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Co-morbidities of environmental diseases: A common cause

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ABSTRACT

The global pandemic of non-vector borne environmental diseases may, in large part, be attributed to chronic exposures to ever increasing levels of exogenous lipophilic chemicals. These chemicals include persistent organic pollutants, semi-volatile compounds and low molecular weight hydrocarbons. Such chemicals facilitate the sequential absorption of otherwise not absorbed more toxic hydrophilic species that attack numerous body organs and systems, leading to environmental disease. Co-morbidities of non-communicable environmental diseases are alarmingly high, with as many as half of all individuals chronically ill with two or more diseases. Co-morbidity is to be anticipated, since all of the causative chemicals identified have independently been shown to trigger the individual diseases.

KEY WORDS: environmental disease; co-morbidity; diabetes; cardiovascular disease; neurological disease

Introduction

The prevalence of non-vector borne environmental disease in the world has reached pandemic proportions (Murray *et al.*, 2012). In the United States alone, half of all adults have at least one environmental disease and more than a quarter of the adult population suffers from two or more co-morbid environmental diseases (Bauer *et al.*, 2014; Jakovljevic *et al.*, 2013; van Oostrom *et al.*, 2012). Indeed, rapid increases in incidences of environmental diseases have not been limited to the industrialized areas of the globe but have also spread to remote areas including those inhabited by indigenous populations in the tropics and near the poles (Vos *et al.*, 2012). The rapid rise in the prevalence of these diseases can only be linked to environmental effects (Boyle *et al.*, 2010). A common thread in many environmental diseases is the presence of exogenous lipophilic toxic chemicals in the bodies of those affected (Zeliger, 2013; Zeliger, 2013a; Zeliger 2013b).

It has been previously reported that chemically sensitive individuals exposed to low molecular weight hydrocarbons (LMWHs) had numerous co-morbidities (Zeliger *et al.* 2012). It can now be reported that exposures

to all exogenous lipophilic chemicals cause co-morbidities and that co-morbidity of environmental disease is not limited to just the chemically sensitive people. Exposure to and retention of lipophilic persistent organic pollutants (POPs) semi-volatile and volatile exogenous lipophilic chemicals has been associated with increased prevalence of type 2 diabetes (T2D) (Carpenter, 2008; Lee *et al.*, 2010; Zeliger 2013), cardiovascular disease (Zeliger, 2013a), and neurological disease (Zeliger 2013b). Many other environmental diseases, that affect virtually all body systems, are also associated with exposure to and retention of exogenous lipophilic chemical species. These include: immunological (Marie *et al.*, 2013), musculoskeletal (Al-Bashri *et al.*, 2013; Struijs *et al.*, 2006); and respiratory diseases (Cazzola *et al.*, 2013; Varela *et al.*, 2013; Molen, 2010); as well as numerous cancers (Habib *et al.*, 2013; Sorensen, 2013; van Baal *et al.*, 2010).

A unifying explanation for induction of environmental disease by absorbed exogenous lipophilic chemicals has been previously presented (Zeliger, 2013). Review of the medical and toxicological literature shows that the onset of these diseases is associated with the accumulation of exogenous lipophilic chemicals in body serum, (Gallo *et al.*, 2011; Lee *et al.*, 2011; Lee *et al.*, 2007; Philibert *et al.*, 2009; Cortu *et al.*, 2007). A dose dependent relationship between POPs serum levels and type 2 diabetes (T2D), for example, has been shown to exist (Cortu *et al.*, 2007; Lee *et al.*, 2006). Lipophilic cell membranes are not permeable to most hydrophilic chemicals. Lipophilic chemicals

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act as solvents and carriers for impermeable hydrophiles to facilitate absorption of species which would not otherwise permeate through the cells' lipophilic barriers (Zeliger 2003).

It has also been previously shown that mixtures of toxic lipophilic and hydrophilic species produce enhanced toxicities, low-level effects and attacks on organs and/or systems not known to be impacted by either species alone (Zeliger, 2003; Zeliger, 2011). Such effects have been observed following simultaneous exposures to mixtures of lipophilic and hydrophilic chemicals. Environmental disease can be triggered by the initial absorption and retention of lipophilic species followed by the sequential uptake of hydrophilic species that then act together as a toxic mixture, with the absorption of different hydrophiles accounting for the onset of different diseases (Zeliger *et al.*, 2012; Zeliger, 2013; Zeliger, 2013a; Zeliger 2013b).

Though different diseases involve attacks on widely disparate organs and systems, co-morbidity rates are high when individuals are exposed to environmental lipophilic toxins (Zeliger *et al.*, 2012). The onsets of co-morbid diseases do not follow set patterns. Published studies show that individuals with two co-morbid diseases, *e.g.*, T2D and hypertension, are just as likely to become ill with one first as the other first (Sowers *et al.*, 2001), for example. The wide prevalence of co-morbid environmental diseases and the lack of a pattern of onset strongly suggests the common cause for these diseases that has been previously reported on (Zeliger, 2013; Zeliger, 2013a; Zeliger, 2013b).

