Environment International 76 (2015) 57–70

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review

Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: A systematic review

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ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 3 December 2014
Accepted 4 December 2014
Available online 26 December 2014

Keywords:
Diabetes
Insulin resistance
Beta-cell function
Asia
Persistent organic pollutants
Non-persistent pesticides

ABSTRACT

Background: Over half of the people with diabetes in the world live in Asia. Emerging scientific evidence suggests that diabetes is associated with environmental pollutants, exposures that are also abundant in Asia.
Objective: To systematically review the literature concerning the association of persistent organic pollutants (POPs) and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia.
Methods: PubMed and Embase were searched to identify studies published up to November 2014. A secondary reference review of all extracted articles and the National Toxicology Program Workshop on the association of POPs with diabetes was also conducted. A total of 19 articles met the inclusion criteria and were evaluated in this review.
Results: To date, the evidence relating POPs and non-persistent pesticides with diabetes in Asian populations is equivocal. Positive associations were reported between serum concentrations of polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and several organochlorine pesticides (DDT, DDE, oxychlordane, *trans*-nonachlor, hexachlorobenzene, hexachlorocyclohexane) with diabetes. PCDD/Fs were also associated with blood glucose and insulin resistance, but not beta-cell function. There were substantial limitations of the literature including: most studies were cross-sectional, few studies addressed selection bias and confounding, and most effect estimates had exceptionally wide confidence intervals. Few studies evaluated the effects of organophosphates.
Conclusions: Well-conducted research is urgently needed on these pervasive exposures to inform policies to mitigate the diabetes epidemic in Asia.

Contents

Abbreviations: BMI, body mass index; CHLs, chlordanes; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EOI, exposure opportunity index; FBG, fasting blood glucose; GIS, geographic information system; GC, gas chromatography; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HRGC, high-resolution gas chromatography; HRMS, high-resolution mass spectrometry; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; MESH, medical subject heading; NA, not applicable; OC, organochlorine; OCDD, octa-chlorodibenzo-p-dioxin; OGTT, oral glucose tolerance test; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCP, pentachlorophenol; PCQs, polychlorinated quarterphenyls; POPs, persistent organic pollutants; PPAR, peroxisome proliferator-activated receptor; QUICKI, quantitative insulin sensitivity check index; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TEQ, toxic equivalent concentration; VAT, visceral adipose tissue.

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http://dx.doi.org/10.1016/j.envint.2014.12.001
0160-4120/

1. Introduction

Rapid agricultural and industrial development over the past 50 years in Asia has led to high exposure levels of potentially toxic chemicals including persistent organic pollutants (POPs) and non-persistent pesticides (pyrethroids and organophosphates). Over half of regional pesticides (including herbicides, insecticides, and fungicides) are used in China, but per hectare of agricultural land, Korea takes the lead at over 50 kg formulated product per hectare agricultural land compared to just over 25 kg formulated product per hectare agricultural land in Malaysia, the second highest consumer per hectare in the region (Food and Agriculture Organization of the United Nations, 2005). Reported pesticide use in India is much lower at less than 5 kg formulated product per hectare agricultural land (Food and Agriculture Organization of the United Nations, 2005). However, in regard to insecticide use for vector control (largely malaria prevention), India accounted for 82% of global use of dichlorodiphenyltrichloroethane (DDT) between 2000 and 2009: over the 10-year period of observation, 3623 metric tons of DDT were used for indoor residual spraying in India compared to only 805 metric tons in all of Africa (Berg et al., 2012).

Concurrent with these increases in chemical exposure, the prevalence of diabetes has increased rapidly in Asia. In 2000, the prevalence of diabetes in China was just 2.7% and in India 5.8% (International Diabetes Federation, 2000). By 2013, these numbers had jumped to 9.6% and 8.6%, respectively (International Diabetes Federation, 2013). Today, 43% of the 382 million adults with diabetes in the world live in just two Asian countries: 98.4 million people in China and 65.1 million people in India (International Diabetes Federation, 2013). While scientific evidence has pointed to changes in dietary intake and physical activity as key culprits in this epidemic (Popkin et al., 2001), the role of non-traditional risk factors such as environmental pollutants remains an emerging area of diabetes research.

The state of the evidence linking POP exposure to diabetes was summarized during a U.S. National Toxicology Program Workshop conducted in January 2011 (Thayer et al., 2012; Taylor et al., 2013). The primary conclusion of the Workshop was that evidence is sufficient to support an association of some organochlorine POPs, particularly *trans*-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyl (PCB) congener 153, and dioxins, with type 2 diabetes (Taylor et al., 2013). While not sufficient to establish causality, the Workshop findings were further supported by a recent meta-analysis and systematic review on the same topic: the first concluded that hexachlorobenzene (HCB) and total PCBs, but not DDE or DDT, are significantly associated with type 2 diabetes (Wu et al., 2013), and the second concluded that dioxins, PCBs, and HCB were associated with the disease (Magliano et al., 2014). More recently, researchers in Belgium confirmed that PCB congener 153, total PCBs, and DDE are significantly associated with abnormal glucose tolerance by oral glucose tolerance test (OGTT) among obese individuals (Dirinck et al., 2014).

Experimental studies in mice and rats tend to support that chronic exposure to low doses of POPs fed as part of fish oil or salmon filets impairs insulin-mediated glucose uptake in muscle and adipose tissue (Ruzzin et al., 2010; Ibrahim et al., 2011). More specifically, for example, dioxins are known to exert their effects through binding with and activating the aryl hydrocarbon receptor, which in turn antagonizes peroxisome proliferator-activated receptor (PPAR)-γ and reduces glucose transport activity (Remillard and Bunce, 2002). However, high doses of POPs tend to have the opposite effect in animal studies (Fried et al., 2010; Ibrahim et al., 2012), highlighting the need for further dose–response characterization. Mechanisms linking the non-persistent pesticides, organophosphates, to hyperglycemia are reviewed elsewhere (Rahimi and Abdollahi, 2007) and likely involve several pathways: oxidative and nitrosative stress, pancreatitis, stimulation of the adrenal gland, and disruption of liver tryptophan metabolism.

Recent reviews presented comprehensive summaries of environmental and human POP exposures in India (Sharma et al., 2014) and POP levels in water in China (Bao et al., 2012), but to our knowledge, no review has summarized the health effects of these exposures in Asian populations. The objective of this study was to systematically review the literature concerning the association of POPs and non-persistent pesticides (pyrethroids and organophosphates) with diabetes and diabetes-related health outcomes in Asia.

