Review Article

The effect of pesticide exposure on cardiovascular system: a systematic review

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ABSTRACT

Cardiovascular diseases (CVD) are the leading cause of death worldwide and along with traditional risk factors, environmental toxicants should be considered as important risk factors for CVD. However, the contribution of pesticide to CVD is still uncertain. In this systematic review we evaluated the evidence on the association between pesticide exposure and CVD in humans. We conducted a comprehensive methods search using Medline (PubMed), ProQuest, EBSCOhost Medical, Scopus and Google Scholar in October 2014. All studies included were epidemiology studies in humans focused on cardiovascular health effects that were published between 2004 and 2014. We had reviewed 26 papers on cardiovascular diseases with pesticide exposure which most studies documented mixed pesticide exposures but the majority of studies examined the health effects of organophosphate. Eight studies examined the long-term effects of chronic low dose exposure to pesticide while the rest were acute poisoning. Overall, there was little evidence of increased risk of myocardial infarction (MI) and MI mortality but individual pesticide evaluation revealed significantly associated with non-fatal MI. Organochlorine is significantly associated with peripheral arterial disease and stroke. In severe poisonings, general impression is that cardiac abnormalities are common. This systematic review suggests that pesticide exposure is associated with increased risk of CVD and CVD mortality. We hope our results will stimulate further evaluation of CVD incidence and mortality in pesticide-exposed cohorts.

Keywords: Pesticide, Cardiovascular, Health effect, Acute poisoning, Chronic exposure

INTRODUCTION

In recent years, cardiovascular diseases are the leading cause of death worldwide.¹ Although since the 1970’s cardiovascular mortality rates have declined in many high-income countries, in 2008, it is reported that 30% of all global death is attributed to cardiovascular diseases.² Dyslipidemia, hypertension, diabetes mellitus and unhealthy lifestyle such as smoking, physically inactive and high cholesterol dietary intake have been appropriately highlighted as established predictors of cardiovascular disease.³ Apart from these fundamental risk factors, environmental toxic substance including pesticides may affect novel pathways of risk such as inflammation and oxidative stress.⁴ Thus, environmental toxicants should be considered as important risk factors for cardiovascular disease. However, after some time since initial reports suggested a link between pesticide exposure and cardiovascular outcomes, the contribution of pesticide to cardiovascular disease is still uncertain.⁵

Pesticide exposure

Pesticides are widely used for agricultural, municipal, home and medical purposes worldwide. Pesticides exposure at certain development of life stages can result in irreversible damage to organ structure and function.
Farmworkers are the population most exposed to pesticide. A previous study found that 72 percent of rice farmers experienced poisoning symptoms when handling pesticide. Occupational exposure to pesticides often occurs in the case of agricultural workers in open fields and greenhouses, workers in the pesticide industry, and home pest exterminators. Nonetheless, it is not just farmers who are exposed to pesticide. Farmworker households are also exposed to this chemical as they live near or on the farms and spend much of their time in close proximity to areas where pesticides are applied on a regular basis. They may also be exposed to pesticide residues brought home by farmworkers on their shoes, clothes and skin; from nearby applications that drift or are directly sprayed on outdoor play areas; and from chemicals used to control pests in and around the home, especially in poor quality housing.

In general population, exposure to pesticides occurs mostly through eating food and drinking water contaminated with pesticide residues, whereas substantial exposure can also occur in or around the home. The exposure is characterized by low dose exposure repeated over time. However, acute high dose exposure may also occur in suicidal cases.

The primary routes by which pesticides enter the body are ingestion in food, soil, or water; inhalation, through the skin, and through the eyes. Dietary ingestion is a significant source of exposure, especially for infants and children. The residue monitoring program conducted by the Food and Drug Administration (FDA) in 2003 found measurable levels of pesticides in baby foods, including dichlorodiphenyltrichloroethane (DDT) (6% of samples), captan + Tetrahydrophthalimide (a possible carcinogen) (9%), carbaryl (carbamate) (6%), endosulfan (9%), dimethoate (4%), malathion (3%), and chlorpyrifos (all organophosphates) (2%).

