Recovery of the NIES CRM-13 was 99%. Quality control included daily calibration verification of high and low ends of the calibration curve, procedural blank, and analysis of NIES CRM-13. Mercury recovery was 90-110%, with >90% precision. The average (lowest, highest) LOD for Hg was 0.00607 µg/g (0.00171, 0.0355 µg/g). Similar to the previous metals, the range of LOD was due to different sample weights.

Blood lead. Blood samples collected from 1992 to 2008 were analyzed for lead. Whole blood samples were collected in lead-free tubes containing edentate calcium disodium (EDTA) and analyzed at ESA Laboratories, Inc., Chelmsford, Massachusetts. After digestion with nitric acid and centrifuge, the laboratory analyzed the supernatant with Zeeman background-corrected graphite furnace atomic absorption, which was calibrated with national Bureau of Standards blood lead standards materials. All glassware were soaked overnight in 20% nitric acid and rinsed with distilled water to prevent lead contamination.

Diet. Dietary data, including supplement use, were obtained via a semi-quantitative food frequency questionnaire administered at each study visit (Willett et al., 1985). For example,

consumption of whole grains (combining wheat, rice, oats, and corn) was grams consumed per day at time of survey.

Outcomes

Psychiatric outcomes were measured via the Brief Symptom Index (BSI); a validated 53-item questionnaire in which respondents rank each item (e.g. “your feelings being easily hurt”) on a 5-point scale ranging from 0 (not at all) to 4 (extremely) (Derogatis & Melisaratos, 1983; Long, Haring, Brekke, Test, & Greenberg, 2007; Meachen, Hanks, Millis, & Rapport, 2008). The BSI is a shortened version of the Symptom Checklist List 90-R (SCL-90-R), and Derogatis (1993) reports correlations between the BSI and SCL-R-90 range from 0.92 to 0.99. BSI asks participants about symptoms experienced in the last 30 days. Selective items (e.g., depression) comprise each of 9 primary symptom dimensions. The BSI has reported 0.71 (psychoticism) to 0.85 (depression) internal consistency (Cronbach’s alpha) for all 9 items (Derogatis & Melisaratos, 1983) and has been used in many studies. Internal consistency for anxiety was 0.81 and for GSI was 0.97 (Derogatis, 1993; Derogatis & Melisaratos, 1983). Correlation of the BSI with SCL-90-R for depression and anxiety symptoms were 0.95 for both when used among 565 psychiatric out-patients (Derogatis & Melisaratos, 1983). The BSI showed good internal consistency reliability in cross-cultural groups and is a relatively reliable measurement of psychological distress (Aroian, Patsdaughter, Levin, & Gianan, 1995). Test-retest reliability for the nine symptom dimensions ranged from 0.68 (Somatization) to 0.91 (Phobic Anxiety), and 0.87 (PSDI) to 0.90 (GSI) for the three Global Indices (Derogatis, 1993).

Dimension scores were calculated by summing the value of the items included in that dimension and dividing by the number of items endorsed in that dimension. For example, 6 of

the items (survey questions) comprise depression, so the results of those 6 questions are added and divided by 6 to obtain the BSI score for depression.

We evaluated depression and anxiety symptom dimensions as well as three global indices for general psychopathologic status: Global Severity Index (GSI) measuring severity of psychopathologic status, Positive Symptom Total (PST), and Positive Symptom Distress Index (PSDI). We also evaluated the combination of depression and anxiety symptoms. These measures have been previously described (Derogatis, 1993; Rhodes et al., 2003; Stewart et al., 2010).

Briefly, the GSI is calculated by adding the sums for the nine symptom dimensions plus the four additional items not included in any of the dimension scores, and dividing by the total number of items to which the individual responded. If no items were skipped, the GSI will be the mean for all 53 items. The PST was the total count of all the items with non-zero responses, and so is the number of symptoms the respondent reports experiencing. The PSDI is calculated by summing the values of the items receiving non-zero responses divided by the PST. This index provides information about the average level of distress the respondent experiences. Raw scores were converted to T scores using the tables provided in the BSI manual, and the GSI is described as the most sensitive single indicator of distress (Derogatis, 1993).

We chose *a priori* to apply the corresponding mean values of the outcome scores that represent a T-score of ≥ 60 (from the standard population table for non-institutionalized adult males from the BSI Manual, and were comparable to one standard deviation above the mean of outcome scores) as the cut-off to define a binary high symptom case for each of the dichotomous outcomes, which is a slightly more inclusive cut-off used to consider further follow-up in clinical settings (Stewart et al., 2010).

Outcomes in this study included the following continuous measures: sum of all 53 BSI questions, depression dimension score, anxiety dimension score, GSI, PST, and PSDI scores. In order to estimate an outcome similar to a clinical finding, dichotomous outcome measures based on the above mentioned criteria for T-score cut-off included the following: high GSI (mean GSI ≥ 0.6), high PST (mean PST ≥ 22), high PSDI (mean PSDI ≥ 1.55), high depression (mean depression dimension score ≥ 0.6), and high anxiety (mean anxiety dimension score ≥ 0.6). We also created a combined depression and anxiety binary outcome, which was defined by both depression and anxiety dimension scores ≥ 0.6 .

Data Analysis

Because toenail metal concentrations were right skewed we log(10)-transformed them for analyses. For the small number of samples that had negative values for Pb (n=1), As (n=2), and Mn (n=1) levels (possible when actual concentrations are near 0), we substituted the LOD for that measurement divided by the square root of two. There were no negative toenail Hg measurements. We took the same substitution approach with Cd despite a larger number of negative Cd values (106, 5.8%). One of these negative Cd measurements did not have an LOD reported so we substituted with the lowest positive toenail Cd measurement in the data set. Toenail Cd levels had many more negative values than other metals due to many more very low Cd levels measured in the toenails.

We considered alternate ways to handle the negative Cd concentrations such as adding the absolute value of the most negative measurement to all toenail Cd measurements (Kurtosis=86.824) or adding the absolute value of the most negative measurement plus one (Kurtosis=112.665). Both of these methods resulted in log toenail Cd distributions that were less-

normal compared to substituting with the log values of the LOD divided by the square root of 2 (Kurtosis=2.880). Other transformations such as taking the square, square root, cube, cube root, and the inverse of these for toenail Cd values also resulted in inferior normal distributions.

We applied penalized splines to assess potential non-linear associations between toenail metal levels and outcomes, with the penalty estimated by using generalized cross-validation. If the association was not dramatically non-linear, we applied repeated measures linear regression models for continuous outcomes to estimate the difference in relative risk of each outcome per unit change in toenail metals. We applied repeated measures logistic regression models for dichotomous outcomes to estimate log odds change per unit increase in the log of toenail metal concentration.

We identified the optimal covariance pattern by determining best model fit with likelihood ratio tests for nested covariance pattern models and Akaike's information criterion (AIC). A hybrid structure combining an exponential and a compound symmetry structure—describing a decreasing correlation among measurements taken further apart superimposed on a baseline non-zero correlation and previously described by Fitzmaurice (2004)—provided the best overall fit for each outcome. Covariates considered in the models were: age at metal biomarker measurement (years), alcohol consumption (>2 drinks per day), smoking status (never, current, former), and education level (years).

We estimated cumulative exposure of metals from toenails by taking the cumulative average of toenails per subject up to the most recent study visit with toenail and BSI data. We applied linear regression models for continuous outcomes and logistic regression for dichotomous outcomes. Models with the cumulative averages of toenail metals also had the

covariates at the most recent study visit with BSI data. Linear and logistic regression models were weighted by number of toenails per subject.