2. Methods

2.1. Search strategy and study selection

PubMed and Embase were searched to identify human studies published in English up to November 2014 (material). The exposure search terms "pesticides," "polychlorinated biphenyls," "persistent organic pollutants," "hydrocarbons, chlorinated," and "organophosphates" were combined using the operator "OR" and then nested. The outcome search terms "diabetes mellitus," "hyperinsulinism," "hyperglycemia," "insulin resistance," "glucose intolerance," "beta-cell function," and "blood glucose" were combined using the operator "OR" and then nested. Medical subject heading (MeSH) terms were expanded to include all narrower terms in the hierarchical list. The nested exposure terms and nested outcome terms were then combined using the operator "AND." We excluded citations with the following, non-relevant terms using the operator "NOT": "warfarin," "mitotane," "diphosphoglycerate," "dichloroacetate,"

and "paraoxonase." We also conducted a secondary reference review of all extracted articles and the U.S. National Toxicology Program Workshop on the association of POPs with diabetes (Taylor et al., 2013).

Exclusion criteria included: studies not published in English; animal or cell model studies; reviews, commentaries, or case studies; studies not reporting on at least one of the exposures of interest (POPs or non-persistent pesticides); studies not reporting on at least one of the outcomes of interest (type 2 diabetes, glucose intolerance, insulin resistance, or beta-cell function); studies reporting only on gestational diabetes, type 1 diabetes, or diabetes-specific mortality; and studies with sample populations outside of Eastern Asia, Southern Asia, and South-Eastern Asia as defined by the United Nations Statistics Division (2013).

2.2. Data extraction

The following information was extracted from each study: first author, publication year, study location, study design, sample size, length of follow-up if applicable, participant characteristics (age, sex, body mass index [BMI]), type of POP or non-persistent pesticide exposure including dose, assessment method, and timing of assessment, outcome including assessment method and timing of assessment, and analysis strategy (exposure contrast, effect estimates, and covariates). Meta Data Viewer was used to visualize results for the outcome "diabetes" sorted by chemical (Boyles et al., 2011).

3. Results

3.1. Extracted study characteristics

The PubMed search yielded 514 citations; 498 citations were excluded based on a priori criteria (Fig. 1). The Embase (mapped to preferred terms in Emtree, searched as free text in all fields, and exploded using narrower Emtree terms) search yielded 584 citations; 579 citations were excluded based on a priori criteria or because they were duplicates of extracted articles from the PubMed search. The full texts of 21 original research articles from the database searches were reviewed. The secondary reference review yielded five additional original research articles that were not identified via the database searches for a total of 26 original research articles.

In five instances, multiple articles were published on the same cohort: one cohort was in Korea (Park et al., 2010; Son et al., 2010), one was in Taiwan (Chang et al., 2010a,b, 2011), one was in Japan (Uemura et al., 2008, 2009; Nakamoto et al., 2013), one was in Vietnam veterans from Korea (Yi et al., 2013, 2014), and one was in Iran (Bayrami et al., 2012; Malekirad et al., 2013).

In the Korean cohort, the first article focused on diabetes as the primary outcome (Son et al., 2010) while the second article focused on metabolic syndrome as the primary outcome with secondary analysis of the components of metabolic syndrome including fasting glucose ≥ 110 mg/dl (Park et al., 2010). Because the exposures were the same in both articles, only the article for which diabetes was the primary outcome was included in this review (Son et al., 2010). Similarly, in the Taiwanese cohort, the first article focused on insulin resistance and beta-cell function (Chang et al., 2010a), the second article focused on metabolic syndrome (Chang et al., 2010b), and the third article focused on the interactive effects of mercury and polychlorinated dibenzodioxins (PCDDs)/polychlorinated dibenzofurans (PCDFs) on insulin resistance and beta-cell function (Chang et al., 2011). All three articles covered 2005–2007 and analyzed non-diabetic participants, thus, only the first article, focusing on the independent effects of PCDD/Fs on insulin resistance and beta-cell function was included in this review (Chang et al., 2010a). In the Japanese cohort, the first article (covering 2002–2006) focused on diabetes as the primary outcome (Uemura et al., 2008), the second (covering 2002–2006) focused on metabolic syndrome (Uemura et al., 2009), and the third (covering 2002–2010) not only focused on atopic dermatitis, but also presented effect estimates for diabetes (Nakamoto et al., 2013). Given that the third article covered a longer period of follow-up and therefore had a greater number of cases compared to the first article (113 versus 65 cases, respectively), and assessed dose–response effects, only the third article was included in this review (Nakamoto et al., 2013).

In the cohort of Vietnam veterans from Korea, the first article assessed self-reported diabetes as the outcome and did not distinguish between type 1 diabetes and type 2 diabetes (Yi et al., 2013), while the second article assessed ICD-10 codes from the Korea National Health Insurance claims data to ascertain diabetes and distinguished between insulin-dependent and non-insulin-dependent diabetes (Yi et al., 2014). We therefore only included the second article in this review (Yi et al., 2014). In the cohort of horticulture farm workers in Iran, the first article analyzed only 40 farm workers and 40 controls (100% male) (Bayrami et al., 2012), while the second article analyzed 187 farm workers and 187 controls (67.4% male) (Malekirad et al., 2013), and therefore only the second, larger and more recent article was

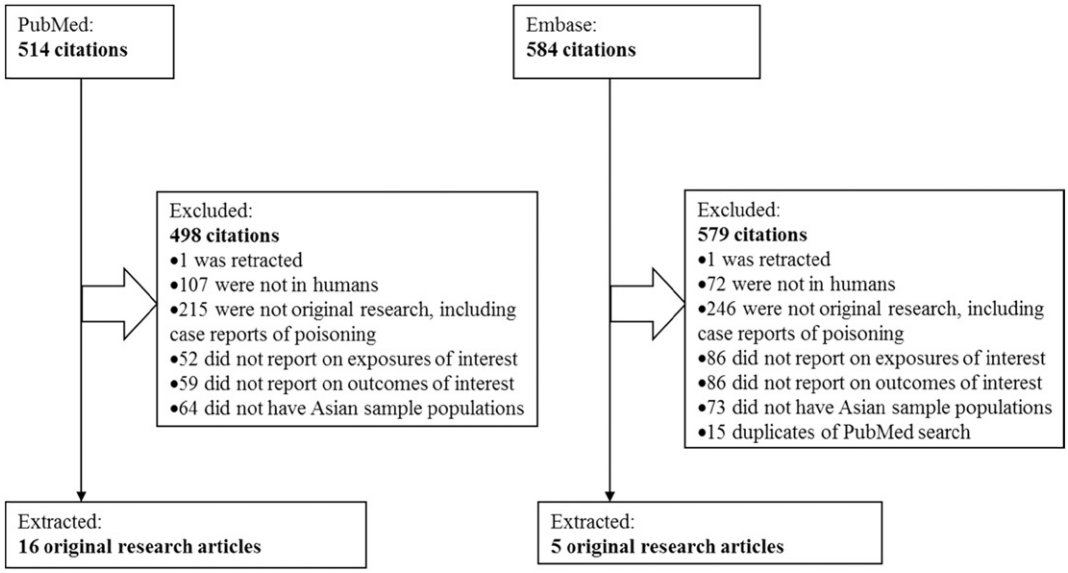

Fig. 1. Results of PubMed and Embase database searches for persistent organic pollutants or non-persistent pesticides and diabetes-related health outcomes in Asia.