In infants, they can be exposed postnatally to pesticides via breast feeding. For instance, persistent organic pollutants (POPs) are still found in breast milk despite having mostly been banned because they are stored in body fat. Apart from that, postpartum weight loss increases the likelihood of the release of POPs into the breast milk. There is some evidence that the maternal body burden is transferred to her children via breast feeding which the pesticide concentrations may decrease with the more number of times a mother has breastfed.

**Pesticide use and its health effect**

Humans are exposed to pesticides, and due to their toxic properties, the consequences of this exposure on humans are being established. Exposure to pesticides at any point in the life cycle has the potential for causing a range of short-term or long-term health problems. Documented health effects include a wide variety of illnesses and diseases, from local effects such as dermatitis and eye irritation to systemic effects such as respiratory problems, neurological damage, birth defects, cancer and death.

The risk and severity of adverse health effects from pesticide exposure varies significantly depending on the toxicity of the pesticide, the measures taken during its application, the dosage applied, exposure circumstances and individual characteristics such as age and health status.

In agriculture, the chemicals used to control pests such as, any unwanted weeds, insects, fungi, rodents and snails vary widely in their target organism and modes of action. These include insecticides, rodenticides, herbicides, fungicides, mollusticides and more. As their biological mechanisms are different, the resulting effects on human health and the environment may also differ.

One of the most potent pesticides is organochlorine (OC) insecticides which are central nervous system stimulators. OCs are classified as persistent organophosphates (POPs), because instead of breaking down rapidly over time, they build up in the environment particularly in soil and in the fatty tissues of wild and domesticated animals. Its half-life in soil can range from months to decades. Over time, OCs accumulate in the food chain, ultimately settling in humans at the end of the food chain. As OCs have tendency to bioaccumulate and cause damage to the environment, most POPs were banned through an international treaty in 2001.

Because of the fact that most of OC pesticides were banned, other types of pesticides came into wide spread use. The largest group of insecticides currently used worldwide includes the organophosphates (OPs), which have both agricultural and residential uses. Unlike OCs, OPs are non-persistent pesticides, which break down in the environment, and do not accumulate in the body over a long period of time. However, OPs are highly toxic to humans and are involved in many poisoning cases in the world. Other than OPs, carbamates and pyrethroids which are neurotoxic are also included in non-persistent pesticides and both have similar effects on human health as the OPs.

Herbicides are also widely used in agriculture to control unwanted plant growth. They have different mechanism of action from insecticides. The most common health effect is irritation to skin and respiratory tract. Nonetheless, acute exposure to highly corrosive herbicides such as paraquat can cause multi-system injury and pulmonary failure. Exposure to multiple pesticides that share a common mechanism can increase their specific toxicity while exposure to more than one class of pesticide at a time may amplify the negative health effects.

As randomized controlled trials on the health effects of potentially harmful chemicals cannot be conducted and because of the limitations innate in observational studies,
there is still uncertainty about the effects of pesticides on human health. There are numerous studies on the effect of pesticide exposure on the human chronic diseases, including cancer, Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, diabetes, aging, and chronic kidney disease but there are only a small number of studies carried out to prove the relationship between pesticide exposure and cardiovascular diseases. Therefore, this paper reviews the state of the research on the cardiovascular health effects of pesticide exposure.

**REVIEW METHODS**

**Search methods**

A comprehensive search using Medline (PubMed), ProQuest, EBSCOhost Medical, Scopus and Google Scholar was undertaken. Keywords used to search for relevant literature included ‘pesticide’, ‘cardiovascular’, and ‘health effect’. In addition, back referencing and citation searching of the selected studies was undertaken. Limits were set at studies published in English or that had an English translation.

Of the 452 articles on health effects of pesticides identified by literature search, 53 articles were on cardiovascular effects, 26 articles were epidemiological studies including cross sectional, cohort and ecological studies that were retrieved for detailed assessment (Figure 1).

