

Review Article

Pesticides and Risk of Obesity and Diabetes

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Abstract

Objective: This study seeks to examine current research evidence and literature linking pesticide exposure with obesity and diabetes.

Study Design and Setting: The review presented here summarizes research studies regarding the association between pesticides and obesity, including diabetes and the metabolic syndrome. Published literature was reviewed between 1996 and 2015. Studies highlighting investigations examining the potential association between pesticides and the outcomes of interest were included.

Results: Although this is not a meta-analysis, a summary of research finding that showed the most studies investigating an association between pesticides and obesity and/or diabetes are presented. Overall, many of the studies demonstrate a positive correlation between pesticide exposure and key measures of these two health conditions (Body Mass Index, Weight, Glycated Hemoglobin (Hemoglobin A1c), Blood Glucose Levels, And Serum Insulin Levels). Likewise, inherent complexities of pesticide chemicals and the multifactorial nature of obesity and diabetes further limit study conclusions.

Conclusions: Literature supports a potential positive association between pesticide exposure and obesity and/or diabetes. However, mechanisms accounting for such an association have yet to be defined, and notable gaps exist in assessing the extent to which an association may exist. In this regard, evidence supports further research to better define these areas.

Abbreviations:

OP	:	Organophosphate pesticides
OC	:	Organ chlorine pesticides
POPs	:	Persistent organic pollutants
BMI	:	Body Mass Index
MB	:	Methanobacteriales
DDT	:	Dichloro diphenyl trichloroethane
DDE	:	Dichloro diphenyl dichloroethylene
PCBs	:	Polychlorinated biphenyls
AHS	:	Agricultural Health Study

Keywords: Diabetes; Metabolic Syndrome; Obesity; Pesticides

Introduction

Several hundred pesticides have been used for centuries throughout various civilizations; yet, their effects on human health remain poorly understood. Each has different mechanisms of action, uptake characteristics, metabolic effects, and elimination features, and likewise, each has varying toxic effects on human health as well. Over the last few decades, associations have been identified between groups of pesticides and specific health conditions. Links between pesticides and neurologic function, immune system function, and endocrine function are increasingly being reported, and these findings help establish foundations for

theories postulating how these chemicals may trigger human disease states. With this in mind, pesticides have been implicated as potential causative factors in two interrelated health disorders, obesity and diabetes [1]. Therefore, this literature review seeks to examine current research evidence supporting the role pesticides may play in these conditions.

By definition, pesticides (Which Include Herbicides and Insecticides) are substances used with the intention to prevent, destroy or control pests, with pests being defined as vectors of disease or unwanted species of plants or animals hindering production [2]. For the sake of organization, pesticides are typically classified based on their chemical structures and/or properties. For example, Organophosphate (OP) pesticides, which are commonly used today in many insecticides, share a common mechanism of action through the disruption of acetyl cholinesterase activity [1]. Organ chlorine (OC) pesticides, which are lipophilic, chlorinated molecules, represent persistent chemicals in the environment of which many have been shown to be associated with serious human health problems [3]. Other pesticides fall into other groups such as bio-pesticides which are derived from animal, plant, and bacterial sources. And still others, like carbamates and pyrethroids, are unique in their formulations and structures and are classified in separate categories [4].

While specific pesticides within each of these categories have unique properties and effects, pesticide groups often share common mechanisms which may be associated with human disease pathogenesis. Research literature has increasingly supported such associations between these various pesticide groups and conditions such as obesity and diabetes [2]. Over the last three decades, obesity prevalence among children and adults has reached epidemic proportions with nearly one-third of adults identified as being obese [5]. Likewise, the number of adults diagnosed with diabetes mellitus has grown in number as well. Currently, more than 11 percent of the U.S. adult population suffers diabetes, and more than 35 percent have prediabetes. Also noteworthy is the fact that in the United States, in 2015, 9.4% (about 30.3 million people of all ages) had diabetes in 2015, in which about 70% of diabetics are either overweight or obese. Population-had diabetes in 2015 (70 percent of all persons with diabetes are concurrently overweight or obese [1,6].