Methods

The results presented here are based upon a literature review of numerous studies on the toxic effects of the chemicals on the body. These studies include epidemiological and case studies. Adverse effects on health were in all instances diagnosed by appropriate clinical examinations. Data for pairs of co-morbidities were carried out by literature searches for the words, "co-morbidity" and the names of the two diseases, "cardiovascular disease" and "musculoskeletal disease", for example.

T2D	X	X	X	X	X	X	X	X	X	X
CVD		X	X	X	X	X	X	X	X	X
NRD			X	X	X	X	X	X	X	
NDV				X	X	X		X	X	
NDG					X					X
MSK						X	X	X	X	X
IMM							X	X		
RES								X	X	X
CMS									X	
OBS										X
CAN										

Figure 1. Co-morbidities of chemically induced environmental diseases. References for co-morbidity disease pairs are contained in Table 2. X denotes the existence of co-morbidity between the two diseases.

Results

Specific lipophilic chemicals associated with multiple environmental diseases include those previously reported to be associated with T2D, cardiovascular disease and neurological disease. These include non-volatile POPs, semi-volatile and volatile species (Zeliger, 2013; Zeliger, 2013a; Zeliger, 2013b).

Major environmental diseases that have been associated with lipophilic exposure include immunological, neurological, neurodegenerative reproductive, cardiovascular, metabolic, musculoskeletal and carcinogenic ones. These are listed in Table 1.

All of the diseases listed in Table 1 are co-morbid with other environmental diseases that are known to be triggered by exposures to lipophilic chemicals. Figure 1 shows the co-morbidities of the 11 types of these diseases with each other. Table 2 lists co-morbid disease pairs and the references for these. It is of note that of the 55 binary combinations possible, 45 (82%) have been shown to be co-morbid to date.

Discussion

The environmental diseases reported here are late onset diseases that generally follow decades of living during which physiological breakdown of many systems occur (Wright *et al.*, 2002). All are triggered by a combination of genetic susceptibility and environmental exposure (Zhang *et al.*, 2010). Several mechanisms have been proposed the account for such breakdowns. These include: oxidative stress (Uttara *et al.*, 2009; Bolanos *et al.*, 2009); epigenetic effects (Jakovcevski *et al.*, 2012; Urduingio *et al.*, 2009; Baccarelli *et al.*, 2009); low intensity inflammation (Miller *et al.*, 2008; Leonhard *et al.*, 2006); and endocrine disruption (Weiss, 2012; Mostafalou *et al.*, 2013; Colborn *et al.*,

Table 1. Major diseases associated with exposures to lipophilic environmental chemicals.

Type 2 diabetes (T2D): Including metabolic syndrome.
Cardiovascular (CVD): Including atherosclerosis, myocardial infarction, hypertension, stroke, coronary heart disease, peripheral heart disease, ischemic heart disease and cardiac autonomic function.
Neurological (NRD): Including central nervous system disorders (cognitive, motor and sensory), and peripheral nervous system disorders (neuropathies).
Neurodevelopmental (NDV) including autism and attention deficit/hyperactivity disorder (ADHD).
Neurodegenerative (NDG) including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS).
Musculoskeletal (MKS) including osteoarthritis and fibromyalgia (FM).
Immunological (IMM) including allergic reaction, autoimmune diseases and chronic fatigue syndrome (CFS).
Respiratory (RES) including asthma and chronic obstructive pulmonary disease (COPD).
Chemical sensitivity (CMS) including hypersensitivity to inhaled and dermal contact moieties.
Obesity (OBS).
Cancers (CAN) in multiple organs.

Table 2. References for environmental disease co-morbidities.