**RESULTS**

**Description of included studies**

We reviewed 26 papers on cardiovascular disease with pesticide exposure and 21 met the quality criteria for inclusion. The results of the review are presented in Table 1. With respect to the geographical composition of our sample, most of the research on the cardiovascular effects of pesticide was conducted in the United States (30% of the studies). 20% of the studies were carried out in India while the rest of the studies in the sample were from South Korea, Turkey, Japan, Malaysia, Denmark, Sweden, Nepal and Iran.

The size of the study population varied from 20 to 57, 311 individuals. Some of the articles were based on cohort studies. The target populations and definitions of the outcome of cardiovascular health effects varied across the studies. Eleven of the studies on the outcome of electrocardiographic (ECG) findings were conducted among patients who were diagnosed with acute pesticide poisoning. Four studies concerned pesticide applicators only, whereas two studies dealt with civilians and two studies dealt with mix pesticide applicators with their householdmembers.

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**Study selection**

Inclusion criteria required that studies’ outcome was the health effect related to pesticide exposure and their citations regarding pesticide exposure and cardiovascular disease. All health effects had to focus on cardiovascular risk or complication. In addition, all studies had to be published in a peer-reviewed journal or under a similar peer reviewed process such as a dissertation. All studies included were epidemiologic studies that were published between 2004 and 2014.

We excluded studies which had multiple co-exposures involved or studies of pesticide applicators without information on which pesticides were used and whether other chemical contamination was possible. Animal studies and studies performed in human cells also have been excluded. We had no population or geographical restrictions.

To enhance totality of the evidence, all types of pesticides have been considered. Exposure to pesticides was defined as reported use of pesticides by the study participant or by government registry data (self-administered questionnaires, interviewer administered questionnaires, job exposure matrix), by residential status (proximity to pesticide exposure), by detecting biomarkers associated with pesticide exposure or by any other means as defined by each study.
Table 1: Evidence of association between exposure to pesticide and cardiovascular risk and complication.