As a comparison with toenail Pb measures, we also conducted analyses with patella, tibia, and blood Pb as exposure variables. We utilized the same covariates as in the primary analyses. For the bone Pb analyses we used the first available bone Pb measurement and either the first or most recent visit with toenail and BSI data. For the blood Pb analyses we utilized the same mixed models and applied the cumulative average of blood Pb up to the most recent study visit with toenail and BSI data to keep consistent with the same BSI data used in the cumulative average toenail metals analyses. All bone and blood Pb measurements were before the most recent visit with toenail and BSI data.

We applied Student's t-test for comparing means and Chi-square or Fisher's exact tests (samples size ≤ 5) for comparing categories. We utilized SAS software (Version 9.4, SAS Institute Inc., Cary, North Carolina) and R (R.Core.Team, 2017) to perform analyses. The level of statistical significance was $p < 0.05$.

Results

Characteristics of subjects

At the first visit, men with donated toenail clippings (participants) were on average 70 years old, almost all white, and just under 4 out of 5 were overweight or obese (Table 4.1). Nearly all participants were never or former smokers, with 95% of smokers having quit by 1990. About 9 out of 10 of those who reported consumption of canned tuna did so up to once per week. Clinical visits were fewest during the winter.

Comparing participants with toenail data (n= 825) to those without (n= 461) found those with toenail data smoked less, had more years of education, a more recent first visit, reported more manganese supplement use, and had a lower PST. Subjects with toenail data also reported a higher prevalence of drinking two or more drinks of alcohol per day, consuming more whole grains, and having a lower prevalence of meeting the threshold of high depression symptoms, high anxiety symptoms, and GSI.

Table 4.1. Characteristics of non-participants and participants at their first visit with donated toenails, 1992 to 2014.

Characteristic	n	Nonparticipants			n	Participants		p-Value
		Mean	S.D.			Mean	S.D.	
Age (years)	461	69.3	± 8.2		825	70.7	± 7.0	<0.01
Smoking (pack-years)	458	26.1	± 27.8		824	21.6	± 26.5	<0.01
Education (years)	329	14.0	± 2.7		803	14.9	± 3.0	<0.01
Alcohol intake (g/day)	353	11.2	± 17.4		112	11.7	± 15.9	0.30
Usually drink ≥2 drinks/day	461	19.7	± 39.9		825	21.2	± 40.9	0.53
Year of visit	461	1993.6	± 2.1		825	1998.6	± 3.9	<0.01
Supplemental Manganese (mg)	306	4.0	± 2.3		732	4.5	± 2.4	<0.01
Whole grain amount in diet (g)	4	22.8	± 18.9		65	25.0	± 16.2	0.78
	n	%			n	%		p-Value
BMI (kg/m ²)								0.37
<25	113	24.5			174	21.1		
25-29	236	51.2			439	53.2		
≥30	112	24.3			212	25.7		
Smoking Status								<0.01
Never Smoker	127	27.6			255	31.0		
Former Smoker	284	61.6			530	64.4		
Current Smoker	50	10.9			38	4.6		
Race/ethnicity								
Non-Hispanic white	453	98.5			806	97.9		0.92
Non-Hispanic black	6	1.3			12	1.5		
Hispanic white	1	0.2			4	0.5		
Hispanic black	0	0.0			1	0.1		
Season of first clinical visit								0.01
Spring	139	30.2			209	25.4		
Summer	137	29.7			233	28.3		
Fall	98	21.3			242	29.4		
Winter	87	18.9			139	16.9		
Canned tuna consumption								0.34
never,<1/month	119	27.6			182	23.7		
1-3/month	142	32.9			277	36.1		
1/week	125	28.9			215	28.0		
2-4/week	38	8.8			85	11.1		
5-6/week	4	0.9			5	0.7		
1/day	3	0.7			3	0.4		
2-3/day	1	0.2			0	0.0		
Depression (≥0.6)	46	14.9			91	11.4		0.13
Anxiety (≥0.6)	44	14.2			85	10.6		0.09
Combined (Depression (≥0.6), Anxiety (≥0.6))	26	8.4			54	6.7		0.36
GSI (≥0.6)	42	13.6			90	11.2		0.30
PST (≥22)	54	20.2			105	14.8		0.04
PSDI (≥1.55)	33	12.4			84	11.8		0.83

Characteristics of exposures

Toenail metals among this cohort were described earlier (Chapter 3). Briefly, individual participants provided toenail clippings on up to six separate study visits. Each subject on average had about two samples analyzed for each toenail metal (Supplemental, Table S2.1). The distribution of years between toenail samples had an average number of years between samples per subject that ranged from 4.73 (SD=2.44) years for Mn to 5.35 (SD=2.69) for Hg. The average years between the first and last sample per subject ranged from 8.21 (SD=4.15) for Hg to 10.08 (SD=4.82) for Pb. Overall, around 46% of measurements were taken roughly three years apart and about 18% taken roughly 6.5 years apart corresponding to typical intervals between NAS study visits. The distribution of years between measurements among the five toenail metals were similar except for Hg, which showed the frequency of years between measurements to occur less around 3 and more around 6.5 years compared with the other metals.

The correlations between the toenail metal concentrations at first visit with donated toenail clippings are shown in Supplemental Table S2.2 along with correlations with blood Pb. Median concentrations of toenail As and Cd remained relatively stable over donated toenail samples while concentrations of Pb, Mn, and Hg tended to decrease more (Supplemental Table S2.3). However, the number of people with toenail samples decreased with each successive donated sample so these trends cannot be interpreted as within individual trends. At the first sample, toenail Pb had the widest range of concentration levels (min 0.007, max 32.52 µg/g) and toenail As had the narrowest range (min 0.0004, max 1.70 µg/g). Toenail Pb had the highest interquartile range (IQR) of concentration levels while toenail Cd had the lowest (Supplemental Table S2.3).

Over 95% of toenail metal measurements came from former or never smokers. (Chapter 3, Supplemental Table S1.4 to S1.8). By 1991, over 95% of NAS participants who smoked had quit, leaving 30 to 35 current smokers (depending on metal) with at least one visit with donated toenails (toenail collection began in 1992). Among these, only 18 had more than one visit. Therefore, we did not describe correlations of subjects' toenail metals stratified by smoking status, but presented median levels of metals by order of donated toenail samples (Supplemental Table S2.4). At the first donated sample, former smokers had slightly higher median metal levels than never smokers, except for Cd, which was the same. At first donated sample, current smokers had the lowest median metal levels for Pb, Cd, and Hg but had the highest median level for Mn.

Over 92% of blood Pb, came from former or never smokers (Supplemental Table S2.4). At first donated toenail sample with blood Pb data, never and current smokers had the same median blood Pb levels. Current smokers had a higher median blood Pb than never and former smokers.

Characteristics of outcomes

BSI data were collected from 1992 to 2014 with 3410 visits measuring BSI. There were 1862 visits that had both toenail and BSI data among 806 subjects (average of 2.31 visits per subject). The average years between visits with both types of data was 3.23 (SD= 0.97 years).

We used linear mixed models to assess correlation between repeated continuous outcome measurements over time. As described above, we applied a hybrid covariance structure to repeated measures of the outcomes. Correlation of repeated measurements of the outcome three

years apart ranged from 0.77 (PSDI) to 0.85 (Total BSI) and 0.69 (PSDI) to 0.83 (Total BSI) at five years apart (95% of visits were ≤ 4.5 years apart). These correlations slightly decreased over increasing time between measurements (Table 4.2, Figure 4.1).