Disease Pair	References	Disease Pair	References
T2D - CVD	Sowers <i>et al.</i> , 1995; Colosia <i>et al.</i> , 2013; Mannino <i>et al.</i> , 2008; Struijs <i>et al.</i> , 2006; Sowers <i>et al.</i> , 2001; Ramakrishnan <i>et al.</i> , 2013.	NRD - MSK	Marrie <i>et al.</i> , 2013; Blackman <i>et al.</i> , 2013; McIntyre <i>et al.</i> , 2008; Hudon <i>et al.</i> , 2008.
T2D - NRD	Blackman <i>et al.</i> , 2013; Sowers <i>et al.</i> , 1995; Uzun <i>et al.</i> , 2009; Katon, 2008; Struijs <i>et al.</i> , 2006; Lee <i>et al.</i> , 2008.	NRD - IMM	Marrie <i>et al.</i> , 2013; Aaron <i>et al.</i> , 2001.
T2D - NDV	Kohane <i>et al.</i> , 2012.	NRD - RES	Marrie <i>et al.</i> , 2013; Karlstad <i>et al.</i> , 2012; Blackman <i>et al.</i> , 2013; van der Molen, 2010; McIntyre <i>et al.</i> , 2008; Cazzola <i>et al.</i> , 2013; Chatila <i>et al.</i> , 2008.
T2D - NDG	Bannon, 2002; Duthie <i>et al.</i> , 2011; Gage <i>et al.</i> , 2003; Struijs <i>et al.</i> , 2006.	NRD - CMS	Zeliger <i>et al.</i> , 2012
T2D - MSK	Al-Bishri <i>et al.</i> , 2013; Mannino <i>et al.</i> , 2008; Slater <i>et al.</i> , 2011.	NRD - OBS	McIntyre <i>et al.</i> , 2008; Khaothiar <i>et al.</i> , 1999; Luppino <i>et al.</i> , 2010.
T2D - IMM	Somers <i>et al.</i> , 2009.	NDV - RES	Fasmer <i>et al.</i> , 2011.
T2D - RES	van der Molen, 2010; Varela <i>et al.</i> , 2013; Cazzola <i>et al.</i> , 2013; Mannino <i>et al.</i> , 2008; Struijs <i>et al.</i> , 2006; Chatila <i>et al.</i> , 2008.	NDV - OBS	Suren <i>et al.</i> , 2014.
T2D - CMS	Zeliger <i>et al.</i> , 2012.	NDV - CAN	Crespi, 2011.
T2D - OBS	Colosia <i>et al.</i> , 2013; Sowers <i>et al.</i> , 2001; Khaothiar <i>et al.</i> , 1999.	NDG - MSK	Gage <i>et al.</i> , 2003.
T2D - CAN	Habib <i>et al.</i> , 2013; van Baal <i>et al.</i> , 2011.	NDG - CAN	Crespi, 2011; Zamrini <i>et al.</i> , 2004; Gage <i>et al.</i> , 2003
CVD - NRD	McIntyre <i>et al.</i> , 2008; Uzun <i>et al.</i> , 2009; Larsen <i>et al.</i> , 2009.	MSK - IMM	Somers <i>et al.</i> , 2009; Ciccone <i>et al.</i> , 2003.
CVD - NDV	Tyler <i>et al.</i> , 2011.	MSK - RES	van der Molen, 2010; Slater <i>et al.</i> , 2011; Chatila <i>et al.</i> , 2008; Hudon <i>et al.</i> , 2008.
CVD - NDG	Armon, 2004; Bannon, 2011; Duthie <i>et al.</i> , 2011; Zamrini <i>et al.</i> , 2004; Gage <i>et al.</i> , 2003; Perju-Dumbrava <i>et al.</i> , 2014.	MSK - CMS	Zeliger <i>et al.</i> , 2012
CVD - MSK	Al-Bishri <i>et al.</i> , 2013; Slater <i>et al.</i> , 2011; Hudon <i>et al.</i> , 2008.	MSK - OBS	Khaothiar <i>et al.</i> , 1999; Hudon <i>et al.</i> , 2008;
CVD - IMM	Marrie <i>et al.</i> , 2013; Aaron <i>et al.</i> , 2000.	MSK - CAN	Sorensen, 2013.
CVD - RES	Karlstad <i>et al.</i> , 2012; van der Molen, 2010; Varela <i>et al.</i> , 2013; Chatila <i>et al.</i> , 2008.	IMM - RES	Karlstad <i>et al.</i> , 2012; Pinart <i>et al.</i> , 2014.
CVD - CMS	Zeliger <i>et al.</i> , 2012.	IMM - CMS	Zeliger <i>et al.</i> , 2012; Ziem <i>et al.</i> , 1995; Jason <i>et al.</i> , 2000.
CVD - OBS	Sowers <i>et al.</i> , 2001; Khaothiar <i>et al.</i> , 1999.	RES - CMS	Zeliger <i>et al.</i> , 2012; Caress <i>et al.</i> , 2005.
CVD - CAN	Kreatsoulas <i>et al.</i> , 2014; Sorensen, 2013.	RES - OBS	van der Molen, 2010; Cazzolam <i>et al.</i> , 2013; Jung <i>et al.</i> , 2014.
NRD - NDV	Cristino <i>et al.</i> , 2013; Simonoff <i>et al.</i> , 2008; Jensen <i>et al.</i> , 2014.	RES - CAN	Varela <i>et al.</i> , 2013; Sorensen, 2013.
NRD - NDG	Varela <i>et al.</i> , 2013; Gage <i>et al.</i> , 2003.	CMS - OBS	Zeliger <i>et al.</i> , 2012.
		CMA - CAN	Zeliger <i>et al.</i> , 2012
		OBS - CAN	Khaothiar <i>et al.</i> , 1999.

Abbreviations: T2D - type 2 diabetes; CVD - cardiovascular disease; NRD - neurological disease; NDV - neurodevelopmental disease; NDG - neurodegenerative disease; MSK - musculoskeletal disease; IMM - immunological disease; RES - respiratory disease; CMS - chemical sensitivity; OBS - obesity; CAN - cancer

1997). One theory of co-morbidities of environmental diseases is that there are phenotype connections between diseases, *i.e.*, that patients are affected by diseases that are connected to other diseases by a Phenotype Disease Network (Hidalgo *et al.*, 2009; Zhang *et al.*, 2010; Lee *et al.*, 2008). All of these theories are consistent with what is reported here, since exposures to all the lipophilic chemical types described above (POPs, semi-volatile organic compounds, and volatile organic compounds) have been independently been associated with each of the diseases listed in Table 1 (Zeliger, 2013; Zeliger, 2013a; Zeliger, 2013b). It is beyond the scope of this paper to examine these mechanisms in detail. Readers are directed to the references cited for elaboration.