| Location/Outcome                          | Subject                                           | Study Design       | Pesticide                                             | Result                     | Reference                  |
|------------------------------------------|---------------------------------------------------|--------------------|-------------------------------------------------------|---------------------------|---------------------------|
| Iowa and North Carolina/myocardial infarction | Female spouses of applicators (n = 23,703) and Female applicators (n = 912) | Cohort             | Chlorpyrifos                                          | 2.1 (1.2, 3.7)            | Dayton et al., 2010[26]    |
|                                          |                                                   |                    | Coumaphos                                             | 3.2 (1.5, 7.0)            |                           |
|                                          |                                                   |                    | Carboturan                                            | 2.5 (1.3, 5.0)            |                           |
|                                          |                                                   |                    | Metaxyl                                               | 2.4 (1.1, 5.3)            |                           |
|                                          |                                                   |                    | Pentamethalin                                          | 2.5 (1.2, 4.9)            |                           |
|                                          |                                                   |                    | Trifluralin                                           | 1.8 (1.0, 3.1)            |                           |
|                                          |                                                   |                    | Ethylene dibromide*                                    | 1.54 (1.05, 2.27)         | Mills et al., 2009[20]    |
|                                          |                                                   |                    | Mancozeb*                                              | 1.34 (1.01, 1.78)         |                           |
|                                          |                                                   |                    | Aldrin*                                               | 2.40 (1.49, 3.86)         |                           |
|                                          |                                                   |                    | DDT*                                                 | 1.20 (1.01, 1.43)         |                           |
|                                          |                                                   |                    | 2,4,5-T*                                               | 1.24 (1.04, 1.46)         |                           |
|                                          |                                                   |                    | *associated with MI mortality                         | 1.21 (1.03, 1.43)         |                           |
|                                          |                                                   |                    | 1*associated with nonfatal MI incidence                |                           |                           |
| Iowa and North Carolina/myocardial infarct | Male pesticide applicators (n = 57,311)            | Cohort             | Organochlorine                                        | Bootstrap CR = 1.15, (-0.035, 0.116) Bootstrap p = 0.043 | McCaffrey et al., 2008[22]|
|                                          |                                                   |                    | - polychlorinated biphenyls (PCBs)                    |                           |                           |
|                                          |                                                   |                    | - hexachlorobenzene                                    |                           |                           |
|                                          |                                                   |                    | - p,p'-DDE                                             |                           |                           |
|                                          |                                                   |                    | - mirex                                               |                           |                           |
| Akwesasne, New York/Serum lipids and cardiovascular disease | Native Americans of the Mohawk Nation (n = 277)     | Cohort             | Organophosphate                                       | Mean: 890.93 vs 990.48 U/ml |                           |
|                                          |                                                   |                    | Lower diazoxonase activity                            | Median: 4.89 vs 2.83 mU/L |                           |
|                                          |                                                   |                    | Higher ox-LDL among the organophosphate - exposed group |                           |                           |
| Kuantan, Malaysia/coronary artery disease | Pesticide sprayers (n = 103)                       | Comparative cross sectional | Chlorophenoxy herbicides                               | 1.08 (1.04, 1.12)         | Zamzila et al., 2011[11]  |
|                                          |                                                   |                    | - Mortality from IHD                                  | 1.20 (1.14, 1.26)         |                           |
|                                          |                                                   |                    | - Mortality from AMI                                  | 0.89 (0.83, 0.96)         |                           |
|                                          |                                                   |                    | - Mortality from CAS                                  | 1.16 (1.08, 1.24)         |                           |
|                                          |                                                   |                    | - Mortality from type 2 DM                            |                           |                           |
| Rural agricultural counties of Minnesota, Montana, North Dakota, and South Dakota/ischemic heart disease and diabetes mortality | Farming communities in wheat-producing states (n = 152 counties) | Ecological study | Chloroalkanes                                          | 1.47 (1.08, 1.99)         | Schreinemachers, 2006[27] |
|                                          |                                                   |                    | - trans-nonachlor                                      | 1.68 (1.10, 2.56)         |                           |
|                                          |                                                   |                    | Oxochlordane                                          | 1.82 (1.09, 3.03)         |                           |
|                                          |                                                   |                    | Dieldrin                                              | 2.36 (1.69, 3.31)         |                           |