Table 4.2. Correlation of repeated measurements of BSI total or depression by time between measurements, among visits with both toenail and BSI data, hybrid covariance structure.

	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs
BSI Total	0.91	0.89	0.87	0.85	0.83	0.81	0.79
Depression	0.92	0.88	0.84	0.81	0.77	0.74	0.71
PST	0.92	0.89	0.87	0.84	0.82	0.79	0.77
GSI	0.92	0.89	0.86	0.84	0.81	0.79	0.77
PSDI	0.85	0.81	0.77	0.73	0.69	0.66	0.63
Anxiety	0.88	0.85	0.83	0.80	0.78	0.75	0.73

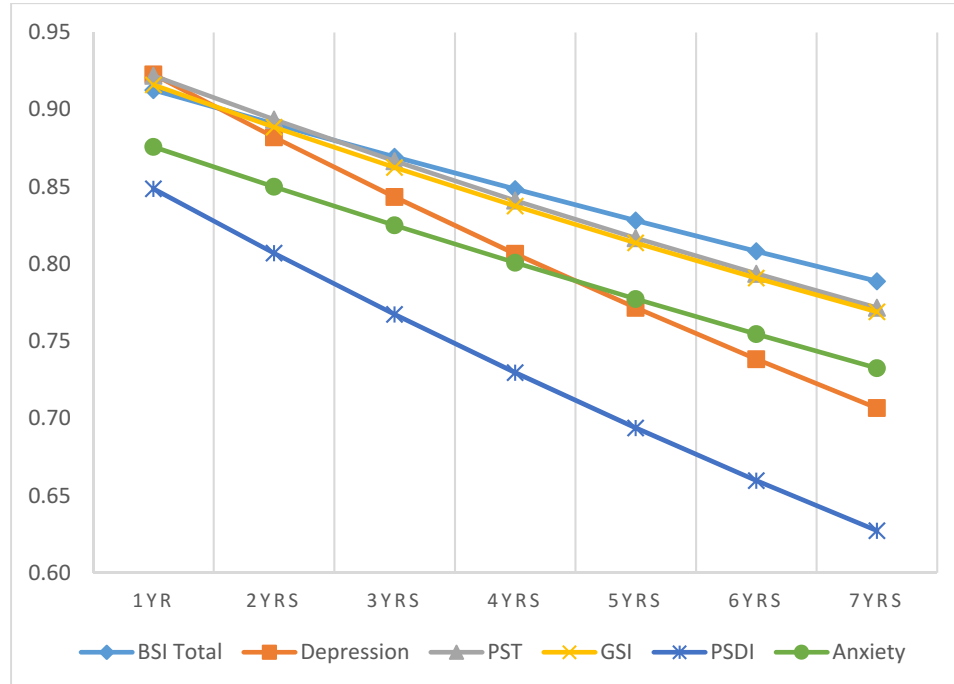


Figure 3.1. Correlation of repeated measurements of BSI total or depression by time (years) between measurements, among visits with both toenail and BSI data, hybrid covariance structure.

Association of toenail metals and outcomes

The associations between toenail metal levels and outcomes were not dramatically non-linear when analyzed with penalized splines.

Mixed models. After adjusting for covariates and multiple toenails per subject, toenail Mn showed a trend of increasing risk of higher anxiety symptoms, and toenail Hg displayed a decreasing risk of higher total symptoms (Table 4.3). Adjusted logistic mixed models had weaker associations between toenail metals and having high depression and anxiety symptoms (Supplemental Table S2.5).

Cumulative average of toenail metals. After adjusting for covariates, a significant positive association existed between both cumulative average toenail Pb and Cd with increasing risk of total symptoms, PST, and GSI scores (Table 4.4). We found a significant association between toenail Cd and more symptoms of depression and anxiety. Toenail Pb trended toward increased risk of more depression symptoms. Increased cumulative average toenail Mn levels were associated with increased GSI scores and trended toward higher total, depression, and anxiety symptoms. Increase in cumulative average toenail Hg were associated with a decrease in PST and anxiety symptoms as well as trended toward having less total symptoms and lower GSI scores. No association was found between cumulative toenail As and increased total symptoms or dimension scores. Other cumulative toenail metals in logistic regression models had similar results except for toenail As having positive associations with high GSI, PST, and PSDI (Supplemental Table S2.6).

Table 4.3. Adjusted¹ estimates of toenail metal or blood Pb alone. Separate linear mixed models for each metal exposure.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg			Log Blood Pb		
# of Subjects ²	735			759			735			723			662			1121		
# of Visits Range ³	1457-1625			1514-1683			1454-1622			1419-1577			1031-1158			2333-2648		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
BSI Total (log)	-0.005	0.019	0.798	-0.014	0.028	0.621	-0.014	0.015	0.374	0.009	0.018	0.636	-0.059	0.033	0.076	-0.020	0.034	0.553
Depression (log)	-0.001	0.004	0.842	-0.001	0.007	0.920	-0.003	0.004	0.445	0.003	0.004	0.531	-0.004	0.008	0.625	-0.002	0.008	0.838
PST (log)	0.004	0.016	0.806	0.001	0.023	0.973	0.001	0.012	0.905	0.018	0.015	0.240	-0.037	0.027	0.169	-0.013	0.027	0.624
GSI (log)	-0.002	0.003	0.625	-0.002	0.005	0.620	-0.002	0.003	0.406	0.003	0.003	0.272	-0.009	0.006	0.139	-0.004	0.006	0.512
PSDI (log)	-0.002	0.003	0.459	-0.003	0.004	0.546	0.001	0.002	0.731	0.002	0.003	0.513	0.000	0.005	0.966	-0.004	0.004	0.355
Anxiety (log)	0.002	0.004	0.714	0.002	0.006	0.729	0.002	0.003	0.557	0.007	0.004	0.080	-0.009	0.007	0.243	0.000	0.007	0.959

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to other studies having interest in specific metals and toenail Hg and blood Pb analysis utilizing different laboratory methods

³Range due to different number of visits having both exposure and outcome data

SE = Standard Error

p = p-value

Table 4.4. Adjusted¹ estimates of cumulative average toenail metal or blood Pb. Separate linear regression models for each exposure. Outcomes are from last visit with exposure and outcome data.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg			Log Blood Pb		
# of Subjects ²	626-686			647-710			626-686			615-674			565-619			950-1058		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
BSI Total (log)	0.109	0.042	0.011	0.044	0.076	0.564	0.126	0.043	0.004	0.093	0.052	0.074	-0.094	0.054	0.082	-0.015	0.069	0.826
Depression (log)	0.015	0.009	0.110	0.013	0.017	0.423	0.020	0.010	0.036	0.022	0.011	0.057	-0.010	0.012	0.415	-0.007	0.016	0.656
PST (log)	0.099	0.034	0.004	0.056	0.061	0.354	0.111	0.035	0.002	0.069	0.041	0.091	-0.093	0.042	0.028	0.028	0.056	0.619
GSI (log)	0.019	0.008	0.018	0.015	0.014	0.294	0.024	0.008	0.004	0.022	0.010	0.027	-0.017	0.010	0.096	0.005	0.013	0.700
PSDI (log)	0.003	0.005	0.556	-0.011	0.009	0.244	0.004	0.005	0.473	0.002	0.006	0.758	0.003	0.006	0.657	0.007	0.009	0.453
Anxiety (log)	0.014	0.009	0.130	0.005	0.016	0.782	0.023	0.009	0.017	0.021	0.011	0.063	-0.020	0.012	0.085	0.004	0.015	0.794

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression

SE = Standard Error

p = p-value

Secondary analysis of patella, tibia, and blood Pb

Patella and tibia regression models. After adjusting for covariates, we found an increase in patella Pb from the first visit with bone Pb data was border-line significantly associated with having high depression and anxiety (combined) among first visit with BSI data (Table 4.5). In addition, a trend toward having high anxiety, PSDI, and GSI scores was seen with higher patella Pb levels. An increase in tibia Pb was associated with having high combined score as well as a trend in having high PSDI and depression. Linear regression models revealed attenuated associations except for PSDI (Supplemental Table S2.7).