Table 1
Characteristics of 19 articles included in the final review of persistent organic pollutants or non-persistent pesticides and diabetes-related health outcomes in Asia, listed by outcome.[a]

First author Year Location	Sample size Exp/Unexp	Sample characteristics Exp/Unexp [b]	Study design	Exposure[b]	Exposure assessment	Outcome assessment	Primary results[c]
Outcome: diabetes							
Wang et al., 2008 Taiwan	Total 378/370 Men 155/152 Women 223/218	41.0% male, ≥30 yrs old BMI (kg/m^2) Men 24.1 (3.1) / 24.0 (3.1) Women 24.3 (8.5)/23.5 (3.4)	Prospective	Yucheng "oil disease" cohort membership, related to possible PCB, PCDF, and/or PCQ exposure Serum PCBs (ppb) at baseline Men: 73.3 (86.3) Women: 87.4 (151.0)	Official cohort registry	Self-report via telephone interview. History of physician-diagnosed diabetes Outcome events (#) Exposed/unexposed Men 44/39 Women 42/19	Women in Yucheng cohort were significantly more likely to develop diabetes compared to residence- and age-matched controls after adjustment for age and BMI: diabetes without therapy, 2.1 (1.1, 4.5), and with therapy, 2.5 (1.0, 6.5). Association was non-significant for men after adjustment for age, BMI, smoking status, and alcohol intake: diabetes without therapy, 1.0 (0.5, 1.9), and with therapy, 1.3 (0.7, 2.7)
Kim et al., 2003 Korea	1224/154	100% male, 45–64 yrs old BMI (kg/m^2) 23.7 (3.1)/24.1 (2.9)	Prospective	Service during Vietnam war, related to possible Agent Orange/TCDD exposure Serum TCDD (pg/g lipid) Random subset of n = 25 non-Vietnam veterans: 0.3 Random subsets of n = 180 per quartile of Vietnam veterans: 0.6, 0.62, 0.78, 0.87	Military records	Blood sample. Fasting status not reported. ICD-9 classification Outcome events (#) Exposed/unexposed 154/9	Vietnam veterans were more likely to have diabetes compared to non-Vietnam veterans after adjustment for age, smoking status, alcohol intake, BMI, education, and marital status: 2.69 (1.09, 6.67)
Yi et al., 2014 Korea	42,421/69,305	High/low Agent Orange exposure Age (yrs) 55.1 (3.1) / 53.9 (3.7)	Prospective	Exposure to Agent Orange High: $\log_{10}$ E4 ≥ 4 low: $\log_1$0 E4 < 4	GIS-based EOI model E4, based on proximity of veteran's military unit to Agent Orange-sprayed area	ICD-10 classification	Vietnam veterans with high Agent Orange exposure were significantly more likely to have diabetes compared to Vietnam veterans with low Agent Orange exposure after adjustment for age, smoking status, alcohol intake, BMI, physical activity, military rank, domestic herbicide use, education, and household income: 1.04 (1.01, 1.07)
Kitamura et al., 2000 Japan	92/na	Municipal waste incinerator workers 95.7% male Age (yrs) Men: 48.2 (15.6) Women: 45.5 (3.1) BMI (kg/m^2) Men: 23.6 (3.4) Women: 20.8 (3.1)	Cross-sectional	Serum PCDD/F, lipid-adjusted Serum concentrations (pg/g lipid) PCDD: 612.89 PCDF: 661.97	GC/HRMS	Self-report via in-person interview. History of diabetes Outcome events (#) 8	Serum PCDD/F (pg TEQ/g lipid, quartiles) was not significantly associated with diabetes after adjustment for age, BMI, and smoking status (data not reported)
Chen et al., 2006 Taiwan	1034/na	Residents near municipal waste incinerators 50.8% male, 18–65 yrs old BMI (mean, kg/m^2) 1st quartile: 20.2 2nd quartile: 23.1 3rd quartile: 25.4 4th quartile: 29.2	Cross-sectional	Serum PCDD/F, lipid-adjusted Serum PCDD/F (pg TEQ/g lipid) Men: 15.8 (8.3) Women: 17.6 (7.8)	HRGC/HRMS	Self-report via in-person interview. History of physician-diagnosed diabetes Outcome events (#) 29	Serum PCDD/F (pg TEQ/g lipid, continuous) was not significantly associated with diabetes after adjustment for age, sex, smoking status, and BMI: 2.44 (0.21, 31.90)