|                                          |                                                   |                    | β-HCH                                                 | 1.37 (0.80–2.35)          |                           |
| United States/peripheral arterial disease | Civilian non-institutionalized U.S. Population (obese persons) (n = 2032) | Comparative cross sectional | Organochlorine                                        | 1.47 (1.08, 1.99)         | Min et al., 2010[24]      |
|                                          |                                                   |                    | - p,p'-DDE                                             | 1.68 (1.10, 2.56)         |                           |
|                                          |                                                   |                    | - trans-nonachlor                                      | 1.82 (1.09, 3.03)         |                           |
|                                          |                                                   |                    | - Oxochlordane                                        | 2.36 (1.69, 3.31)         |                           |
|                                          |                                                   |                    | - Dieldrin                                             | 1.37 (0.80–2.35)          |                           |
| United States/cardiovascular disease     | Noninstitutionalized U.S. civilian population (n = 889) | Cross sectional | Dioxin-like PCBs                                      | 2.0 (0.5, 7.6)            | Ha et al, 2007[25]        |
|                                          |                                                   |                    | Nondioxin-like PCBs                                    | 1.2 (0.4, 4.2)            |                           |
|                                          |                                                   |                    | OC pesticides                                         | 1.7 (0.4, 7.1)            |                           |
| Iowa and North Carolina/stroke mortality | Private pesticide applicators (n = 51,603)         | Cohort             | 50 commonly used pesticide                            | 0.91 (0.52, 1.58)         | Rinsky et al., 2013[22]   |
|                                          |                                                   |                    | - High pesticide exposure event                        | 1.73 (0.77, 3.92)         |                           |
|                                          |                                                   |                    | - Diagnosed pesticide-poisoning event                  |                           |                           |
| Uppsala, Sweden/stroke mortality         | Participants aged 70 years (n = 898)               | Cohort             | Polychlorinated biphenyl                              | 0.8 (0.2–2.5)             | Lee et al., 2012[23]      |
|                                          |                                                   |                    | - p,p'-DDE                                             | 1.2 (0.4–3.4)             |                           |
| Study Location | Case Description | Study Design | Exposure | Key Findings | Reference |
|----------------|------------------|--------------|----------|--------------|-----------|
| Wonju Severance Christian Hospital, South Korea/myocardial injury | Organophosphate patient (n = 99) | Cross sectional | Organophosphate insecticide | ST depression and elevation (11.1%) Elevation of Troponin I within 48 h (34.3%) | Cha et al., 2014 |
| Chandigarh, India/cardiac abnormality | Patient with acute Organophosphate poisoning (n = 36) | Cross sectional | Organophosphate - dimethoate - monocrotophos - methylparathion - chlorpyrifos - phorate - malathion - mixture | Cardiac discoloration or blotchiness (33.3%) Patchy pericarditis (16.7%) Auriculmonary thrombus (16.7%) Right ventricular hypertrophy (11.1%) Myocardial interstitial edema and vascular congestion (36.1%) Patchy interstitial inflammation (22.2%) Mural thrombus (16.7%) | Anand et al., 2009 |
| Turkey/ECG findings | Patients with organophosphate poisoning (n = 85) | Cross sectional | Organophosphate | Mean corrected QT interval = 0.435 ± 0.052 s Prolongation of the QTc interval (55.5%) Sinus tachycardia (31.8%) Elevation of the ST segment and low amplitude T waves (17.6%) | Yurumez et al., 2009 |
| Andhra Pradesh, India/ECG findings | Patients with organophosphate poisoning (n = 20) | Cross sectional | Organophosphate | Prolonged QTc interval >0.43 s (60%) Mild elevated ST segment and low amplitude T waves (40%) | Vijayakumar et al., 2011 |
| Gumma Prefecture, Japan/Long QT and ST-T change | Patients with organophosphate poisoning within 24 hour of exposure to aerial spray of organophosphate pesticide (n = 39) | Cross sectional | Organophosphate | Prolonged QTc interval >430 ms (56%) Nonspecific ST-T change (90%) Supraventricular arrhythmia (33%) | Kumiko et al., 2006 |
| Changwon, South Korea/Corrected QT interval | Patients with acute glyphosate-surfactant ingestion (n = 153) | Cross sectional | Glyphosate-surfactant herbicide | QTc interval Survivors: 453.4 ± 33.6 ms Nonsurvivors: 542 ± 32.0 ms (p < 0.001) | Yong et al., 2014 |
| Kisanganj, India/ECG manifestation | Patients with organophosphate poisoning (n = 107) | Cross sectional | Organophosphate | Prolonged Q-Tc interval (62.6%) Sinus tachycardia (33.6%) Sinus bradycardia (30.8%) ST elevation (25.2%) T inversion (19.6%) First-degree heart block (8.4%) Atrial fibrillation (4.6%) | Paul, Bhattachary 2012 |
| Nepal/cardiac complication | Patients with organophosphate and carbamate poisoning (n = 107) | Cohort | Organophosphate Carbamate | Sinus tachycardia (40.5%) Prolonged Q-Tc interval (37.8%) ST-T changes (29.7%) Non-cardiogenic pulmonary oedema (21.6%) Sinus bradycardia (18.9%) Hypertension (13.5%) Hypotension (10.8%) | Karki et al., 2004 |
| Study Area/Adverse Effect | Patients with Organophosphorous Poisoning (n) | Study Design | Pesticide Type | Study Findings | Authors and Year |
|---------------------------|-----------------------------------------------|--------------|----------------|----------------|------------------|
| Kayseri, Turkey/Poisoning severity score (PSS), Glasgow coma scale, QTC interval | Patients with organophosphorous poisoning (n = 54) | Cross sectional | Organophosphate | Prolonged QTc interval (48.1%) Mean PSS of men and women = 1.8 +/- 1.0 No significant correlation between PSS and QTc intervals | Akdur et al., 201036 |
| Beijing, China/Cardiac abnormalities | Patients with severe acute dichlorvos poisoning (n = 92) | Cohort | Dichlorvos | Sinus tachycardia (90.2%) ST-T changes (80.4%) | He et al., 201128 |
| Guilan, Iran/Electrocardiographic Findings | Patients with organophosphorous poisoning (n = 100) | Cross sectional | Organophosphate | Sinus tachycardia (31%) Nonspecific ST-T change (24%) | Taromsari et al., 201343 |
| Hyderabad, India/ECG manifestations | Patients with organophosphorous poisoning (n = 112) | Cross sectional | Organophosphate | Bradycardia (14.9%) Tachycardia (12.6%) ST elevation (10.3%) T inversion (11.5%) Prolonged P-R interval (8.0%) Atrial fibrillation (5.7%) Prolonged Q-T interval (17.2%) Ventricular tachycardia (8.0%) Mix finding (11.5%) | Balouch et al., 201258 |