Table 4.5. Estimates of first bone lead and first visit with BSI. Adjusted¹ logistic regression models.

	Patella Pb, Adjusted			Tibia Pb, Adjusted		
# of Subjects ²	450-531			450-530		
Outcome	beta	SE	p-value	beta	SE	p-value
GSI high	0.011	0.008	0.184	0.015	0.013	0.261
PST high	0.005	0.008	0.547	0.011	0.012	0.365
PSDI high	0.014	0.009	0.123	0.023	0.013	0.081
Depression high	0.007	0.009	0.419	0.026	0.014	0.059
Anxiety high	0.012	0.008	0.135	0.010	0.013	0.439
Combined high	0.020	0.010	0.051	0.037	0.017	0.027

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no).

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.
SE = Standard Error

Blood Pb mixed and cumulative regression models. No associations were found between blood Pb and any outcomes among linear mixed models and cumulative average linear regression models (Table 4.3 & 3.4).

Additional analyses. Crude and exploratory analyses are given in Supplementary Tables S2.8 to S2.21.

Discussion

We found significant associations between cumulative average toenail metals levels and psychiatric outcomes measured via the BSI, a shortened version of the Symptom Checklist List 90-R (SCL-90-R), among NAS participants—a cohort of elderly men with low levels of toenail metals. Cumulative average toenail Cd levels were associated with the largest increase in depression and anxiety dimension scores followed by toenail Mn and Pb. In addition, cumulative average toenail Cd was associated with the largest increase in total psychiatric symptoms followed by toenail Pb. Cumulative average toenail Cd also was associated with the largest increase in GSI, an indicator of severity of psychopathological status and the most sensitive single indicator of distress (Derogatis, 1993) followed by toenail Mn. Interestingly, cumulative average toenail Hg levels were associated with a decrease in PST and anxiety, and showed a trend in decreasing total psychiatric symptoms and GSI. We found no associations between toenail metals and any outcomes after applying multivariate mixed models to account for multiple toenails per subject.

This is the first study to evaluate the association between metal levels from multiple toenail samples per participant and depression and anxiety, among a general population of elderly men residing in Boston. Past literature have found negative associations between blood Hg and psychiatric outcomes, particularly depression. Two studies utilizing the National Health and Nutrition Examination Survey (NHANES) data for adults over 18 years of age found negative associations between blood Hg with depression that one study suggested could be related to protection from fish consumption (Berk et al., 2014). Although the other study attempted to control for fish consumption and fish oil intake (Ng, Mossey, & Lee, 2013). In addition, urinary manganese and tin, but not arsenic, were found to be associated with depression (Shiue, 2015).

A few studies have explored lower-level environmental exposure to lead in association with psychological disturbances (Bouchard et al., 2009), which describe an association between patella bone lead and blood lead with depression and phobic anxiety in men (Rajan et al., 2007; Rhodes et al., 2003), and tibia bone lead and depressive symptoms among older women (Eum et al., 2012). Although these studies evaluate low-level environmental lead exposure, they do not evaluate other metals or utilization of toenail samples as a biomarker of lead.

Regression modeling of cumulative average toenail metals resulted in more associations between toenail metals and outcomes than linear mixed models. We believe this could be due to cumulative average capturing a chronic exposure to metals. This would suggest psychiatric outcomes from our study were not as associated with acute exposures to toenail metals as modeled in mixed models. Another possible reason for finding no association among mixed regression models is metals deposited in toenail matrix is not an accurate reflection of blood metal levels at the same time when toenails were collected.

The levels of toenail Pb in our study were similar to adults in the U.S. general population from another study (Slotnick, Meliker, AvRuskin, Ghosh, & Nriagu, 2007). In addition to the description of the health effects of Pb in the introduction, studies have shown blood Pb increases the release of dopamine in the brain, but inhibits release of neurotransmitters from potassium pathways by mimicking or inhibiting calcium mediated pathways (Minnema, Greenland, & Michaelson, 1986; Minnema, Michaelson, & Cooper, 1988). One study on rats chronically exposed to Pb found a decrease of dopamine and serotonin activity in the rat brain, particularly the nucleus accumbens (Kala & Jadhav, 1995). As mentioned by Rhodes et al. (2003), chronic exposure to Pb could play a significant role in influencing mood.

The levels of toenail Hg in our study were similar to those found in other studies on the general population (Garland et al., 1993a; Rees, Sturup, Chen, Folt, & Karagas, 2007). However, a study on U.S. health professionals reported higher toenail Hg levels than our study (Joshi et al., 2003). Other studies have shown toenail Hg to be a valid biomarker of long-term exposure to Hg (Garland et al., 1993a; Joshi et al., 2003; MacIntosh et al., 1997; Rees et al., 2007).

Increased cumulative average toenail Hg showed a trend in decreasing anxiety dimension scores, GSI, and total symptoms, as well as significantly decreasing PST. We believe this could be due to uncontrolled confounding from fish consumption being a source of Hg and being good for overall brain health (e.g., nutrients such as omega-3 fatty acids) and decreasing psychiatric symptoms (Appleton et al., 2007; Barberger-Gateau et al., 2005; Bountziouka et al., 2009; Smith et al., 2014; Tanskanen et al., 2001). As mentioned earlier, studies have found a negative association with blood Hg and depression even after attempts to adjust for fish consumption (Berk et al., 2014; Ng et al., 2013). That said, a study of Australians found no association with fish consumption and depression among young adult men (Smith et al., 2014). However, a study

of those from Greek islands and Cyprus found a negative association for elderly men and women (Bountziouka et al., 2009). A limitation of our study was significant missing data for total fish consumption since there were many other sources of fish consumption that we could not account for beyond canned tuna.

Cumulative toenail Mn had a relationship with GSI, anxiety, and depression. The levels of toenail Mn in our study population were much lower than the welders and slightly lower than another study of U.S. general population living in a highly industrialized area (Slotnick et al., 2005). Bowler, Mergler, Sassine, Larribe, and Hudnell (1999) found associations between blood Mn levels and anxiety measured with BSI. Among men less than 50 years of age, higher blood Mn was associated with significantly lower anxiety scores, while among men 50 years and older higher blood Mn levels were associated with significantly higher anxiety scores.

As with depression, another study of the same population suggested that those at higher risk for alcohol use disorders showed a significant association between blood Mn and anxiety (Sassine, Mergler, Bowler, & Hudnell, 2002). A study measuring depression and anxiety symptoms via the Symptom Checklist-90-Revised (SCL-90-R) among residents in Ohio found significantly higher anxiety symptoms in the exposed town than the control, although the two groups had similar blood manganese levels (Rosemarie M. Bowler et al., 2012). Researchers posit these results could be due to the tight homeostatic control of blood Mn levels.