Since all of the diseases listed in Table 1 have been related to exogenous lipophilic adsorption (Zeliger, 2013; Zeliger 2013a; Zeliger 2013b) it is to a great extent predictive that individuals ill with one of these diseases will be co-morbidly ailing with at least one other of these diseases (Zeliger *et al.*, 2012). This can be stated emphatically, as there are numerous studies in the literature showing, that where individuals are co-morbid with two of these diseases, the co-morbidities are independent of the order of onset of the two diseases, *i.e.*, that either of the diseases can precede the other. The following serve as examples

of these studies. Somers *et al.* reported that individuals with autoimmune disease show higher than expected co-morbidities with musculoskeletal disease and type 2 diabetes and that in both instances either of the diseases could precede the other (Somers *et al.*, 2009). In people co-morbid with metabolic syndrome and mental health disorders, either condition can precede the other (Nousen *et al.*, 2013). Obesity and depression are common co-morbid conditions and either one can precede the other (Luppino *et al.*, 2012). Hypertension is about twice as common in diabetics as in those without diabetes and either disease can precede the other (Sowers *et al.*, 1995; Sowers *et al.*, 2001).

Based on the above, it can be stated that one cause of numerous environmental diseases and co-morbidities is chronic lipophilic exposure to lipophiles such as persistent organic pollutants (POPs), semi-volatile exogenous chemicals (SVOCs) and low molecular weight hydrocarbons (LMWHCs). Examples of POPs are polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCs). Examples of semi-volatile compounds are bisphenol A, phthalates and polynuclear aromatic hydrocarbons. Examples of volatile organic compounds are 8 carbon or less aliphatic and single-chain aromatic hydrocarbons. POPs are slowly metabolized and eliminated and

are stored in white adipose tissue, from where they are slowly released into the blood stream. SVOCs are more rapidly metabolized and eliminated and LMWHs are very rapidly metabolized and eliminated, but continued exposure to SVOCs and LMWHs leads to continuous levels in the blood as well. A steady state of lipophilic load is in effect in the body, and since lipophiles facilitate the absorption of hydrophiles, a body containing high levels of lipophiles is more likely to absorb toxic levels of hydrophiles when exposure to these occurs than one with low levels of lipophiles. This is shown by the dose-response relationships for the onset of T2D, cardiovascular disease and neurological disease (Cortu *et al.*, 2007; Lee *et al.*, 2006; Zeliger, 2013a; Zeliger, 2013b). As a wide variety of exogenous lipophiles have been shown to cause all of the diseases in Table 1, it is total exogenous lipophilic load, regardless of chemical species, that is more predictive of the onset of disease than single chemical considerations.

Further credence to the theory just proposed is provided by the following considerations:

1. Not only do exogenous lipophiles cause these diseases, but one of these diseases, obesity has also been shown to cause the absorption of lipophiles (See below).
2. One in four individuals with one of these diseases is likely to be stricken with at least one more of these diseases (Bauer *et al.*, 2014; Jakovljevic *et al.*, 2013; van Oostrom *et al.*, 2012).
3. Eleven (11) types of environmental diseases are listed in Table 1. Of the 55 binary combinations of diseases possible, 45 (82%), have been shown to be co-morbid (see Figure 1).
4. All the diseases in Table 1 are late-onset ones, coming mostly after decades of exposures (Fortin *et al.*, 2005).

A consideration of obesity is in order here. Body Mass Index (BMI) of 30 or greater is considered obese (Luppino *et al.*, 2010). BMI is a predictor of human adipose tissue concentration of POPs (Vaclavik *et al.*, 2006). This is consistent with the fact that obesity is usually associated with CVS, T2D and other diseases, as adipose tissue releases the lipophiles it holds to the blood stream. Obesity is itself caused by POPs, phthalates, bisphenol A and other exogenous lipophiles (Dirinick *et al.*, 2014; Choi *et al.*, 2014; Langer *et al.*, 2014; Lee *et al.*, 2014; Simmons *et al.*, 2014; Lee *et al.*, 2011a). Being obese and having high serum endogenous lipophiles (cholesterol and triglycerides) contributes to the absorption of these exogenous lipophiles (Wang *et al.*, 2007; Vaclavik *et al.*, 2006). This sets up what is termed here as the Obesity (OBS) – Lipophile (LIP) – Disease (DIS) triangle:

Obesity causes the absorption of toxic lipophiles which in turn cause disease. Toxic lipophiles cause obesity which in turn causes the further absorption of lipophiles which cause disease. Disease causes obesity which causes the absorption of lipophiles which in turn causes further disease. (Dirinick *et al.*, 2014; Choi *et al.*, 2014; Langer *et al.*, 2014; Lee *et al.*, 2014; Simmons *et al.*, 2014).

Finally, it is not implied that lipophilic exposure is the only cause for environmental disease. For example, heavy metals (including arsenic, cadmium, chromium, cobalt, copper, mercury and nickel) are known trigger environmental diseases, including type 2 diabetes, cardiovascular diseases and neurological diseases (Carocci *et al.*, 2014; Caciari *et al.*, 2013; Kuo *et al.*, 2013; Baccarelli *et al.*, 2009; Khan, et al., 2014; Agarwal *et al.*, 2011; Mates *et al.*, 2010).