Given these statistics, the rapid increase in the percentage of the population suffering both obesity and diabetes raises concerns about environmental causes. For obesity, dietary and physical activity changes can be attributed as causative agents to a degree, but exposure to environmental chemicals, including pesticides, has been implicated as a potential factor as well. Similarly, diabetes mellitus (particularly Type 2) risk increases with poor diet and physical activity levels, but pesticides have been shown to result in elevated glucose levels, insulin resistance, and concurrent hepatic changes which also heighten the risk for developing diabetes [1].

Objective

In this report, we summarize current research result based on a literature review elucidate current knowledge concerning pesticide exposure and its association with obesity and diabetes mellitus. These findings will be examined in relation to different pesticide categories and based on these distinctions; different theoretical considerations about mechanisms of pathogenesis will also be presented. Likewise, key gaps in research will also be identified to better guide future research in these areas of interest. Through this endeavor, conclusions can be made about our current understanding of pesticides and their role in these specific human health conditions.

Evidence of Pesticide Exposure and Obesity Risk

Literature Review Process

The literature review process involved a widespread search of various databases using a select group of keywords representative of pesticides and obesity. Relevant literature pertaining to subjects'between 1996-2015 were reviewed through abstract assessment. The specific databases through which literature searches were performed included Google, Google Scholar, PubMed/NCBI, EBSCO (Academic Search Premier), SAGE, ELSEVIER, and Questa. Keywords specifically included pesticides, obesity, overweight, organ chlorines, organophosphates, adiposity, environmental chemicals, weight gain, and weight loss.

Organochlorine Pesticides and Obesity Risk

Considering OCs, these organic chemicals are lipophilic in nature and are naturally stored in fatty adipose tissues within the body after exposure. While most OC pesticides have been banned for use in the U.S. and other countries, many OCs persist in the environment due to their lipophilic nature. In addition, bioaccumulation of OCs among top-of-the-chain species occurs which poses ongoing human health risks [3]. Research has demonstrated that persistent organic pollutants (POPs), of which the majority is OCs, remain present in over 80 percent of the population today despite their elimination from use for nearly four decades [7]. Thus, the potential for OCs in causing detrimental health effects remain.

Examining the literature, research linking OC pesticide exposure with obesity risk exist. Wei and colleagues demonstrated a dose-dependent effect of dichlorophenols in relation to obesity among adults after adjusting for age, gender, race, education, total fat intake, and physical activity [8]. Likewise, large national health and nutrition surveys in the U.S. and France have shown concentrations of select OC pesticides to be higher as body mass indices (BMIs) increase in adult subjects [7,9]. Furthermore, other studies have found a positive link between OC metabolites and

childhood obesity [8]. Each of these studies supports positive association between OCs and obesity.

While the association is noteworthy, causation has yet to be well established in the literature. Questions remain regarding whether OC pesticide levels are higher among obese individuals because of increased storage within adipose tissue, or whether OC pesticides in part cause the development of obesity. Hue and coworkers demonstrated the concentration of POPs and OCs measured per gram of adipose tissue between obese subjects and lean controls were comparable suggesting obese individuals have higher OC pesticide levels due to greater volumes of adipose tissue [10]. Notably, however, another study showed that dramatic weight loss in obese subjects resulted in a rise in serum POP levels over 6 to 12 months as adipose tissue declined by 15 percent on average [11]. Weight loss associated with a rise in serum OC pesticide levels was supported in another study of 39 obese subjects placed on a hypo caloric diet. Five of 26 OC pesticides measured showed statistically significant rises in serum levels in these subjects when compared to lean controls.³ Thus, while most of the literature supports a positive correlation between OC pesticide levels and BMI, the association may simply be reflective of OC pesticides' lipophilic nature and greater volumes of adipose tissue among obese individuals in which these chemicals can be biologically stored.

Other Pesticides and Obesity Risk

In addition to research involving OC pesticides and obesity risk, other groups of pesticides have also been studied in relation to weight changes but to a much lesser extent. Specifically, OP pesticides, being non-lipophilic in nature, have received less attention in this area. However, in searching the literature, a relevant study associating the OP pesticide chlorpyrifos and weight gain in rats deserves notice. Moggs and colleagues performed serial weight checks among rats injected with low-level chlorpyrifos as well as controls over a 4-month span. At each serial assessment, injected rats gained statistically significant amounts of weight compared to controls, and the weight gain was attributable to additional adipose tissue and no other organ enlargement [12].