Toenail As did not have a significant relationship with any of the outcomes in our study after adjusting for covariates. Toenails are a validated biomarker of exposure to arsenic (Slotnick et al., 2007; Slotnick & J. O. Nriagu, 2006). Levels in our study were similar to other studies of the U.S. general population (Garland et al., 1993a; Karagas et al., 2001; Kwong et al., 2010; Slotnick et al., 2007; Slotnick et al., 2005; Tsuji et al., 2005). Our median levels were lower than

those found in a study of people living in Nevada (Adair, Hudgens, Schmitt, Calderon, & Thomas, 2006) and residents across the U.S. (MacIntosh et al., 1997) but were higher than another study of people residing in Iowa (Beane Freeman, Dennis, Lynch, Thorne, & Just, 2004).

Our study found significant increase in all outcome symptoms or dimension scores, except for PSDI, with an increase in cumulative toenail Cd. Studies of the elderly have shown a significant association between increasing blood Cd levels and greater risk of depression (Han, Lim, & Hong, 2016; Kim, Lee, Choi, Lee, & Hong, 2016). A study of toenail clippings of welders exposed to heavy metal fumes revealed toenails can discriminate metals and exposure windows for different metals including Cd (Grashow et al., 2014). Other studies have found an association between environmental Cd exposure and toenail Cd levels (Anwar, 2005; Mortada, Sobh, el-Defrawy, & Farahat, 2002; Vinceti et al., 2007). Our study had median toenail Cd levels lower than studies of the U.S. general population living in a heavy industrialized area (Slotnick et al., 2005).

Secondary analyses found positive associations between cumulative average bone lead and combined (high depression and high anxiety), which agrees with past studies (Rhodes et al., 2003). The similarities with this past study and the difference between the findings of our study supports the delineation of these tissues as different markers of exposure.

An important implication of this study is whether collection of toenails for metals exposures for evaluating psychiatric symptoms adds relevant information to other well studied biomarkers (e.g., blood, bone). We believe toenails do. Our study found associations between toenail metals and overall psychiatric symptoms, depression, and anxiety. Toenail collection is minimally invasive and cheaper to collect, store, and transport than blood and urine samples.

This is mainly due to toenails can be stored in paper envelopes at room temperature while blood and urine require deep freezing and sterile vessels.

Potential limitations of the study included low number of participants who completed all BSI assessments resulting in heavily unbalanced data and lack of clinical assessment for psychiatric disorder among study participants. Loss to follow-up from those who do not complete all follow-up BSI questionnaires could introduce bias if those that did not complete assessments are not similar to participants who remain in the study. For example, if those lost to follow-up had higher lead exposure and depression symptoms, then the study would underestimate the association between toenail Pb and depression.

Other limitations include potential underreporting of depression symptoms due to social stigma. However, the underreporting of outcome is more likely not to be related to exposure and therefore would bias results toward the null. Moreover, the study did not provide clinical assessment for psychiatric disorder. Although this would be ideal, and could be considered in future studies, extensive use of the BSI questionnaire assessments in research supports its reliability and validity.

Another limitation is the NAS study population does not include women. This would be something that could be considered for future research since women tend to have higher reported depression levels. Furthermore, the study population is nearly all white elderly men who were enrolled after passing the health screening, which included chronic diseases, at enrollment. This limits the generalizability to other races and ethnicities and likely underestimates the measures of associations in the study due to participants being healthier than the general population of elderly white males.

In addition, there is not clear evidence supporting toenails as a validated biomarker of exposure to Cd and Mn (Mordukhovich et al., 2012). However, our study (Chapter 3) on the characteristics of toenail metals among the same cohort over repeated toenail samples per subject found Cd and Mn to have a correlation of 0.40 to 0.45 for measurements taken four years apart (95% of participants had toenail samples taken up to 4.5 years apart).

Another limitation is this study did not set out to address mixtures and their associations with outcomes. This was due to modest positive correlation among most toenail metals (Supplemental Table S2.2).

Lastly, our study only examined depression, anxiety, a combination of the two, and the three global indices for general psychopathologic status. We did not focus on the other seven symptom dimensions of BSI in this study.

Conclusion

Our study tentatively suggests that toenails from NAS participants may be an adequate biomarker to measure the association between metals and symptoms of depression or anxiety measured via the BSI. That said, toenails are an adequate biomarker for some global indices for general psychopathologic status such as high PST and high PSDI among NAS subjects. Collection of toenail clippings are minimally invasive compared to blood and urine, and toenails are much cheaper to store and transport. In addition, compared to bone and blood Pb, toenail Pb represent a shorter and longer exposure window, respectively. The weeks to several month exposure window from toenails adds exposure information to the time-window between blood and bone measurements. We suggest that due to these reasons researchers should still consider

collecting toenails in addition to other biomarkers from NAS participants and similar populations.

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Appendix: Chapter 4 Supplemental

SD = standard deviation

beta = beta coefficient

SE = standard error

p = p-value

Table S2.1. Toenail metal measurements among NAS participants, 1992 to 2014

	People	# of samples	Mean # of samples per subject	Mean years btw. samples	S.D.	Median years btw. samples	Mean years btw. 1st and last sample	S.D.	Median years btw. 1st and last sample
Lead	790	1818	2.03	4.81	2.45	3.48	10.08	4.82	10.41
Arsenic	804	1866	2.04	4.79	2.57	3.34	9.96	4.81	10.43
Cadmium	789	1812	2.03	4.82	2.46	3.49	10.06	4.79	10.41
Manganese	766	1757	2.02	4.73	2.44	3.35	9.82	4.63	10.46
Mercury	711	1266	1.63	5.35	2.69	4.20	8.21	4.15	8.46

Table S2.2. Correlations between metal measurements at first visit with donated toenails, 1992 to 2014 (top: Spearman's rho, middle: p-value, bottom: number of participants)

	Pb	As	Cd	Mn	Hg	Blood Pb
Pb	1	0.40	0.55	0.46	-0.03	0.31
		<.0001	<.0001	<.0001	0.395	<.0001
	813	791	812	792	678	749
As		1	0.27	0.54	0.08	0.10
			<.0001	<.0001	0.045	0.0056
		815	790	791	656	751
Cd			1	0.39	0.02	0.17
				<.0001	0.653	<.0001
			812	791	678	749
Mn				1	-0.05	0.04
					0.186	0.263
				792	657	728
Hg					1	-0.03
						0.398
					678	632

Table S2.3. Number of participants and median (IQR) metal concentration by order of donated toenail sample¹, 1992 to 2014.

	1	2	3	4	5	6
Lead, n	790	490	302	170	55	11
%	100.0	62.0	38.2	21.5	7.0	1.4
Median, µg/g	0.323	0.261	0.242	0.192	0.184	0.116
IQR	0.541	0.475	0.406	0.414	0.301	0.171
Arsenic, n	804	511	304	176	58	13
%	100.0	63.6	37.8	21.9	7.2	1.6
Median, µg/g	0.071	0.077	0.075	0.071	0.069	0.054
IQR	0.063	0.060	0.052	0.060	0.051	0.019
Cadmium, n	789	490	302	169	52	10
%	100.0	62.1	38.3	21.4	6.6	1.3
Median, µg/g	0.018	0.014	0.012	0.012	0.011	0.010
IQR	0.033	0.021	0.019	0.019	0.015	0.024
Manganese, n	766	478	290	167	47	9
%	100.0	62.4	37.9	21.8	6.1	1.2
Median, µg/g	0.270	0.283	0.281	0.248	0.257	0.205
IQR	0.398	0.398	0.324	0.397	0.423	0.089
Mercury, n	711	362	145	42	5	1
%	100.0	50.9	20.4	5.9	0.7	0.1
Median, µg/g	0.252	0.192	0.161	0.155	0.156	0.165
IQR	0.339	0.252	0.191	0.123	0.068	0.000

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S2.4. Number of subjects and median blood lead levels ordered by donated toenail sample¹ and stratified by smoking status, 1992 to 2008

	1	2	3	4	5
All (n)	1256	1012	728	389	78
%	100.0	80.6	58.0	31.0	6.2
Median (ug/dL)	5.00	4.00	4.00	3.00	3.00
Never Smokers (n)	377	301	227	121	32
%	100.0	79.8	60.2	32.1	8.5
Median (ug/dL)	5.00	4.00	3.00	3.00	3.00
Former Smokers (n)	779	650	468	253	42
%	100.0	83.4	60.1	32.5	5.4
Median (ug/dL)	5.00	4.00	4.00	3.00	3.00
Current Smokers (n)	100	61	33	15	4
%	100.0	61.0	33.0	15.0	4.0
Median (ug/dL)	6.00	5.00	5.00	3.00	3.00

¹Not all visits had toenail samples. Order of samples donated (1=first, 2=second, etc.) utilized to standardize table.