**Pesticide exposure**

As in most of the studies on pesticide, the authors made great efforts to measure exposure in a range of ways, since there is no single biomarker for chronic exposure for the full spectrum of frequently used pesticides. The American studies used an algorithm to estimate long-term chemical-specific pesticide exposures while ten studies that examined the outcome of ECG findings used history of exposure to OPs within 24 hours, clinical effects, and serum cholinesterase activity.20,22,24,25

An ecological paper assigned exposure according to the wheat acreage per county or percentage of the county’s land area dedicated to wheat farming as a surrogate measure of exposure to chlorophenoxy herbicides, because information on herbicide use by county was not available.27 Use of this surrogate exposure measure was a reasonable choice because chlorophenoxy herbicides are the predominant herbicides applied to wheat. The rest of studies used subjects’ occupational information to measure pesticide exposures.

Most studies documented mixed pesticide exposures but the majority of studies examined the health effects of OPs which twelve out of thirteen studies that involved OPs focused only on OPs such as Chlorpyrifos, Coumaphos, Monocrotophos, Dichlorvos and Malathion.28 Other than that, the insecticides involved in these studies were OCs which were Aldrin, Dieldrin, trans-nonachlor, dichlorodiphenyltrichloroethane (DDT), Oxychloridane, β-hexachlorocyclohexane (β-HCH) and p,p’-Dichlorodiphenyldichloroethylene (p,p’-DDE); and also carbamate which was Carbofuran. The rest of the pesticides involved were herbicide such as Pendimethalin, Trifluralin, Chlorophenoxy and Glyphosate-surfactant, fungicide which were Metalaxyl, Mancozeb, and Ziram; and fumigant which was Ethylene dibromide.27-29

**Cardiovascular effects of pesticide exposure**

There were eight studies that examined the long-term effects of chronic low dose exposure to pesticide. Three of them looked into the outcome of myocardial infarction (MI),20,26,27 Overall, there was no significant association or little evidence of increased risk of MI mortality or non-fatal MI with the occupational use of pesticides. However, when they evaluated the individual pesticides, they were significantly associated with non-fatal MI, including chlorpyrifos, coumaphos, carbofuran, metaflaxyl, pendimethalin, trifluralin, Aldrin, DDT, and 2,4,5-Trichlorophenoxyacetic acid which all had odds ratios greater than 1.2 whereas Ethylene dibromide, Mancozeb, Ziram and Chlorophenoxy herbicides were significantly associated with MI mortality with odds ratios ranging from 1.2 to 2.4.

In this review, there was an article that found a significant association between OPs and the risks of coronary artery disease. Zamzila N et al, 2011 demonstrated that subjects who were exposed to OPs had lower diazoxonase activity and higher oxidized-LDL level compared to non-exposed group.21 In contrast, Schreinemachers 2006 illustrated that mortality from coronary artery disease in high-wheat counties which have higher exposure to Chlorophenoxy herbicides.
decreased with Poisson relative risks of 0.89 compared with low-wheat counties.

Apart from that, there was a study that examined the link between OC pesticides with peripheral arterial disease. Min et al, 2010 found that high levels of OC pesticides (p,p’-DDE, trans-nonachlor, oxychlordane, and dieldrin) and high sum of the five OC pesticide levels were significantly associated with the development of peripheral arterial disease and that obesity adversely modulates serum levels of these compounds.