Other categories of pesticides have been evaluated infrequently in relation to obesity risk if at all. Triclosan, a phenolic biocide used to control bacteria and fungi, exists in numerous consumer products including toothpaste, cleaning supplies and soaps. Approximately 75 percent of the population demonstrates detectable levels of triclosan metabolites in their urine [13]. Using data from the National Health and Nutritional Examination Survey from 2003 to 2008, researchers have shown that detectable triclosan levels are associated with a 0.9-point increase in BMI [13]. While these few studies support a relationship between non-OC pesticides and obesity risk, this area specifically has not been well studied to date.

Theoretical Mechanisms for Obesity Risk from Pesticide Exposure

Throughout the literature, several potential pathophysiological mechanisms have been proposed relating pesticide exposure to obesity risk. Among the most prevalent is the theory involving endocrine disruption results from the exposure to various pesticides [3]. Some researchers have suggested pesticides, both lipophilic and non-lipophilic, may affect thyroid hormone levels as well as the hypothalamic-pituitary-adrenal (HPA) axis resulting in changes in appetite, satiety, and food selection [8,14]. Others suggest disruption of estrogen and testosterone functions in addition to disruption of thyroid hormone function [13]. Environmental chemicals have been shown to negatively affect endocrine systems, and this helps support this notion as a leading theory connecting obesity to pesticide exposure [12].

Alternative, or concurrent, theories relating pesticides to obesity risk involve adipogenesis theories. By activating peroxisome proliferator-activated receptor gamma, immature adipocytes might be stimulated to further differentiate leading to progressive risk for obesity [8]. However, limited research of OP pesticides has failed to support this pathophysiological mechanism [12]. Other researchers postulate pesticides trigger diffuse inflammatory changes within the body via the immune system which makes obesity more likely [15]. Obesity has been characterized as a chronic inflammatory state evidenced by higher levels of circulating inflammatory cytokines resulting from an activated innate immune system [5]. Thus, this mechanism represents yet another potential pathway.

One additional intriguing theory relates to pesticide disruption of gut microflora. By disrupting existing intestinal flora, specific bacterial species associated with obesity may gain access to the intestinal lining and replace existing flora [13]. In one study, Lee and coworkers examined 83 women for the presence of methanobacteriales (MB), (a bacterium that prefers petroleum-based environments and has been linked to obesity), and the presence of OC pesticide exposure. Their results demonstrated high correlations between the presence of MB and OC exposures, and likewise both BMI and waist circumference were significantly higher in women with MB present. [16]. In essence, by changing intestinal micro flora, pesticides could potentially enhance weight gain and obesity risks through nutritional pathways.

Evidence of Pesticide Exposure and Diabetes Risk

Literature Review Process

The literature review process involved a widespread search of various databases using a select group of keywords representative of pesticides and diabetes mellitus, both Type 1 [17]. and Type 2. While randomized trials and systematic reviews were favored, all

relevant literature pertaining to the subject between 1996 and 2015 was reviewed through abstract assessment. Those which contributed to the topic were included in this review. The specific databases through which literature search was performed included Google, Google Scholar, PubMed/NCBI, EBSCO (Academic Search Premier), SAGE, ELSEVIER, and Questia. Keywords specifically included pesticides, diabetes mellitus, diabetes, hyperglycemia, organochlorines, organophosphates, environmental chemicals, insulin resistance, and blood glucose.

Organochlorine Pesticides and Diabetes Risk

In examining the literature regarding OC pesticides and diabetes risk, associated conditions of insulin resistance, metabolic syndrome, altered glucose metabolism as well as Type 1 and Type 2 diabetes mellitus were considered. In existing reviews of POPs (of which the majority are OC pesticides), reportedly 75 studies have examined the effects of OC, organ fluorine, and organ bromine pesticides in relation to altered glucose metabolism and diabetes risk.¹Of these, strong associations between diabetes and various OC pesticides exist including dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyltrichloroethane (DDE), and polychlorinated biphenyls (PCBs) [1]. though each of these is no longer used as active pesticides, each persist in the environment and in human beings due to bioaccumulation effects.