Table S2.5. Adjusted¹ estimates of toenail metal with covariates. Each toenail metal with covariates in separate logistic mixed model.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg			Log Blood Pb		
# of Subjects ²	685-735			709-759			685-735			675-723			613-662			997-1058		
# of Visits Range ³	1457-1625			1514-1683			1454-1622			1419-1577			1031-1158			2333-2648		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
High GSI	0.219	0.207	0.291	0.154	0.357	0.666	0.335	0.190	0.079	0.369	0.236	0.119	-0.234	0.285	0.411	0.080	0.303	0.791
High PST	0.355	0.207	0.087	0.357	0.350	0.309	0.391	0.190	0.040	0.373	0.234	0.111	-0.089	0.280	0.751	0.192	0.289	0.507
High PSDI	0.041	0.203	0.839	-0.100	0.359	0.781	-0.104	0.196	0.598	0.076	0.233	0.746	-0.030	0.287	0.917	0.237	0.287	0.410
High Depression	0.106	0.208	0.611	0.022	0.364	0.951	0.092	0.193	0.636	0.064	0.239	0.790	-0.044	0.289	0.878	0.013	0.293	0.965
High Anxiety	0.197	0.208	0.345	-0.152	0.365	0.678	0.170	0.194	0.383	0.249	0.239	0.298	-0.262	0.294	0.375	0.272	0.305	0.373
Combined	0.156	0.251	0.535	-0.169	0.448	0.706	0.041	0.236	0.864	0.142	0.289	0.623	-0.292	0.356	0.413	0.475	0.374	0.204

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to other studies having interest in specific metals and toenail Hg analysis utilizing a different laboratory method.

³Range due to different number of visits having both toenail and outcome data

Table S2.6. Adjusted¹ estimates of cumulative average toenail metals alone in each logistic model. Outcomes are at last visit with toenail and BSI data.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg			Log Blood Pb		
# of Subjects	626-686			647-710			626-686			615-674			565-619			950-1058		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
High GSI	0.619	0.183	0.001	0.838	0.328	0.011	0.668	0.187	0.000	0.840	0.224	0.000	-0.520	0.227	0.022	0.161	0.274	0.557
High PST	0.516	0.167	0.002	0.602	0.304	0.048	0.559	0.175	0.001	0.579	0.203	0.004	-0.480	0.210	0.023	0.527	0.261	0.044
High PSDI	-0.135	0.183	0.461	-0.689	0.351	0.049	-0.178	0.195	0.361	0.090	0.220	0.683	0.430	0.233	0.065	0.152	0.269	0.571
High Depression	0.328	0.175	0.061	-0.255	0.329	0.439	0.447	0.177	0.012	0.349	0.211	0.097	-0.145	0.219	0.508	0.373	0.268	0.163
High Anxiety	0.260	0.190	0.170	0.487	0.341	0.153	0.492	0.191	0.010	0.521	0.229	0.023	-0.547	0.235	0.020	0.362	0.283	0.202
Combined	0.257	0.229	0.263	-0.021	0.427	0.960	0.267	0.233	0.254	0.554	0.274	0.043	-0.504	0.281	0.073	0.668	0.341	0.050

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.7. Estimates of first bone lead and first visit with BSI. Crude and adjusted¹ linear regression models.

	Patella Pb, Adjusted			Tibia Pb, Adjusted		
# of Subjects ²	450-531			450-530		
Outcome	beta	SE	p-value	Estimate	SE	p-value
BSI Total (log)	0.000	0.001	0.804	0.002	0.002	0.436
Depression Total (log)	0.001	0.001	0.159	0.002	0.001	0.133
PST (log)	0.001	0.001	0.198	0.002	0.002	0.181
GSI (log)	0.000	0.000	0.230	0.000	0.000	0.178
PSDI (log)	0.000	0.000	0.030	0.000	0.000	0.045
Anxiety Total (log)	0.001	0.001	0.458	0.001	0.001	0.460

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.8. Crude estimates of toenail metal alone in each logistic mixed model.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg		
# of Subjects ¹	701-753			716-767			701-753			680-729			628-678		
# of Visits Range ²	1473-1643			1522-1692			1470-1640			1424-1583			1046-1174		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
GSI	0.146	0.201	0.469	0.049	0.341	0.886	0.269	0.185	0.146	0.336	0.231	0.145	-0.462	0.268	0.085
PST	0.329	0.202	0.105	0.274	0.336	0.414	0.361	0.185	0.051	0.344	0.229	0.133	-0.270	0.262	0.304
PSDI	-0.023	0.196	0.908	-0.358	0.341	0.294	-0.143	0.187	0.444	-0.002	0.225	0.992	-0.265	0.271	0.327
Depression	0.041	0.201	0.838	-0.094	0.349	0.787	0.054	0.186	0.774	0.040	0.236	0.866	-0.244	0.270	0.366
Anxiety	0.185	0.203	0.362	-0.148	0.351	0.674	0.163	0.190	0.391	0.264	0.237	0.267	-0.449	0.278	0.107
Combined	0.087	0.244	0.721	-0.287	0.427	0.502	-0.006	0.230	0.980	0.114	0.284	0.689	-0.544	0.335	0.105

¹Difference due to other studies having interest in specific metals and toenail Hg analysis utilizing a different laboratory method.²Range due to different number of visits having both toenail and outcome data

Table S2.9. Crude estimates of toenail metals together in each logistic mixed model.

	GSI			PST			PSDI			Depression			Anxiety			Combined		
# of subjects ¹	650			605			605			648			650			650		
# of Visits ²	1113			996			996			1111			1113			1113		
	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	-0.105	0.284	0.711	0.041	0.276	0.883	0.401	0.282	0.156	-0.028	0.286	0.922	0.010	0.295	0.973	0.118	0.347	0.735
Log As	-0.080	0.450	0.859	-0.054	0.440	0.903	-0.472	0.476	0.322	-0.237	0.465	0.611	-0.393	0.477	0.411	-0.492	0.583	0.399
Log Cd	0.350	0.244	0.153	0.371	0.241	0.124	-0.214	0.262	0.415	0.196	0.251	0.435	0.108	0.262	0.680	-0.076	0.315	0.809
Log Mn	0.131	0.317	0.680	0.017	0.309	0.955	0.131	0.320	0.682	-0.009	0.325	0.977	0.304	0.330	0.358	0.238	0.396	0.549
Log Hg	-0.472	0.279	0.092	-0.288	0.272	0.290	-0.156	0.280	0.578	-0.265	0.281	0.346	-0.463	0.290	0.111	-0.542	0.345	0.117

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression²Difference due to different number of visits having both toenail and outcome data

Table S2.10. Adjusted¹ estimates of toenail metals together with covariates in logistic mixed model.