Conclusions

In conclusion, it has been previously shown that chemically sensitive individuals had numerous co-morbidities when exposed to LMWHs (Zeliger *et al.*, 2012). It can now be stated that exposures to all exogenous lipophiles (POPs and SVOCs, as well as LMWHs) also produce co-morbidities of environmental diseases in all segments of the population. Exposures to lipophiles result in numerous co-morbid disease pairs affecting widely differing organs and systems. It is theorized that all chronic exposures to lipophilic exogenous chemicals lead to steady states of such compounds in human blood and can cause of a wide range of environmental diseases that affect numerous body organs and systems. Since the lipophiles serve as carriers for the sequential absorption of more toxic hydrophiles, disease onset is dictated not by the individual chemistries of the lipophiles, but by total lipophilic load in the blood. Lipophilic exposure promotes obesity, which promotes the absorption of additional exogenous lipophiles that promote further environmental disease. An obesity-lipophile-disease triangle which promotes the furthering of environmental disease is thus defined.

REFERENCES

- Aaron LA, Burke MM, Buchwald MD. (2012). Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* **160**: 221–227.
- Aaron LA., Herrell R, Ashton S, Belcourt M, Schmalting K, Goldberg J *et al.* (2001). Comorbid clinical conditions in chronic fatigue. *J Gen Intern Med* **16**: 24–31.
- Agarwal S, Zaman T, Tuzcu EM, Kapadia SR. (2011). Heavy metals and cardiovascular disease: results from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. *Angiology* **62**(5): 422–29.
- Al-Bishri J, Attar SM, Bassuni N, Al-Yofaiey, Qutbuddeen H, Al-Harthi S *et al.* (2013). Comorbidity profile among patients with rheumatoid arthritis and the impact on prescription trend. *Clin Med Insights: Arthritis and Musculoskeletal Disorders* **6**: 11–18.
- Antshel KM, Zhang-James Y, Faraone SV. (2013). The comorbidity of ADHD and autism spectrum disorder. *Expert Rev Neurother* **13**(10): 1117–28.
- Baccarelli A, Bollati V. (2009). Epigenetics and environmental chemicals. *Curr Opin Pediatr* **21**(2): 243–51.