Nakamoto et al., 2013 Japan	2264/na	47.0% male, 15–76 yrs old BMI (kg/m^2) Men 23.8 (3.5) Women 22.3 (3.3)	Cross-sectional	Serum PCDD/F, dioxin-like PCBs, and total dioxins, lipid-adjusted Serum concentrations (pg TEQ/g lipid) (median) PCDD: 6.9 PCDF: 2.8 dioxin-like PCBs: 5.6	HRGC/HRMS	HbA1c >6.1% or history of physician-diagnosed diabetes Outcome events (#) 113	A significant trend of increasing odds of diabetes with increasing serum PCDD/F concentrations was observed after adjustment for age, sex, smoking status, alcohol intake, BMI, regional block, and survey year (p-trend = 0.002): OR (95% CI) comparing 4th, 3rd, and 2nd quartiles to 1st quartile (referent), 10 (2.9–66), 6.8 (1.9–44), 6.8 (1.9–43), respectively. Similarly, significant trends were observed for dioxin-like PCBs and total dioxins after adjustment (p-trend < 0.0001 for both): OR (95% CI) comparing 4th, 3rd, and 2nd quartiles to 1st quartile (referent), 11 (3.0–76), 6.7 (1.8–44), 2.5 (0.61–17), and 23 (4.6–430), 14 (2.8–260), 8.9 (1.7–160), respectively
Tanaka et al., 2011 Japan	117/na	Saku Control Obesity Program participants 50.4% male, 40–64 yrs old BMI ≥ 28.3 kg/m^2	Cross-sectional	Serum PCB congeners, lipid-adjusted Serum concentrations (ng/g lipid) PCB 146: 3.7 (2.6) PCB 180: 12.8 (8.5) PCB 163/164: 6.1 (4.1) total PCBs: 92.5 (60.8)	HRGC/HRMS	FBG ≥ 126 mg/dl, HbA1c ≥ 6.5%, prescription for hypoglycemia medicine, or history of physician-diagnosed diabetes. Type 1 diabetes not eligible Outcome events (#) 32	Serum PCB 146 (ng/g lipid) and PCB 180 (ng/g lipid) were significantly positively associated with diabetes after adjustment for age, sex, and BMI: 29.2 (1.89, 451) and 1.76 (1.01, 3.08), respectively. Serum PCB 163/164 (ng/g lipid) was significantly negatively associated with diabetes after adjustment: 0.14 (0.03, 0.58). No other PCB congeners (74, 99, 118, 138, 153, 156, 170, 182/187) were significantly associated with diabetes
Kim et al., 2014 Korea	50/na	48% male, (mean) 63.8 yrs old BMI (kg/m^2) Diabetes: 23.3 (3.2) No diabetes: 23.5 (3.5)	Cross-sectional	OC pesticides and PCB congeners in VAT and SAT VAT and SAT concentrations presented in figure only	HRGC/HRMS	FBG ≥126 mg/dl or history of physician-diagnosed diabetes Outcome events (#) 25	A trend of increasing odds of diabetes with increasing SAT concentration of PCB congeners with ≤5 chlorides approached significance (p = 0.08), but OR (95% CI) comparing 2nd and 3rd to 1st tertile (referent) were not significant after adjustment for age, sex, smoking status, alcohol intake, and BMI: 2.1 (0.46, 12.8) and 5.7 (0.8, 40.1), respectively. A trend of increasing odds of diabetes with increasing VAT concentration of DDTs was significant (p = 0.02), as was the OR (95% CI) comparing 3rd to 1st tertile (referent) after adjustment: 9.0 (1.3, 62.9). OR (95% CI) comparing 2nd to 1st tertile not significant: 2.3 (0.3, 15.1). All other exposures (PCB congeners with ≤5 chlorides in VAT and PCB congeners with ≥6 chlorides, CHLs, HCHs, HCB in SAT and VAT) not significantly associated with diabetes
Son et al., 2010 Korea	40 (cases)/40 (controls)	52.5% male, (mean) 55.6 yrs old BMI (kg/m^2) Cases: 25.3 (2.7) Controls: 23.8 (3.0)	Case–control	Serum OC pesticides, lipid-adjusted Serum concentrations (ng/g lipid) Oxychlordane: 11.1 (6.8) Trans-nonachlor: 31.3 (28.1) HCB: 24.2 (13.0) β-HCH: 57.9 (24.5) p,p′-DDE: 652.3 (646.7) p,p′-DDT: 34.2 (21.3) o,p′-DDT: 4.5 (3.0)	GC/HRMS	FBG ≥ 126 mg/dl or meds	OR (95% CI) for diabetes adjusted for age, sex, smoking status, alcohol intake, and BMI were significant comparing the 3rd and 1st (referent) tertiles for oxychlordane [26.0 (1.3, 517.4)], trans-nonachlor [8.1 (1.2, 53.5)], HCB [6.1 (1.0, 36.6)], β-HCH [8.2 (1.3, 53.4)], p,p′-DDE [12.7 (1.9, 83.7)], p,p′-DDT [10.6 (1.3, 84.9)], o,p′-DDT [12.3 (1.3, 113.2)]. Heptachlor epoxide, mirex, and p,p′-DDD were not significantly associated with diabetes

(continued on next page)

Table 1 (*continued*)

First author Year Location	Sample size Exp/Unexp	Sample characteristics Exp/Unexp [b]	Study design	Exposure[b]	Exposure assessment	Outcome assessment	Primary results[c]
Outcome: abnormal glucose regulation (diabetes + prediabetes)							
Wang et al., 2011 China	1347/1733	72.5% male, 20–60 yrs old BMI (kg/m^2) Men 26.8 (4.7)/24.7 (5.2) Women 22.2 (6.5)/23.2 (5.8) Waist circumference (cm) Men 90.8 (11.4)/82.0 (14.1) Women 82.5 (16.3)/79.9 (16.1)	Cross-sectional	Working at pyrethroid factory Serum pyrethroid concentrations not reported	Employee rosters	Diabetes: self-reported history or FBG ≥ 7.0 mM or OGTT 20 or 120 min values ≥ 7.0 mM or ≥11.1 mM, respectively IFG: FBG 6.1–6.9 mM or OGTT 20 or 120 min values 6.1–6.9 mM or <7.8 mM, respectively IGT: OGTT 20 or 120 min values < 7.0 mM or 7.8–11.0 mM, respectively Outcome events (#) Exposed/unexposed 394 / 370	Workers exposed to pyrethroids were significantly more likely to have abnormal glucose regulation compared to workers not exposed to pyrethroids after adjustment for age, sex, smoking status, and alcohol intake: 1.48 (1.24, 1.77)
Outcome: blood glucose							
Kanagawa et al., 2008 Japan	501/na	Yusho "oil disease" cohort Characteristics not reported	Cross-sectional	Serum PCB, PCQ, and PCDF Serum PCB, PCQ, and PCDF concentrations not reported	Not reported	Blood sample. Fasting status not reported	Serum PCDF ≥ 50 pg/g lipids vs. <50 pg/g lipids was positively associated with BG after adjustment for age, sex, PCB blood level, PCQ blood level, and several clinical factors: Beta (SE), 0.038 (0.011), p-value = 0.0008. Serum PCB and PCQ were not associated with BG
Kitamura et al., 2000 Japan *See also "Outcome: diabetes"	92/na	Municipal waste incinerator workers 95.7% male Age (yrs) Men: 48.2 (15.6) Women: 45.5 (3.1) BMI (kg/m^2) Men: 23.6 (3.4) Women: 20.8 (3.1)	Cross-sectional	Serum PCDD/F, lipid-adjusted Serum PCDD/F (pg TEQ/g lipid) 99.69 (135.47) Serum concentrations (pg/g lipid) PCDD: 612.89 PCDF: 661.97	GC/HRMS	Blood sample. Fasting status not reported	Serum PCDD/Fs (pg TEQ/g lipid, continuous) were not significantly associated with blood glucose (mg/dl, continuous) (data not shown)
Chen et al., 2006 Taiwan *See also "Outcome: diabetes"	1034/na	Residents near municipal waste incinerators 50.8% male, 18–65 yrs old BMI (mean, kg/m2) 1st quartile: 20.2 2nd quartile: 23.1 3rd quartile: 25.4 4th quartile: 29.2	Cross-sectional	Serum PCDD/F, lipid-adjusted Serum PCDD/F (pg TEQ/g lipid) Men 15.8 (8.3) Women 17.6 (7.8)	HRGC/HRMS	Blood sample. Fasting status not reported	Serum PCDD/Fs (pg TEQ/g lipid, continuous) were significantly associated with blood glucose (mg/dl, continuous) after adjustment for age, sex, BMI, and smoking status: beta, 0.349, p-value = 0.009
Chang et al., 2012 Taiwan	156/645	Retired PCP factory workers/Taiwan general population Male: 76.3%/53.5% Age (yrs): 72.9 (8.7)/57.9 (5.4) BMI (kg/m^2): 24.7 (3.7)/25.0 (3.3) T2D (yes): 28.9%/11.3%	Cross-sectional	Retired PCP factory workers, related to possible PCDD/F exposure Serum PCDD/F (pg TEQ/g lipid) Retired PCP factory workers who moved: 27.9 (21.3) Retired PCP factory workers eating a normal diet: 95.8 (102.5) Retired PCP factory workers eating a polluted diet: 109.6 (94.5) Note: Serum PCDD/F concentration not reported for all retired PCP factory workers combined General population: 22.9 (10.0)	Employee roster	Fasting blood sample, FBG > 100 mg/dl	Retired PCP factory workers were significantly more likely to have blood glucose levels > 100 mg/dl compared to a referent Taiwanese population: 7.22 (4.04, 12.90)