For stroke complication, there were inconsistent results between studies which Lee et al, 2012 did a large cohort study on agricultural exposures to look for development of stroke in the elderly. They demonstrated that polychlorinated biphenyl pesticides which were trans-nonachlor and octachlorodibenzo-p-dioxin were significantly associated with stroke and the odds ratios was 1.2 and 2.1 respectively. This was contrary to Rinsky et al, 2013 who found that there was no evidence of an association between pesticide use and stroke mortality.

We found eleven papers that focused exclusively on electrocardiographical manifestations of acute OP poisoning. Out of eleven papers, ten studies found prolonged corrected QT (QTc) interval as the main ECG finding. Other than that, sinus tachycardia and ST elevation were the most common findings. Anand et al, 2009 examined cardiac abnormalities in acute OP poisoning and revealed that there were cardiac discoloration or blotchiness, patchy pericarditis, auricular thrombus, right ventricular hypertrophy, myocardial interstitial edema, vascular congestion, patchy interstitial inflammation and mural thrombus.

Information on confounders was available and the important confounders in cardiovascular study are exposures that cause atherosclerosis such as smoking, alcohol consumption, diet, and physical inactivity. Most studies measured all confounders; most excluded smokers and some studies did stratified analysis for obese subjects. All of the articles applied quantitative methods. Some used different regression analysis techniques. However, confounding factors related to agricultural work such as biological exposures including animal viruses and heavy metals were not controlled for in any of the studies.

**DISCUSSION**

In general, the epidemiologic evidence supports an association of pesticide exposure with cardiovascular disease (CVD) involving the heart primarily for instance, myocardial infarction and less so with cerebrovascular disease. Studies that were not included in the main analysis such as animal studies and recent reviews provide additional information on the possible nature of the relationship between pesticide exposure and CVD.

Although cross-sectional and ecologic studies are not ideal for informing the quantitative dose–response assessment for CVD, they should be considered in the overall weight of evidence. An ecologic study of CVD mortality 1979–1988 and 1989–1998 for Minnesota, Montana, North Dakota, and South Dakota highlights the importance of average versus peak exposures over time. Mortality risks were elevated for all circulatory diseases which are ischaemic heart disease, myocardial infarction, type 2 diabetes mellitus, but not for coronary artery disease. Mortality rate for ischaemic heart disease, myocardial infarction and coronary artery disease in 1979 - 1988 for both male and female were higher than for subjects in 1989 - 1998 (decreased more than 30%). This might be due to improved dietary patterns and treatment, decreased smoking, and increased physical activity.

Chronic pesticide exposure particularly OPs and OCs classes is found to potentiate the risk of coronary artery disease. This has been demonstrated by Zamzila et al, 2011 and supported by an animal study by Lasram et al, 2009 which explained that chronic exposure to OPs pesticides will diminish paraoxonase (PON1) activity. OPs are hydrolyzed by paraoxonase (PON1) which is a high density lipoprotein (HDL) associated enzyme known for its function to hydrolyze OPs into a relatively harmless substance. PON1 is also known to prevent atherosclerosis by hydrolyzing oxidized-low density lipoprotein (ox-LDL) as well as preventing the accumulation of lipid peroxides on LDL. The study showed that there was low PON1 activity among OPs-exposed individuals, while low PON1 activity was associated with a high risk of coronary artery disease.

The association of pesticides with atherosclerosis have also been studied by Jin Young et al, 2011 who reported that organochlorine (OC) pesticides are a potent risk factor for peripheral arterial disease while McCaffrey et al, 2008 illustrated that polychlorinated biphenyls (PCBs) are directly involved in increased synthesis of cholesterol and triglycerides, substances known to be major risk factors for cardiovascular disease.

Other than that, OCs were also found to have association with cerebrovascular disease. A prospective study by Lee et al, 2012 found that individuals with elevated levels of pesticide which were polychlorinated biphenyl (PCBs) and DDT in their blood run a greater risk of having a stroke. The researchers compared participants’ levels of pesticides to the health of their arteries, measured by the amount of plaque build-up in the carotid artery.