- Bauer UE, Briss PA, Goodman RA, Bowman BA. (2014). Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. *Lancet* **384**(9937): 45–52.
- Blackman JA, Conaway MR. (2013). Developmental, emotional and behavioral co-morbidities across the chronic health condition spectrum. *J Pediatr Rehabil Med* **6**(2): 63–71.
- Bolanos JP, Moro MA, Lizasoain I, Almeida A. (2009). *Adv Drug Deliv Rev* **61**(14): 1299–1315.
- Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. (2010). Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality and prediabetes prevalence. *Popul Health Metr* **8**: 29–41.
- Caciari T, Sancini A, Fioravanti M, Capozzella A, Casale T, Montuori L. *et al.* (2013). Cadmium and hypertension in exposed workers: a meta-analysis. *Int J Occup Med Environ Health* **26**(3): 440–56.
- Caress SM, Steinemann AC. (2005). National prevalence of asthma and chemical hypersensitivity: an examination of potential overlap. *JOEM* **47**(5): 518–22.
- Carocci A, Rovito N, Sinicropi MS, Genchi G. (2014). Mercury toxicity and neurodegenerative effects. *Rev Environ Contam Toxicol* **229**: 1–18.
- Carpenter DO. (2008). Environmental contaminants as risk factors for developing diabetes. *Rev Environ Health* **23**(1): 59–74.
- Cazzola M, Segreti A, Calzetta L, Rogliani P. (2013). Comorbidities of asthma: current knowledge and future research needs. *Curr Opin Pulm Med* **19**(1): 36–41.
- Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. (2008). Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* **5**: 549–55.
- Choi J, Eom J, Kim J, Lee S, Kim Y. (2014). Association between some endocrine-disrupting chemicals and childhood obesity in biological samples of young girls: a cross-sectional study. *Environ Toxicol Pharmacol* **38**(1): 51–57.
- Ciccone DS, Natelson BH. (2003). Comorbid illness in women with chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosomatic Med* **65**: 268–75.
- Colborn T, Dumanoski D, Myers JP. (1997). *Our stolen future*. Penguin Books, New York.
- Colosia AD, Palencia R, Khan S. (2013). Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. *Diabetes Metab Syndr* **6**: 327–38.
- Cordu N, Schymura MJ, Nogotia S, Rej R, Carpenter DO. (2007). Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult native Americans. *Environ Health Perspect* **115**(10): 1442–47.
- Crespi B. (2011). Autism and cancer risk. *Autism Research* **4**: 302–10.
- Cristino AS, Williams SM, Hawi Z, An JY, Bellgrove MA, Schwartz CE *et al.* (2013). Neurodevelopment and neuropsychiatric disorders represent an interconnected molecular system. *Mol Psychiatry* **19**(3): 294–301.
- Dirinck EL, Dirlu AC, Govindan M, Covaci A, Van Gaal LF, Jorens PG. (2014). Exposure to persistent organic pollutants: relationship with abnormal glucose metabolism and visceral adiposity. *Diabetes Care* **37**(7): 1951–58.
- Duthie A, Chew D, Soiza RL. (2011). Non-psychiatric comorbidity associated with Alzheimer's disease. *QJ Med* **104**: 913–20.
- Fasmer OB, Riise T, Eagan TM, Lund A, Dilsaver SC, Hundal O *et al.* (2011). Comorbidity of asthma with ADHD. *J Atten Disord* **15**(7): 564–71.
- Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe MA. (2005). Prevalence of multimorbidity among adults seen in family practice. *Ann Family Med* **3**(3): 223–28.
- Gage H, Hendricks A, Zhang S, Kazis L. (2003). The relative health related quality of life of veterans with Parkinson's Disease. *J Neurol Neurosurg Psychiatry* **74**: 163–69.
- Gallo MV, Schell LM, DeCaprio AP, Jacobs A. (2011). Levels of persistent organic pollutant and their predictors among young adults. *Chemosphere* **83**: 1374–82.
- Habib SL, Rojna M. (2013). Diabetes and risk of cancer. *ISRN Oncology* **2013**: Article ID 583786, 16 pages.
- Hidalgo CA, Blumm N, Barabasi AL, Christakis NA. (2009). A dynamic network approach for the study of human phenotypes. *PLoS Computational Biol* **5**(4): e1000353.
- Hudon C, Fortin M, Soubhi H. (2008). Chronic musculoskeletal conditions and comorbidities in primary care settings. *Canadian Family Physician* **54**: 74–5.
- Jakovcevski M, Akbarian S. Epigenetic mechanisms in neurological disease. *Nat Med* **18**(8): 1194–1204.
- Jakovljevic M, Ostojic L. (2013). Comorbidity and multimorbidity in medicine today: challenges and opportunities for bringing separated branches of medicine closer to each other. *Psychiatr Danub* **25**(Suppl 1): 18–28.
- Jason LA, Taylor RR, Kennedy CL. (2000). Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue-like symptoms. *Psychosomatic Med* **62**: 655–63.
- Jensen CM, Steinhausen HC. (2014). Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord* June 19, [Epub ahead of print].
- Jung KH, Perzanowski M, Rundle A, Moors K, Yan B, Chillrud SN *et al.* (2014). Polycyclic aromatic hydrocarbon exposure, obesity and childhood asthma in an urban cohort. *Environ Res* **128**: 35–41.
- Karlstad O, Nafstad P, Tverdal A, Skurtveit S, Furu K. (2012). Comorbidities in an asthma population 8–29 years old: a study from the Norwegian prescription database. *Pharmacoepidemiol* **21**(10): 1045–52.
- Katon WJ. (2008). The comorbidity of diabetes mellitus and depression. *Am J Med* **121**(11 Suppl 2): S8–15.
- Khan AR, Awan FR. (2014). Metals in the pathogenesis of type 2 diabetes. *J Diabetes Metabolic Disorders* **13**: 16. doi: 10.1186/2251-6581-13-16.
- Khaodhlar L, McCowen KC, Blackburn GL. (1999). Obesity and its comorbid conditions. *Clin Cornerstone* **2**(3): 17–31.
- Kohane IS, McMurry A, Weber G, McFadden D, Rappaport L, Kunkel L *et al.* (2012). The co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS ONE* **7**(4): e33224.
- Kreatsoulas C, Anand SS, Subramanian SV. (2014). An emerging double burden of disease: the prevalence of individuals with cardiovascular disease and cancer. *J Intern Med* **275**(5): 494–505.
- Kuo CC, Moon K, Thayer KA, Navas-Acien A. (2013). Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Curr Diab Rep* **13**(6): 831–49.
- Langer P, Ukropec J, Kocan A, Drobna B, Radikova Z, Huckova M *et al.* (2014). Obesogenic and diabetogenic impact of high organochlorine levels (HCB, p,p-DDE, PCBs) on inhabitants in the highly polluted Eastern Slovakia. *Endocr Regul* **48**(1): 17–24.
- Larsen BA, Christenfeld NJS. (2009). Cardiovascular disease and psychiatric comorbidity: the potential role of perseverative cognition. *Cardiovascular Psychiatry Neurology* **2009**: Article ID 791017, 8 pages, doi: 10.1155/2d009/791017.
- Lee DH, Porta M, Jacobs DR Jr, Vandenberg LN. (2014). Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. *Endocr Rev* **35**(4): 557–601.
- Lee DH, Lind PM, Jacobs, Jr. DR, Salihovic S, van Bavel B, Lind L. (2011). Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala seniors (PIVUS) study. *Diabetes Care* **34**(8): 1778–84.
- Lee DH, Steffes MW, Sjoden A, Jones RS, Needham LL, Jacobs DR Jr. (2011a). Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. *PLoS One* **26**(6): e15977.
- Lee DS, Park J, Kay KA, Christakis NA, Oltavi ZN, Barabasi AL. The implications of human metabolic network topology for disease comorbidity. (2008). *PNAS* **105**(29): 9880–85.
- Lee DH, Steffes MW, Sjoden A, Jones RS, Needham LL, Jacobs, Jr. DR. (2010). Low dose of some persistent organic pollutants predicts type 2 diabetes: A nested case-control study. *Environ Health Perspect* **118**(9): 1235–42.
- Lee DH, Jacobs, Jr., DR, Steffes M. (2008). Association of organochlorine pesticides with peripheral neuropathy in patients with diabetes or impaired fasting glucose. *Diabetes* **57**: 3108–11.
- Lee DH, Lee IK, Porta M, Steffes M, Jacobs, Jr. DR. (2007). Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetologia* **50**: 1841–51.
- Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, Jacobs, Jr. DR. (2006). A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes. *Diabetes Care* **29**(7): 1638–44.
- Leonhard BE, Myint A. (2006). Inflammation and depression: is there a causal connection with dementia? *Neurotox Res* **10**: 149–60.

- Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. (2011). Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. *PLoS ONE* **6**(10): e25978.
- Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers Penninx BWJH *et al.* (2009). Overweight, obesity, and depression. *Arch Gen Psychiatry* **67**(3): 220–29.
- Mannino DM, Thorn D, Swensen A, Holguin F. (2008). Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *European Resp J* **32**(4): 962–69.
- Marie RA, Hanwell H. (2013). General health issues in multiple sclerosis: comorbidities, secondary conditions and health behaviors. *Continuum (Minneapolis Minn)* **19**(4): 1046–57.
- Mates JM, Segura JA, Alonso FJ, Marquez J. (2010). Roles of dioxins and heavy metals in cancer and neurological diseases using ROS-mediated mechanisms. *Free Rad Biol Med* **49**(9): 1328–41.
- Matson JL, Rieske RD, Williams LW. (2013). The relationship between autism spectrum disorders and attention-deficit/hyperactivity disorder: an overview. *Res Dev Disabil* **34**(9): 2475–84.
- McIntyre RS, Nguyen HT, Soczynska JK, Lourenco MTC, Woldeyohannes HO, Konarski JZ. (2008). Medical and substance-related comorbidity in bipolar disorder: translational research and treatment opportunities. *Dialogues Clin Neurosci* **10**: 203–13.
- Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. (2008). Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* **26**: 971–82.
- Mostafalou S, Abdollahi M. (2013). Pesticides and human chronic diseases: evidences, mechanisms and perspectives. *Toxicol Appl Pharmacol* **268**(2): 157–77.
- Murray DJL, Vos T, Lozano R, Naghavi M, Flaxman AD *et al.* (2012). Disability adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**: 2197–2223.
- Nousen EK, Franco JG, Sullivan EL. (2013). Unraveling the mechanisms responsible for the comorbidity between metabolic syndrome and mental health disorders. *Neuroendocrinology* **98**(4): 254–66.
- O'Dwyer L, Tanner C, van Dongen EV, Greven CU, Bralten J, Zwiers MP *et al.* (2014). Brain volumetric correlates of autism spectrum disorder symptoms in attention deficit/hyperactivity disorder. *PLoS ONE* **9**(6): e101130.
- Perju-Dumbrava L, Muntean ML, Muresanu DF. (2014). Cerebrovascular profile assessment in Parkinson's Disease patients. *CNS Neurol Discord Drug Targets* **13**(4): 712–17.
- Philibert A, Schwartz H, Mergler D. (2009). An exploratory study of diabetes in First Nation community with respect to the serum concentrations of p,p'-DDE and PCBs and fish consumption. *In J Environ Res Public Health* **6**(12): 3179–89.
- Pinar M, Benet M, Annesi-Maesano I, von Berg A, Berdel D, Carlsen KC *et al.* (2014). Comorbidity of eczema, rhinitis, and asthma in IgE-sensitized and non-IgE-sensitized children in MeDALL: a population-based cohort study. *Lancet Respir Med* **2**(2): 131–40.
- Ramakrishnan J, Majgi SM, Premarajan KC, Lakshminarayanan S, Thangaraj S, Chinnakali P. (2013). High prevalence of cardiovascular risk factors among policemen in Puducherry South India. *J Cardiovasc Disease Res* **4**: 112–15.
- Simmons AL, Schlezinger JJ, Corkey BE. (2014). What are we putting in our food that is making us fat? Food additives, contaminants, and other putative contributors to obesity. *Curr Obes Res* **3**(2): 273–85.
- Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. (2008). Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in population-derived sample. *J Am Acad Child Adolesc Psychiatry* **47**(8): 921–29.
- Slater M, Perruccio AV, Badley EM. (2011). Musculoskeletal comorbidities in cardiovascular disease, diabetes and respiratory disease: the impact on activity limitations; a representative population-based study. *BMC Public Health* **11**: 77. doi: 10.1186/1471-2458-11-77.
- Somers EC, Thomas SL, Smeeth L, Hall AJ. (2009). Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? *Am J Epidemiol* **169**: 749–55.
- Sorensen HT. (2013). Multimorbidity and cancer outcomes: a need for more research. *Clin Epidemiol* **5**(Suppl 1): 1–2.
- Sowers JR, Epstein M. (1995). Diabetes mellitus and associated hypertension, vascular disease, and nephropathy. *Hypertension* **26**: 869–79.