Malekirad et al., 2013 Iran	187/187	Horticulture farm workers/age-matched, non-agricultural workers 67.4% male Age (yrs) 37.94 (12.41) / 37.05 (11.78)	Cross-sectional	Horticulture farm workers, related to possible organophosphate exposure, but exact pesticide exposure not reported	Not reported	Fasting blood sample	Farmer workers had significantly ($p = 0.0001$) higher median (Q1–Q3) blood glucose levels (mg/dl) compared to controls: 84.90 (76.25–94) versus 78.31 (62–84), respectively. No adjusted results were reported
Patil et al., 2009 India	60/30	Pesticide sprayers of grapes/age-matched controls 100% male, 20–45 yrs, non-smokers, non-alcoholics	Cross-sectional	Sprayers for 5–15 years, related to possible organophosphate exposure, but exact pesticide exposure not reported	Not reported	Blood sample. Fasting status not reported	Sprayers had significantly ($p < 0.01$) higher mean (SD) blood glucose levels (mg/dl) compared to controls: 104 (13.66) versus 94 (13.34), respectively. No adjusted results were reported
Bhatnagar et al., 1980 India	42/15	Pesticide factory workers/"healthy subjects" 97.6% male	Cross-sectional	Pesticide factory workers, related to possible DDT, aldrin, β-HCH, malathion, parathion, and carbaryl exposure	Self-reported	Blood sample. Fasting status not reported	Factory workers had significantly ($p < 0.001$) lower mean (SD) blood glucose levels (mg/dl) compared to controls: 79.28 (13.92) versus 101.06 (11.34), respectively. No adjusted results were reported. Difference could be due to higher manual work in cases
Narendra et al., 2008 India	12/12/12	Allethrin exposed subjects/prallethrin exposed subjects/controls 100% male, 35–45 yrs old, non-smokers	Controlled trial	Subjects exposed for 8–10 h/day to either allethrin mosquito repellent coils, prallethrin-treated mosquito repellent mats, or no mosquito repellent. Length of intervention not reported	Assigned	Fasting blood sample	Subjects exposed to either allethin or prallethrin had significantly ($p \leq 0.05$) higher mean (SD) blood glucose levels (mg/dl) compared to controls: 98.49 (1.30) and 101.58 (2.38) versus 87.75 (2.60), respectively. No adjusted results were reported
Chen et al., 2008 Taiwan	40/na	Pregnant women, 21–39 yrs old BMI (kg/m^2) Pre-pregnancy: 20.7 (3.1) Perinatal: 25.0 (3.3)	Cross-sectional	Serum PCDD/F and PCB congeners, lipid adjusted Serum concentrations (pg TEQ/g lipid) PCDD/F: 9.76 (6.03) PCB: 5.15 (2.83)	HRGC/HRMS	Fasting blood sample	Participants with glucose > 4.66 mmol/l (median) had significantly ($p < 0.05$) higher total mean (SD) congener concentrations (pg TEQ/g lipid) compared to participants with glucose ≤ 4.66 mmol/l: 16.94 (10.00) versus 12.95 (5.98), respectively. No significant differences were observed when PCDDs, PCDFs, and PCBs were analyzed separately. No adjusted results were reported
Teeyapant et al., 2014 Thailand	1137/na	42.6% male Age (yrs) Men: 48 (10) Women: 46 (10) BMI (kg/m^2), mean (95% CI) Men: 22.44 (22.14–22.74) Women: 24.26 (23.97–24.57)	Cross-sectional	Serum p,p′-DDE and p,p′-DDT, lipid adjusted p,p′-DDE (ng/g lipid), mean (95% CI) Men: 1539 (1242–1837) Women: 1547 (1293–1806) p,p′-DDT (ng/g lipid), mean (95% CI) Men: 135 (116–164) Women: 133 (112–147)	GC/MS	Fasting blood sample	Fasting blood glucose (continuous, mg/dl) was significantly ($p \leq 0.001$) positively associated with p,p′-DDE (continuous, ng/g lipid): Spearman rank correlation coefficient = 0.162. No significant association was observed with p,p′-DDT: Spearman rank correlation coefficient = 0.116. No adjusted results were reported
Outcome: insulin resistance							
Chang et al., 2010a Taiwan	1234/na	Residents near deserted PCP factory 52% male, 25–80 yrs old Non-diabetic BMI (kg/m^2) <21.7: 25% 21.7–24.0: 25% 24.0–26.7: 25% >26.7: 25%	Cross-sectional	Serum PCDD/F, lipid adjusted Serum PCDD/F concentration (pg TEQ/g lipid) Men: 17.8 (range: 4.5–374.1) Women: 23.4 (range: 4.7–403.0)	HRGC/HRMS	Fasting blood sample IR = glucose (mmol/l) × insulin (mU/l) / 22.5 Dichotomized as ≥75th percentile	Residents with PCDD/F concentrations > 20.5 pg TEQ/g lipid (median) were significantly more likely to have IR compared to residents with PCDD/F concentrations ≤ 20.5 pg TEQ/g lipid after adjustment for age, sex, BMI, smoking status, physical activity, body weight control, and family history of diabetes: 1.7 (1.2, 2.4)