In addition to this summative review, others have examined data from the Agricultural Health Study(AHS) which was a prospective study of cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses from Iowa and North Carolina between 1993 and 1997 [18]. With a sample of more than 33,000 participants, studies have found increased incidence of diabetes among agricultural workers using the OC pesticides aldrin, chlordane and alachlor [19]. Likewise, agricultural workers' wives also have heightened diabetes risk when exposed to dieldrin and 2, 4, 5-Trichlorophenoxyacetic acid [20]. In addition, Saldana and colleagues examining over 11,000 pregnant women within the AHS over the course of the study found a positive association between commercial exposure to 2,4,5-Trichlorophenoxyacetic acid and 2,4,5-trichlorophenoxypropionic acid and gestational diabetes (odd ratio = 2.2) [21]. Gestational diabetes is known to be a risk factor for subsequent development of diabetes in later life [22].

The study conducted by Montgomery and colleagues involving the AHS provided some specific statistics for diabetes risk in relation to select OC pesticides. In assessing 50 different pesticides, of which many were OC pesticides, seven OC pesticides were associated with increased risk for diabetes. The ones with the highest risk included heptachlor with a 94% increase in risk; chlordane with a 63% increase in risk; and Aldrin with a 51% increase in risk [19]. Given the number of research studies

examining OC pesticides and diabetes risk, and given the large population samples surveyed, the evidence of the association between exposure to a variety of OC pesticides and the development of diabetes is quite strong.

Organophosphate Pesticides and Diabetes Risk

Though less well studied in terms of diabetes mellitus when compared to OCs, OPs have been assessed in a few studies in relation to diabetes risk. Of those reported, each has demonstrated positive correlations between exposures and risk at least to a degree. The largest reports studies have involved those using AHS data from agricultural workers and their wives. Notable among OPs, dichloros and trichlofon have been identified as being associated with heightened diabetic risk among occupational workers in the AHS study. Increases odds were found for these OPs when examining both ever-use and cumulative lifetime use of these pesticides [19]. Using the same AHS dataset, other researchers examined the wives of agricultural workers who used or were exposed to pesticides. This study also supported an association between OPs and diabetes risk among these women. OPs specifically cited included fonofos, phorate and parathion [20]. Thus, though limited, research does support an association between OPs and heightened diabetes risk when exposure is significant.

A couple of other studies involving agricultural workers also deserve comment in relation to OPs and diabetes risk. Raafat and colleagues evaluated nearly 100 Egyptian farmers over a 20-year period measuring serum Malathion levels (an OP), fasting blood glucose, and fasting insulin levels. Interestingly, higher levels of malathion were associated with evidence of higher levels of insulin resistance over time [23]. Another study involved a comparison of 187 agricultural farmers in Iran with OP exposure with the same number of controls by measuring fasting blood glucose and an oral glucose tolerance test. Both measures demonstrated greater occurrence of diabetes among the farmers [24]. Again, these studies support a positive association between OPs and diabetes.

The only other notable research relating OPs to diabetes risk pertained to examining pesticide exposure to the onset of gestational diabetes. Again, the AHS dataset was used with over 500 women identified as developing gestational diabetes during their pregnancies. Based on self-reported data from these women, several herbicides and insecticides were found to have a significant hazards risk for being associated with gestational diabetes in these participants. Specifically, phorate and diazinon were two OP insecticides found among the seven total agents identified [21]. It is notable to mention that in this same study only women reporting commercial use exposure had such a risk while those with home and gardening exposure did not [21]. This may suggest a dose-dependent effect in relation to this phenomenon.