	GSI			PST			PSDI			Depression			Anxiety			Combined		
# of subjects ²	646			601			601			644			646			646		
# of Visits ³	1109			992			992			1107			1109			1109		
	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	-0.077	0.291	0.792	0.041	0.282	0.883	0.374	0.291	0.199	-0.003	0.292	0.993	0.021	0.298	0.945	0.136	0.352	0.699
Log As	0.045	0.468	0.923	0.029	0.459	0.949	-0.260	0.498	0.603	-0.057	0.481	0.905	-0.343	0.492	0.486	-0.344	0.603	0.569
Log Cd	0.356	0.249	0.154	0.347	0.246	0.160	-0.171	0.270	0.528	0.190	0.258	0.460	0.078	0.267	0.771	-0.088	0.324	0.785
Log Mn	0.145	0.327	0.658	0.083	0.318	0.795	0.169	0.333	0.614	-0.029	0.331	0.930	0.314	0.333	0.347	0.261	0.403	0.517
Log Hg	-0.256	0.297	0.391	-0.095	0.292	0.745	0.053	0.298	0.860	-0.107	0.300	0.721	-0.293	0.307	0.340	-0.311	0.367	0.397

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression

³Difference due to different number of visits having both toenail and outcome data

Table S2.11. Crude estimates of cumulative average of toenail metals together in each linear model. Outcomes are at last visit with toenail and BSI data.

	BSI			Depression			PST			GSI			PSDI			Anxiety		
# of Subjects ¹	672			671			613			672			613			672		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	0.096	0.056	0.086	0.039	0.036	0.280	0.098	0.044	0.028	0.015	0.011	0.158	0.008	0.007	0.224	0.034	0.035	0.334
Log As	-0.052	0.096	0.587	-0.009	0.062	0.878	-0.016	0.076	0.835	-0.004	0.018	0.830	-0.028	0.012	0.017	-0.027	0.060	0.648
Log Cd	0.106	0.058	0.066	0.040	0.037	0.286	0.082	0.047	0.082	0.016	0.011	0.140	0.004	0.007	0.627	0.059	0.036	0.104
Log Mn	-0.003	0.067	0.966	-0.003	0.043	0.949	-0.031	0.052	0.550	-0.001	0.013	0.948	0.008	0.008	0.337	-0.001	0.042	0.985
Log Hg	-0.129	0.052	0.013	-0.059	0.033	0.077	-0.127	0.040	0.002	-0.027	0.010	0.006	-0.001	0.006	0.891	-0.082	0.032	0.012

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression

Table S2.12. Adjusted¹ estimates of cumulative average toenail metals together in each linear model. Outcomes are at last visit with toenail and BSI data.

	BSI			Depression			PST			GSI			PSDI			Anxiety		
# of Subjects ¹	607			606			554			607			554			607		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	0.084	0.058	0.147	0.027	0.037	0.473	0.070	0.046	0.127	0.010	0.011	0.360	0.005	0.007	0.431	0.013	0.036	0.718
Log As	-0.066	0.102	0.518	-0.010	0.065	0.876	-0.009	0.080	0.907	-0.002	0.019	0.918	-0.021	0.012	0.081	-0.044	0.064	0.490
Log Cd	0.088	0.059	0.133	0.043	0.038	0.252	0.074	0.048	0.121	0.015	0.011	0.165	0.003	0.007	0.653	0.054	0.037	0.141
Log Mn	0.044	0.069	0.528	0.024	0.044	0.591	-0.002	0.054	0.970	0.012	0.013	0.352	0.008	0.008	0.319	0.034	0.043	0.434
Log Hg	-0.084	0.055	0.127	-0.034	0.035	0.335	-0.093	0.043	0.031	-0.016	0.010	0.132	0.005	0.006	0.431	-0.066	0.035	0.055

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression

Table S2.13. Crude estimates of cumulative average of toenail metals alone in each logistic model. Outcomes are at last visit with toenail and BSI data.

	Log Pb			Log As			Log Cd			Log Mn			Log Hg		
# of Subjects ¹	701-771			713-785			701-771			679-747			635-696		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
GSI	0.586	0.164	<0.001	0.561	0.297	0.059	0.630	0.171	0.000	0.602	0.204	0.003	-0.852	0.202	<0.001
PST	0.641	0.149	<0.001	0.395	0.274	0.150	0.508	0.159	0.001	0.355	0.185	0.056	-0.670	0.184	<0.001
PSDI	-0.161	0.168	0.339	-0.922	0.326	0.005	-0.126	0.178	0.480	0.077	0.201	0.701	-0.007	0.201	0.972
Depression	0.392	0.159	0.014	-0.186	0.302	0.538	0.438	0.165	0.008	0.277	0.198	0.162	-0.505	0.196	0.010
Anxiety	0.337	0.173	0.051	0.151	0.321	0.639	0.435	0.179	0.015	0.411	0.215	0.056	-0.774	0.211	<0.001
Combined	0.183	0.213	0.390	-0.364	0.409	0.373	0.196	0.222	0.378	0.416	0.259	0.109	-0.937	0.254	<0.001

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression

Table S2.14. Crude estimates of cumulative average of toenail metals together in each logistic model. Outcomes are at last visit with toenail and BSI data.

	GSI			PST			PSDI			Depression			Anxiety			Combined		
# of Subjects ¹	672			613			613			671			672			672		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	0.296	0.224	0.186	0.625	0.202	0.002	0.063	0.228	0.782	0.366	0.214	0.088	0.259	0.236	0.272	0.166	0.286	0.562
Log As	0.207	0.382	0.588	0.181	0.353	0.609	-1.682	0.424	<0.001	-0.676	0.387	0.081	-0.058	0.407	0.886	-0.666	0.506	0.188
Log Cd	0.387	0.230	0.092	0.145	0.218	0.508	-0.060	0.245	0.808	0.316	0.222	0.155	0.120	0.245	0.624	-0.017	0.299	0.955
Log Mn	0.085	0.275	0.757	-0.215	0.250	0.390	0.756	0.264	0.004	0.128	0.265	0.628	0.108	0.288	0.708	0.440	0.345	0.202
Log Hg	-0.817	0.211	<0.001	-0.653	0.192	0.001	0.183	0.210	0.385	-0.412	0.204	0.044	-0.762	0.220	0.001	-0.867	0.263	0.001

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression.

Table S2.15. Adjusted¹ estimates of cumulative average toenail metals together in each logistic model. Outcomes are at last visit with toenail and BSI data.

	GSI			PST			PSDI			Depression			Anxiety			Combined		
# of Subjects ²	607			554			554			606			607			607		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
Log Pb	0.241	0.246	0.327	0.273	0.225	0.227	0.112	0.249	0.654	0.269	0.231	0.244	0.027	0.257	0.915	0.200	0.301	0.506
Log As	0.343	0.427	0.422	0.308	0.397	0.438	-1.532	0.479	0.001 ³	-0.898	0.430	0.037 ³	0.379	0.438	0.387	-0.456	0.541	0.400
Log Cd	0.324	0.248	0.191	0.256	0.235	0.277	-0.200	0.267	0.453	0.341	0.233	0.144	0.204	0.258	0.429	-0.058	0.311	0.852
Log Mn	0.472	0.295	0.110	0.209	0.271	0.440	0.849	0.301	0.005	0.427	0.279	0.126	0.248	0.304	0.414	0.617	0.360	0.087
Log Hg	-0.495	0.238	0.037 ³	-0.477	0.218	0.029	0.621	0.242	0.010	-0.045	0.227	0.843	-0.586	0.244	0.016 ³	-0.443	0.289	0.125

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

³Became non-significant after including tuna consumption in the adjusted models

Table S2.16. Estimates of cumulative average of bone lead and last visit with BSI. Crude and adjusted¹ linear regression models. Outcomes are last visit with toenail and BSI data (all bone lead measurements occurred prior to outcomes).