(continued on next page)

Table 1 (*continued*)

First author Year Location	Sample size Exp/Unexp	Sample characteristics Exp/Unexp [b]	Study design	Exposure[b]	Exposure assessment	Outcome assessment	Primary results[c]
Kim et al., 2014 Korea *See also "Outcome: diabetes"	50/na	48% male (mean) 63.8 yrs old BMI (kg/m^2) Diabetes: 23.3 (3.2) No diabetes: 23.5 (3.5)	Cross-sectional	OC pesticides and PCB congeners in VAT and SAT VAT and SAT concentrations presented in figure only	HRGC/HRMS	Fasting blood sample HOMA-IR	DDTs in VAT, CHLs in VAT and SAT, HCB in VAT, and PCBs with ≤5 chlorides in VAT and SAT were all significantly correlated with HOMA-IR after adjustment for age, sex, smoking status, alcohol intake, and BMI: Spearman correlation coefficients +0.29, +0.33, +0.31, +0.32, +0.34, and +0.35, respectively
Chen et al., 2008 Taiwan *See also "Blood glucose"	40/na	Pregnant women, 21–39 yrs old BMI (kg/m^2) Pre-pregnancy: 20.7 (3.1) Perinatal: 25.0 (3.3)	Cross-sectional	Serum PCDD/F and PCB congeners, lipid adjusted Serum concentrations (pg TEQ/g lipid) PCDD/F: 9.76 (6.03) PCB: 5.15 (2.83)	HRGC/HRMS	Fasting blood sample Insulin (pmol/l) Insulin sensitivity (inverse of HOMA index) QUICKI	Serum PCB concentration (pg TEQ/g lipid), particularly PCB 123, 126, and 169, was marginally non-significantly ($p = 0.07$; $p = 0.12$ after adjustment for age and pre-pregnancy BMI) positively associated with insulin (pmol/L), Pearson correlation coefficient = 0.30; significantly ($p = 0.009$; $p = 0.02$ after adjustment) negatively associated with insulin sensitivity, Pearson correlation coefficient = -0.42; and marginally non-significantly ($p = 0.07$; $p = 0.12$ after adjustment) negatively associated with QUICKI, Pearson correlation coefficient = −0.23. Serum PCDD/F concentration was not significantly associated with any markers of insulin resistance
Outcome: beta-cell function							
Chang et al., 2010a Taiwan *See also "Outcome: insulin resistance"	1234/na	Residents near deserted PCP factory 52% male, 25–80 yrs Non-diabetic BMI (kg/m^2) <21.7: 25% 21.7–24.0: 25% 24.0–26.7: 25% >26.7: 25%	Cross-sectional	Serum PCDD/F. lipid adjusted Serum PCDD/F concentration (pg TEQ/g lipid) Men: 17.8 (range: 4.5–374.1) Women: 23.4 (range: 4.7–403.0)	HRGC/HRMS	Fasting blood sample Beta-cell function = 20 × insulin (mU/l) / [glucose (mmol/l) − 3.5] Dichotomized as ≥75th percentile	Association with beta-cell function was non-significant after adjustment for age, sex, BMI, smoking status, physical activity, body weight control, and family history of diabetes: 1.3 (0.9, 1.8)

[a] Abbreviations: BMI, body mass index; CHLs, chlordanes; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EOI, exposure opportunity index; FBG, fasting blood glucose; GC, gas chromatography; GIS, geographic information system; HCB, hexachlorobenzene; HCH, hexachlorocyclohexanes; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HRGC, high-resolution gas chromatography; HRMS, high-resolution mass spectrometry; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; NA, not applicable; OC, organochlorine; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCP, pentachlorophenol; PCQs, polychlorinated quarterphenyls; POPs, persistent organic pollutants; QUICKI, quantitative insulin sensitivity check index; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TEQ, toxic equivalent concentration; VAT, visceral adipose tissue.

[b] Values are mean (SD) or median (range) unless otherwise specified.

[c] Values are adjusted OR and 95% CI estimated from multivariable logistic regression unless otherwise specified.

included (Malekirad et al., 2013). Given these exclusions, the final review included 19 articles (Table 1).

Most of the studies were conducted in Eastern Asia: two in Korea, two in Koreans exposed in Vietnam, four in Japan, five in Taiwan, and one in mainland China. One study was conducted in South-Eastern Asia (Thailand) and four studies were conducted in Southern Asia: three in India and one in Iran.

Two of the studies evaluated diabetes/diabetes-related health outcomes in cohorts or regions exposed to rice oil contaminated with PCBs, polychlorinated quarterphenyls (PCQs), and/or PCDFs: the Yucheng "oil disease" cohort in Taiwan (exposed 1978–1979) (Wang et al., 2008) and a study of residents in an area severely affected by contaminated rice oil in Japan (Kashima et al., 2011). Eleven other studies evaluated diabetes/diabetes-related health outcomes in occupational/accidental/source-related exposure populations: Vietnam veterans in Korea (Kim et al., 2003; Yi et al., 2014); individuals living near a municipal waste incinerator in Taiwan (Chen et al., 2006); individuals working at municipal waste incinerators in Japan (Kitamura et al., 2000); individuals living near a deserted pentachlorophenol (PCP) factory in Taiwan (Chang et al., 2010a); retired PCP factory workers in Taiwan (Chang et al., 2012); individuals working at pesticide factories in mainland China (Wang et al., 2011) and India (Bhatnagar et al., 1980); farm workers in Iran (Malekirad et al., 2013) and India (Patil et al., 2009); and subjects participating in a controlled trial of mosquito repellents in India (Narendra et al., 2008). The remaining six studies were conducted in the general population (Chen et al., 2008; Son et al., 2010; Tanaka et al., 2011; Nakamoto et al., 2013; Kim et al., 2014; Teeyapant et al., 2014).

Hereafter, results are presented according to the outcome and where applicable by sample population (occupational/accidental/source-related exposure populations versus general population).

3.2. Outcome: diabetes

Reported associations between serum concentrations of POPs and diabetes are summarized in Fig. 2.