- Sowers JR, Epstein M, Frolich ED. (2001). Diabetes, hypertension, and cardiovascular disease an update. *Hypertension* **37**: 1053–59.
- Struijs JN, Baan CA, Schellevis FG, Westert GP, van den Bos GAM. (2006). Comorbidity in patients with diabetes mellitus: impact on medical health care utilization. *BMC Health Serv Res* **6**: 84–93.
- Suren P, Gunnes N, Roth C, Bresnahan M, Hornig M, Hirtz D *et al.* (2014). Parental obesity and risk of autism spectrum disorder. *Pediatrics* **133**(5): 1128–38.
- Tyler CV, Schramm SC, Karafa M, TAng AS, Jain AK. (2011). Chronic disease risks in young adults with autism spectrum disorder: forewarned is forearmed. *Am J Intell Dev Disabil* **116**(5): 371–80.
- Urdinguio RG, Sanchez-Mut JV, Esteller M. (2009). Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. *The Lancet Neurology* **8**(11): 1056–72.
- Uttara B, Singh AV, Zamboni P, Mahajan RT. (2009). Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* **7**(1): 65–74.
- Uzun S, Kozumplik O, Topic R, Jakovljevic M. (2009). Depressive disorders and comorbidity: somatic illness vs. side effect. *Psychiatry Danub* **21**(3): 391–98.
- Vaclavik E, Tjonneland A, Stripp C, Overvad K, Philippe-Weber J, Raaschou-Nielsen O. (2006). Organochlorines in Danish women: predictors of adipose tissue concentrations. *Environ Res* **100**(3): 362–70.
- Valera MVL, de Oca MM, Halbert R, Muino A, Talamo D, Perez-Padilla R *et al.* (2013). Comorbidities and health status in individuals with and without COPD in five Latin American cities: the PLATINO study. *Arch Bronconeumol* **49**(11): 468–74.
- van Baal PH, Engelfriet PM, Boshuizen HC, van de Kasstele, Schellevis FG, Hoogenveen RT. (2011). Co-occurrence of diabetes, myocardial infarction, stroke and cancer: quantifying age patterns in the Dutch population using health survey data. *Population Health Metrics* **9**: 51. doi: 10.1186/1478-7954-9-51/
- van der Molen T. (2010). Co-morbidities of COPD in primary care: frequency, relation to COPD, and treatment consequences. *Primary Care Resp J* **19**(4): 326–34.
- van Oostrom SH, Picavet HSJ, van Gelder BM, Lemmens LC, Hoeymans N, van Dijk CE *et al.* (2012). Multimorbidity and comorbidity in the Dutch population – data from general practices. *BMC Public Health* **12**: 715. doi: 10.1186/1471-2458-12-715/
- Vos T, Flaxman AD, Naghavi M, Lorenzo R, Michaud C *et al.* (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**: 2163–96.
- Wang RY, Needham LL. (2007). Environmental chemicals: from the environment to food, to breast milk, to the infant. *J Toxicol Environ Health B Crit Rev* **10**(8): 597–609.
- Weiss B. (2012). The intersection of neurotoxicology and endocrine disruption. *Neurotoxicology* **33**(6): 1410–19.
- Wright A, Charlesworth B, Rudan I, Carothers A, Campbell H. (2003). A polygenic basis for late-onset disease. *Trends in Genetics* **19**(2): 97–106.
- Zamrini E, Parrish JA, Parsons D, Harrell LE. (2004). Medical comorbidity in black and white patients with Alzheimer's Disease. *Southern Med J* **97**(1): 2–16.
- Zeliger HI, Pan Y, Rea WJ. (2012). Predicting co-morbidities in chemically sensitive individuals from exhaled breath analysis. *Interdiscip Toxicol* **5**(3): 123–6.
- Zeliger HI. (2013). Lipophilic chemical exposure as a cause of type 2 diabetes (T2D). *Rev Environ Health* **28**(1): 9–20.
- Zeliger HI. (2013a). Lipophilic chemical exposure as a cause of cardiovascular disease. *Interdiscip Toxicol* **6**(2): 55–62.
- Zeliger HI. (2013b). Exposure to lipophilic chemicals as a cause of neurological impairments, neurodevelopmental disorders and neurodegenerative diseases. *Interdiscip Toxicol* **6**(3): 103–10.
- Zeliger HI. *Human toxicology of chemical mixtures*, 2nd ed., (2012). Elsevier, London, pp 40–41.
- Zeliger HI. (2003). Toxic effects of chemical mixtures. *Arch Environ Health* **58**(1): 23–29.
- Zhang Y, De S, Garner JR, Smith K, Wang SA, Becker KG. (2010). Systematic analysis, comparison, and integration of disease based human genetic association data and mouse genetic phenotype information. *BMC Med Genomics* **3**: 1. doi: 10.1186/1755-8794-3-1.
- Ziem G, Donnay A. (1995). Chronic fatigue, fibromyalgia, and chemical sensitivity: overlapping disorders. *Arch Int Med* **155**(17): 1913.