Other Pesticides and Diabetes Risk

In addition to the major groups of OC and OP pesticides, relatively few have received research attention in relation to diabetes occurrence. One such compound, however, included pyrethroids which are commonly used as insecticides. Hansen and coworkers evaluated 116 pesticide sprayers with primary exposure to pyrethroids in relation to 92 controls who had no exposure. Each participant had HgBA1C measures obtained with an abnormally high HgA1C being greater or equal to 5.6%. Notably, 61% of the sprayers had abnormal HgA1C measures while less than 8% of the controls were affected. These findings led the researchers to correlate cumulative pyrethroid exposure to the development of prediabetes [25].

The remaining literature is relatively scant concerning other pesticides in relation to diabetes risk. In the study conducted by Saldana and colleagues cited previously, carbofuran as well as atrazine and butylate was identified as being associated with higher gestational diabetes risk among farmers' wives exposed to commercial pesticides [21]. Laboratory studies of adipocytes have shown that tolylfuanid, a fungicide, appears to disrupt glucose regulation pathways via a glucocorticoid agonist effect [26]. And while carbamate is well known to cause acute toxicity and affect acetylcholine neurotransmitter function, long-term effects in relation to diabetes risk have not been shown [19].

Theoretical Mechanisms for Diabetes Risk Associated with Pesticide Exposure

Depending on which class of pesticides are considered, varying degrees of research support exist linking these chemicals to diabetes risk. Among these studies, numerous theories have been proposed in terms of etiologic mechanisms, and some of these demonstrate good support for such associations. The most common explanation links various pesticides to insulin resistance. In terms of OPs, some researchers suggest these pesticides activate serine kinases which then result in inhibitory phosphorylation of cellular enzymes. As a result, greater insulin resistance develops within cells [27]. Others have supported similar mechanisms of alterations in enzymatic processes which then cause metabolic changes and insulin resistance [21]. In terms of OCs, persistent organic pollutants in adipose tissue have been proposed to heighten insulin sensitivity and result in altered glucose-insulin homeostasis [11]. And yet other pesticides, such as Malathion and pyrethroids which are known to affect insulin response and glucose regulation, lack clear evidence of association with diabetes risk [23,25]. Thus, while research evidence supports the association of various pesticides with insulin resistance and impaired glucose-insulin regulation, clear mechanisms behind these findings are yet to be well defined.

Other possible theories in this regard relate to altered lipid metabolism and secondary hepatic effects. POPs have been noted

to raise hepatic enzymes, increase lipid levels and lead to liver dysfunction [11]. Several OCs have been associated with elevated hepatic enzymes and liver disease [28]. OPs have been shown to increase glucose release from the liver while also altering lipid metabolism [20]. Though how these chemicals cause these effects are not clear, lipotoxicity and glucotoxicity resulting from hepatic dysfunction is commonly associated with Type 2 diabetes [19]. Therefore, it stands to reason that pesticide effects on the liver may underlie their association with diabetes risk elevation.

The above reflect primary theories behind pesticides and diabetes associations, but additional ones exist and may also play a role in explaining these association, especially in particular pesticide situations. For instance, the fungicide tolylfuanid may disrupt insulin sensitivity and lipid metabolism through agonist effects on glucocorticoid receptors while also promoting adipose cell differentiation [26]. Some have suggested various pesticides may cause autoimmune reactions resulting in Type 2 diabetes mellitus development [27]. And oxidative stress and inflammatory causes have also been proposed via secondary effects on the pancreas, liver and beta-cells [24]. Each of the theories considered in the literature have valid rationales, and many have laboratory support at a minimum. As a result, exact mechanisms linking pesticides to diabetes are likely complex and vary depending on the exact pesticide used, inherent risk of the individual, and other environmental and lifestyle factors.

Discussion and Conclusions

Prior to the mid-twentieth century, the use of pesticides was relatively rare. But subsequent to World War II, the manufacturing and use of these chemicals increased dramatically [3]. Despite the discontinuance of many of these agents due to human health effects, in some instances, bioaccumulation and environmental persistence have resulted in these agents continuing to exert potentially toxic effects [3]. Addition, many health conditions during this same time have risen significantly in incidence suggesting environmental etiologies may be at least partially involved [2]. Two such conditions include obesity and diabetes.