3.2.1. Occupational/accidental/source-related exposure populations

Female Yucheng "oil disease" cohort members (n = 223; 59%) were significantly more likely to report having developed diabetes in the 24 years after exposure to the contaminated rice oil compared to residence- and age-matched female controls (n = 218) after adjustment for age and BMI: odds ratio (OR) (95% confidence interval [CI]) for self-reported diabetes without therapy, 2.1 (1.1, 4.5), and with therapy, 2.5 (1.0, 6.5) (Wang et al., 2008). The association was not significant for men after adjustment for age, BMI, smoking status, and alcohol intake: OR (95% CI) for diabetes without therapy, 1.0 (0.5, 1.9), and with therapy, 1.3 (0.7, 2.7). Additionally, within the Yucheng cohort, women with chloracne (mean serum PCBs of 121.4 ppb) were significantly more likely to report having diabetes (without therapy) compared to Yucheng women without chloracne (mean serum PCBs of 72.6 ppb) after adjustment for age and BMI, suggesting a positive dose–response relationship: OR (95% CI), 5.5 (2.3, 13.4) (Wang et al., 2008).

Two studies examined exposure to Agent Orange (a herbicide known to contain 2,3,7,8-tetrachlorodibenzodioxin [TCDD]) in Korean Vietnam veterans (Kim et al., 2003; Yi et al., 2014). In the first, Vietnam veterans (n = 1224 men) were significantly more likely to have diabetes compared to non-Vietnam veterans (n = 154 men) after adjustment for age, smoking status, alcohol intake, BMI, education, and marital status: OR (95% CI), 2.69 (1.09, 6.67) (Kim et al., 2003) (see Kim et al., 2001 for details of Agent Orange exposure assessment methodology). However, there was no difference in diabetes prevalence across categories of estimated Agent Orange exposure among Korean Vietnam veterans, suggesting a lack of dose–response relationship in this sample: diabetes prevalence from lowest to highest quartile of Agent Orange exposure was 12.1%, 11.5%, 12.8%, and 14.1% (Kim et al., 2003). In the second, Vietnam veterans with high levels of Agent Orange exposure, as assessed using geographic information system (GIS) technology and the veteran's military unit's proximity to areas sprayed with Agent Orange, were significantly more likely to have diabetes compared to Vietnam veterans with low levels of Agent Orange exposure after adjustment for age, smoking status, alcohol intake, BMI, physical activity, military rank, domestic herbicide use, education, and household income: OR (95% CI), 1.04 (1.01, 1.07) (Yi et al., 2014).

Two studies evaluated diabetes in cohorts exposed to municipal waste incinerators (Kitamura et al., 2000; Chen et al., 2006). In the first, no association was observed between serum PCDD/F concentrations and self-reported diabetes among Japanese municipal waste incinerator workers (n = 92, 95.7% male) after adjustment for age, BMI, and smoking status (Kitamura et al., 2000). In the second study, conducted in Taiwanese residents living within 5 km of a municipal waste incinerator for at least 5 years and without occupational exposure to PCDD/Fs (n = 1034), a positive association was observed between serum PCDD/F concentrations and self-reported diabetes after adjustment for age, sex, BMI, and smoking status, but it was not statistically significant, potentially as a result of limited power to detect an effect: OR (95% CI) for PCDD/F modeled continuously (pg TEQ/g lipid), 2.44 (0.21, 31.90) (Chen et al., 2006). When comparing the highest 10% (n = 103) to the lowest 10% (n = 103) of participants in regard to serum PCDD/F concentrations, there was still no significant association with self-reported diabetes, again, potentially due to limited power stemming from the small sample size: OR (95% CI), 3.10 (0.26, 55.89) (Chen et al., 2006). Neither study reported on dose–response assessment.

3.2.2. General population

The association between PCDD/Fs and dioxin-like PCBs and diabetes was first evaluated in a general population sample outside the United States and Europe in Japan (Uemura et al., 2008, 2009; Nakamoto et al., 2013). In the most up-to-date analysis of this sample, a significant, positive trend was observed between serum PCDD/F concentrations and diabetes after adjustment for age, sex, smoking status, alcohol intake, BMI, regional block, and survey year (p-trend = 0.002): OR (95% CI) comparing the 4th, 3rd, and 2nd quartiles to the 1st quartile (referent), 10 (2.9, 66), 6.8 (1.9, 44), and 6.8 (1.9, 43), respectively (Nakamoto et al., 2013). Similarly, significant trends were observed for dioxin-like PCBs and total dioxins after adjustment (p-trend < 0.0001 for both): OR (95% CI) comparing the 4th, 3rd, and 2nd quartiles to the 1st quartile (referent), 11 (3.0, 76), 6.7 (1.8, 44), and 2.5 (0.61, 17), and 23 (4.6, 430), 14 (2.8, 260), and 8.9 (1.7, 160), respectively (Nakamoto et al., 2013). In a second cross-sectional study in Japan (n = 117), serum PCB 180 and PCB 146 concentrations were associated with increased odds of diabetes after adjustment for age, sex, and BMI: OR (95% CI) for PCB 180 and PCB 146 modeled continuously (ng/g lipid), 1.76 (1.01, 3.08) and 29.2 (1.89, 451), respectively (Tanaka et al., 2011). This second study did not report on dose–response assessment (Tanaka et al., 2011).

Two studies conducted in the Korean general population also evaluated the association between POPs and diabetes. In a cross-sectional study of patients undergoing surgery for either cancer or benign lesions in the liver, pancreas, or gallbladder (n = 50), concentrations of organochlorine pesticides (DDTs, chlordanes [CHLs], hexachlorocyclohexanes [HCHs], and HCB) and PCBs (congeners with ≤5 chlorides and congeners with ≥6 chlorides) were measured in visceral adipose tissues (VAT) and subcutaneous adipose tissue (SAT) (Kim et al., 2014). A dose–response association of concentrations of PCB congeners with ≤5 chlorides in SAT and DDTs in VAT with diabetes was observed after adjustment for age, sex, smoking status, alcohol intake, and BMI: OR (95% CI) for the 2nd and 3rd tertiles compared to the 1st tertile (referent) was 2.1 (0.46, 12.8) and 5.7 (0.8, 40.1), respectively, for PCB congeners with ≤5 chlorides in SAT (p-trend = 0.08) and 2.3 (0.3, 15.1) and 9.0 (1.3, 62.9), respectively, for DDTs in VAT (p-trend = 0.02) (Kim et al., 2014). The one case–control study included in this review