Various ECG changes have been described in acute OP poisoning. Prolonged QTc interval is the commonest abnormality and was observed in eight papers. The QT interval on the ECG, measured from the beginning of the QRS complex to the end of the T wave, represents the duration of activation and recovery of the ventricular myocardium. A QT interval corrected for heart rate (QTc) that is longer than 0.44 seconds is generally considered to
be abnormal. The QT interval represents the duration of activation and recovery of the ventricular myocardium. Prolonged recovery from electrical excitation increases the likelihood of dispersing refractoriness, when some parts of myocardium might be refractory to subsequent depolarization.\textsuperscript{35} In animal experiments, prolongation of the QT interval is a direct myocardial pesticide effect and is independent of cholinergic effects.\textsuperscript{34}

Other common cardiac manifestations include sinus tachycardia. Sinus tachycardia occurs as a result of intense sympathetic stimulation, nicotinic stimulation of ganglionic sites by excess acetylcholine, atropine administration, and dehydration.\textsuperscript{35} However, sinus tachycardia is a non-specific ECG abnormality with many causes such as electrolyte disturbances, acidosis, hypovolemia and hypoxemia.

Autopsy and microscopic examination of the heart found patchy myocardial involvement as a result of direct cardiac toxicity. As myocardial involvement is patchy, it may not manifest clinically or on echocardiography. However, the general impression is that in severe poisonings cardiac abnormalities are common. To detect these dynamic cardiac changes, some form of continuous cardiac monitoring seems advisable.

**Limitations**

The major limitation of studies of the health effects of pesticides is their inability to demonstrate cause-effect relationships. Study subjects cannot be deliberately exposed to potentially harmful toxins, and few exposure reduction options are tested in randomized controlled trials. The evidence generated by well-constructed clinical and epidemiologic observational studies is the highest level of evidence we can ethically obtain. The studies reviewed might have methodological problems, such as exposure misclassification, inadequate exposure assessment and recall bias in retrospective comparative studies. Furthermore, unpublished literature on cardiovascular health effects that was not accessed would be useful to determine whether there is a publication bias toward positive studies. The effect of unpublished positive or negative studies generated by chemical industry–funded research also cannot be assessed.

Most studies on ECG findings were retrospective study and involved only one hospital. As a result, not all relevant assessment parameters could be included. In particular, the ingested amount of pesticide and the environmental department arrival time after ingestion may be overestimated or underestimated. Apart from that, since the exact percentages of OP, solvent, and surfactant are unknown, their clinical influence could not be predicted. In addition, studies involving populations with more constant, long-term exposure are therefore preferable for evaluating health-protective doses for CVD.

**Recommendations**

Health care providers are in an ideal position to identify and assess a patient’s risk for exposure. The environmental history that covers residential and employment histories, types of work activities performed currently and in the relevant past, and possible sources of exposure to biological or chemical agents are essential step to be obtained. For each exposure source identified, additional information needs to be collected, such as frequency, duration, and intensity.

Occupational exposure is almost certainly the primary source of exposure for farmworkers and their families. Therefore, awareness of the ways in which pesticide exposure occurs and the danger it poses are a crucial component of comprehensive care for farmworkers.

Education about pesticide safety is an important measure for preventing exposure. Spouses living in farmworker households should be offered additional education on ways they and the farmworkers with which they live can reduce take-home exposure such as remove work clothes and shoes before entering the home; shower or bath upon returning home and before touching other people; and store and launder dirty work clothes separately from other clothing.

**CONCLUSION**

This systematic review provides clear evidence that pesticide exposure increases risk to human health across a range of exposure situations and vulnerable populations. The results of this systematic review suggest that pesticide exposure is associated with increased risk of CVD and CVD mortality. We hope our results will stimulate further evaluation of CVD incidence and mortality in pesticide-exposed cohorts, especially using internal comparisons with detailed exposure assessments, and careful control for confounding factors.

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