The literature reviewed in this current discussion offers some important considerations related to pesticides, obesity and diabetes. Though not extensive, randomized trials and systematic reviews have been conducted to assess this relationship. The majority, as reviewed, demonstrate positive correlations between specific groups of pesticides with various measures related to either obesity or diabetes. These measures include weight gain, increases in body mass indices, and enlargement of waistline circumferences as well as abnormalities in fasting glucose levels, HgBA1C levels, fasting insulin levels, lipids, and hepatic function [7,11,16,18-21,23,25,26]. Given this information, further research and investigations should be strongly considered to better understand these phenomena.

Unfortunately, efforts to explain areas where insights are lacking are numerous when it comes to both pesticides and these two specific health disorders. First, the number of pesticides are in the hundreds, and while many may be classified according to common mechanisms of action, each has nuances in metabolism, bioavailability, absorption rates, protein binding, side effects and toxicities [2]. Likewise, biomarkers for these chemicals in the human body have yet to be well developed making measurement of exposure challenging at best [1]. Additional problems relate to the conditions of obesity and diabetes since both are multifactorial disorders likely resulting from a complex interaction among numerous genetic and environmental factors [1]. Therefore, the degree to which pesticides may be etiologic, if at all, is difficult to prove. Combine these challenges with a lack of in-depth understanding of age-related changes in human metabolism, detailed immune system functions, glucose homeostasis, and endocrine system interactions, it is understandable why answers from the current research pursuits have been limited [1]. Not only are large samples of study participants required, but advancements in our understanding of these areas is also essential to better identify the relationship between pesticides, obesity and diabetes.

While limitations in the current literature exists concerning these topics, some important insights are noteworthy. The first observation relates to the high number of individuals exposed to pesticides in both developed and developing countries as well as their persistence within human beings due to bioaccumulation effects; [3,24] this observation is most notable with lipophilic pesticides such as OCs, but in several studies, both agricultural workers and their families appear to have high risks for all types of pesticide exposures [19,20,29] Without knowing the effects such pesticides have in relation to obesity, diabetes and other health conditions, this raises concerns specifically from an occupational health perspective.

The other notable observation is the commonality of many of the theories linking pesticides to both obesity and to diabetes risk. Endocrine theories ascribe pesticide effects on the hypothalamic-pituitary-adrenal axis, thyroid function and/or glucocorticoid receptors in accounting for these health conditions [7,8,14]. Immune and inflammatory theories link elevated cytokine levels, heightened oxidative stress, and altered gut flora as potential mechanisms [13]. Theories related to metabolism suggest dysfunctions in glucose homeostasis, liver function, adipose cell differentiation, and cellular functions resulting in insulin resistance may play a role [11,21,24,26,28]. Last, pesticide interference with various neurotransmitters have been proposed as a common pathway by which pathologic changes may occur [1]. Each of these has some support from the literature, and they likewise offer directions for ongoing research.

In summary, current literature supports some associations among numerous pesticides, obesity and diabetes mellitus. Many studies have utilized large sample populations, and some have

utilized effective research methodologies and designs in this endeavor. However, challenges exist due to variability among pesticides, complexities related to obesity and diabetes, and a lack of adequate biomarkers and understanding of potential physiological systems [1]. These will remain research challenges, but despite this, many potential theories relating pesticides to these disorders exist with rationale supports. Given the rapid advancement of obesity and diabetes prevalence, and the widespread exposure of human populations to pesticides, efforts to further elucidate additional insights into these relationships should be pursued. Furthermore, building upon current theoretical frameworks and research evidence is essential to advance this understanding. (Table 1)

Summary:

What is new? An updated review summary of current literature examines the associations between pesticide exposures and two health conditions, obesity and diabetes.

Key findings: Majority of studies available support a potential association between pesticide exposure with the development of obesity and/or diabetes. However, research has significant gaps and limitations in defining mechanisms or causation and extent of an association.

Added knowledge: Current literature suggests pesticide exposure could play a role in the development of obesity and/or diabetes. Multiple theories of causation exist, including endocrine, metabolic, immune and neurotransmitter theories, but none have been validated to date.

Implications: Literature review supports further research in these areas to better define mechanism of causation and degree of risk between pesticide exposure with obesity and/or diabetes development.

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