	Patella Pb, Crude			Patella Pb, Adjusted			Tibia Pb, Crude			Tibia Pb, Adjusted		
# of Subjects ²	477-524			472-519			477-524			472-519		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
BSI Total (log)	0.001 6	0.001 3	0.20 0	0.000 5	0.001 4	0.72 4	0.002 2	0.001 9	0.24 8	0.000 7	0.002 1	0.72 4
Depression Total (log)	0.000 8	0.000 8	0.33 1	0.000 8	0.000 9	0.36 9	0.001 3	0.001 2	0.27 9	0.001 9	0.001 3	0.15 0
PST (log)	0.002 7	0.001 1	0.01 5	0.002 0	0.001 2	0.09 6	0.003 8	0.001 6	0.01 4	0.003 2	0.001 8	0.06 9
GSI (log)	0.000 5	0.000 2	0.03 7	0.000 3	0.000 3	0.21 5	0.000 7	0.000 3	0.06 0	0.000 5	0.000 4	0.20 0
PSDI (log)	0.000 3	0.000 2	0.05 3	0.000 3	0.000 2	0.10 0	0.000 3	0.000 2	0.28 5	0.000 2	0.000 3	0.43 4
Anxiety Total (log)	0.000 7	0.000 8	0.37 3	0.000 9	0.000 9	0.28 5	0.000 7	0.001 2	0.53 8	0.001 6	0.001 3	0.22 3

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no)

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.17. Estimates of first bone lead and first visit with BSI. Crude linear regression models.

	Patella Pb, Crude			Tibia Pb, Crude		
# of Subjects ²	456-537			456-536		
Outcome	beta	SE	p	beta	SE	p
BSI Total (log)	0.002	0.001	0.114	0.004	0.002	0.053
Depression Total (log)	0.001	0.001	0.059	0.002	0.001	0.103
PST (log)	0.003	0.001	0.011	0.004	0.001	0.015
GSI (log)	0.001	0.000	0.009	0.001	0.000	0.011
PSDI (log)	0.000	0.000	0.002	0.001	0.000	0.006
Anxiety Total (log)	0.001	0.001	0.180	0.001	0.001	0.239

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.18. Estimates of first bone lead and last visit with BSI. Crude and adjusted¹ linear regression models.

	Patella Pb, Crude			Patella Pb, Adjusted			Tibia Pb, Crude			Tibia Pb, Adjusted		
# of Subjects ²	482-532			437-479			481-532			437-480		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
BSI Total (log)	0.002	0.001	0.074	0.002	0.001	0.233	0.003	0.002	0.172	0.002	0.002	0.397
Depression Total (log)	0.001	0.001	0.081	0.001	0.001	0.156	0.001	0.001	0.225	0.002	0.001	0.225
PST (log)	0.003	0.001	0.005	0.002	0.001	0.039	0.003	0.001	0.064	0.002	0.002	0.139
GSI (log)	0.001	0.000	0.006	0.000	0.000	0.050	0.001	0.000	0.041	0.001	0.000	0.117
PSDI (log)	0.000	0.000	0.013	0.000	0.000	0.039	0.000	0.000	0.044	0.001	0.000	0.055
Anxiety Total (log)	0.002	0.001	0.042	0.001	0.001	0.110	0.002	0.001	0.188	0.002	0.001	0.179

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no). ²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.19. Estimates of first bone lead and first visit with BSI. Crude logistic regression models.

	Patella Pb, Crude			Tibia Pb, Crude		
# of Subjects ¹	456-537			456-536		
Outcome	beta	SE	p	beta	SE	p
GSI high	0.017	0.007	0.016	0.024	0.011	0.037
PST high	0.009	0.007	0.159	0.015	0.010	0.128
PSDI high	0.020	0.008	0.008	0.031	0.011	0.006
Depression high	0.008	0.007	0.276	0.019	0.011	0.089
Anxiety high	0.015	0.007	0.034	0.017	0.011	0.130
Combined high	0.021	0.008	0.014	0.034	0.013	0.011

¹Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.20. Estimates of first bone lead and last visit with BSI. Crude and adjusted¹ logistic regression models.

	Patella Pb, Crude			Patella Pb, Adjusted			Tibia Pb, Crude			Tibia Pb, Adjusted		
# of Subjects ²	482-532			437-479			481-532			437-480		
Outcome	beta	SE	p	beta	SE	p	beta	SE	p	beta	SE	p
GSI high	0.015	0.006	0.014	0.015	0.007	0.039	0.017	0.010	0.105	0.018	0.012	0.125
PST high	0.011	0.006	0.088	0.011	0.007	0.111	0.003	0.010	0.778	0.006	0.012	0.620
PSDI high	0.019	0.006	0.004	0.019	0.007	0.008	0.033	0.010	0.001	0.038	0.012	0.001
Depression high	0.012	0.006	0.072	0.009	0.007	0.192	0.014	0.010	0.172	0.014	0.012	0.223
Anxiety high	0.010	0.007	0.119	0.011	0.007	0.126	0.007	0.011	0.532	0.012	0.012	0.345
Combined high	0.018	0.007	0.018	0.016	0.008	0.051	0.019	0.012	0.120	0.019	0.014	0.170

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no).

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.

Table S2.21. Estimates of blood Pb for both linear and logistic regression outcomes adjusted¹ for covariates.

	1st Blood Pb, 1st BSI			Last Blood Pb, Last BSI		
	Log Blood Pb			Log Blood Pb		
# of Subjects ²	908-1058			950-1058		
Linear Regression	Estimate	SE	p-value	Estimate	SE	p-value
BSI Total (log)	-0.060	0.062	0.331	-0.002	0.058	0.979
Depression Total (log)	-0.054	0.037	0.139	-0.019	0.036	0.603
PST (log)	-0.028	0.049	0.559	0.014	0.046	0.758
GSI (log)	-0.003	0.011	0.790	0.005	0.011	0.654
PSDI (log)	-0.001	0.007	0.937	0.001	0.007	0.899
Anxiety Total (log)	-0.018	0.035	0.603	0.019	0.035	0.584
# of Subjects ²	908-1058			950-1058		
Logistic Regression	Estimate	SE	p-value	Estimate	SE	p-value
GSI high	0.475	0.416	0.254	0.270	0.353	0.445
PST high	0.246	0.359	0.493	0.372	0.344	0.280
PSDI high	0.379	0.440	0.389	0.218	0.358	0.542
Depression high	-0.097	0.377	0.798	0.112	0.349	0.748
Anxiety high	0.694	0.405	0.086	0.333	0.365	0.362
Combined	1.009	0.522	0.053	0.347	0.443	0.433

¹Adjusted for age, age centered squared, years of education, BMI (continuous), smoking status (never, former, current), usually drink alcohol ≥ 2 drinks per day (yes, no).

²Difference due to missing responses to questions comprising PST, PSDI, and Depression and missing covariates.