Reference	Chemical	Study description (n)	Outcome Assessment	Exposure contrast
Wang 2008	PCBs, PCQs, PCDFs	Taiwan, Yucheng oil disease cohort; prospective, ≥30 yrs, ♂ (307)	Self-report	Exposed vs. unexposed
Wang 2008	PCBs, PCQs, PCDFs	Taiwan, Yucheng oil disease cohort; prospective, ≥30 yrs, ♀ (441)	Self-report	Exposed vs. unexposed
Kim 2003	Agent Orange/TCDD	Korea, Vietnam veterans; prospective, 45-64 years, ♂ (1378)	Blood sample. Details not reported	Veterans vs. non-veterans
Yi 2014	Agent Orange/TCDD	Korea, Vietnam veterans; prospective, ♂ (111,726)	National health insurance claims data	High vs. low Agent Orange
Chen 2008	PCDD/Fs	Taiwan, residents near waste incinerators; cross-sectional, 18-65 years, ♂ ♀ (1034)	Self-report	Per pg TEQ/g lipid increase
Nakamoto 2013	PCDD/Fs	Japan, general population; cross-sectional, 15-76 yrs, ♂ ♀ (2264)	A1C>6.1% or self-report	Q4 vs. Q1 (pg/g lipid)
Nakamoto 2013	Dioxin-like PCBs	Japan, general population; cross-sectional, 15-76 yrs, ♂ ♀ (2264)	A1C>6.1% or self-report	Q4 vs. Q1 (pg/g lipid)
Nakamoto 2013	Total dioxins	Japan, general population; cross-sectional, 15-76 yrs, ♂ ♀ (2264)	A1C>6.1% or self-report	Q4 vs. Q1 (pg/g lipid)
Tanaka 2011	PCB 74	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 99	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 118	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 138	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 146	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 153	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 156	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 163/164	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 170	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 180	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Tanaka 2011	PCB 182/187	Japan, obesity control program; cross-sectional, 40-64 years, ♂ ♀ (117)	FBG≥126mg/dl, A1C≥6.5%, meds, or self-report	Per ng/g lipid increase
Son 2010	Oxychlordane	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	Trans-nonachlor	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	Heptachlor epoxide	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	HCB	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	β-HCH	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	Mirex	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	p,p'-DDE	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	p,p'-DDD	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	p,p'-DDT	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)
Son 2010	o,p'-DDT	Korea, general population; case-control, ≥40 years, ♂ ♀ (80)	FBG≥126mg/dl or meds	T3 vs. T1 (ng/g lipid)

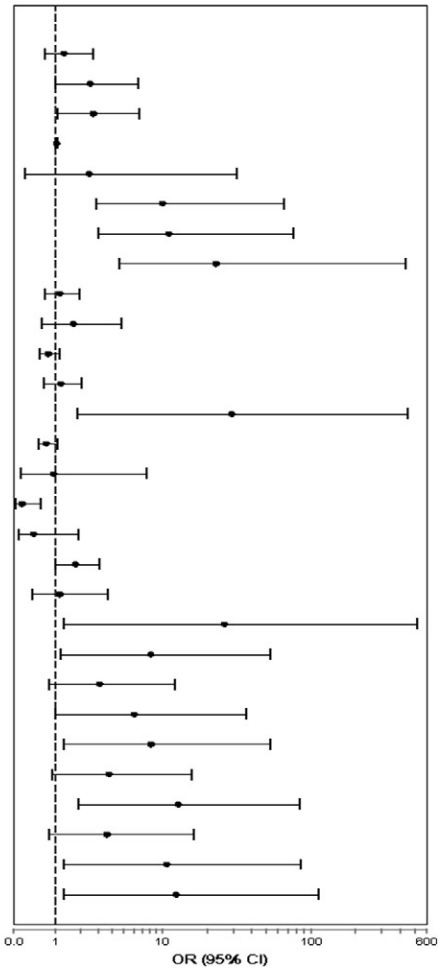

Fig. 2. Summary of reported associations between serum concentrations of persistent organic pollutants and diabetes. Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; FBG, fasting blood glucose; GIS, geographic information system; HCB, hexachlorobenzene; HCH, hexachlorocyclohexanes; HRGC, high-resolution gas chromatography; HRMS, high-resolution mass spectrometry; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCQs, polychlorinated quarterphenyls; Q1, quartile 1; Q4, quartile 4; T1, first tertile; T3, third tertile; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TEQ, toxic equivalent concentration.

had a sample size of only 40 cases and 40 controls, and while the confidence intervals were wide, significant ($p < 0.05$) ORs comparing the 3rd and 1st (referent) tertiles were reported for oxychlordane, *trans*-nonachlor, HCB, β-HCH, p,p′-DDE, p,p′-DDT, and o,p′-DDT (Son et al., 2010). For example, for p,p′-DDT, the OR (95% CI) comparing the 3rd and 1st (referent) tertiles was 12.7 (1.9, 83.7) (Son et al., 2010). p-Trends were significant ($p < 0.05$) for all of the aforementioned POPs, and p-trends were marginally non-significant for heptachlor epoxide ($p = 0.05$), mirex ($p = 0.08$), and p,p′-DDD ($p = 0.09$) (Son et al., 2010).

3.3. Outcome: abnormal glucose regulation (diabetes + prediabetes)

One study reported on abnormal glucose regulation defined as having diabetes, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), in Chinese factory workers. While workers exposed to pyrethroid insecticides were significantly more likely to have abnormal glucose regulation compared to workers not exposed to pyrethroids [OR (95% CI), 1.48 (1.24, 1.77)] after adjustment for age, sex, smoking status, and alcohol intake, they also had significantly higher BMIs and waist circumferences, which were not adjusted for in the analysis. Further, there was no dose–response assessment.

3.4. Outcome: blood glucose

3.4.1. Occupational/accidental/source-related exposure populations

Eight studies evaluated the association of environmental pollutants and blood glucose in occupational/accidental/source-related exposure populations. A significant association was observed between serum PCDF concentrations and blood glucose measured 33–37 years after the Yusho incident in exposed cohort members after adjustment for age, sex, PCB blood level, PCQ blood level, and several clinical factors ($n = 501$, beta [SE], 0.038 [0.011], p-value = 0.0008) (Kanagawa et al., 2008). In contrast, serum concentrations of PCDD/Fs were not significantly associated with blood glucose among Japanese municipal waste incinerator workers ($n = 92$, 95.7% male) (data not reported in article) (Kitamura et al., 2000).

Among Taiwanese residents living within 5 km of a municipal waste incinerator for at least 5 years and without occupational exposure to PCDD/Fs ($n = 1034$), a significant association was observed between serum PCDD/F concentrations and blood glucose (beta = 0.349, p-value = 0.009) after adjustment for age, sex, and BMI (Chen et al., 2006). Similarly, another study in Taiwan found that non-diabetic, retired PCP factory workers ($n = 156$; PCDD/Fs are byproducts of PCP production) were significantly more likely to have a FBG > 100 mg/dl compared to a referent Taiwanese population, even after adjustment for age, sex, smoking status, and alcohol intake: OR (95% CI), 7.22 (4.04, 12.90) (Chang et al., 2012). None of the aforementioned studies reported on dose–response assessment.

Two studies conducted in farm workers with possible exposure to organophosphates, one in Iran ($n = 374$) (Malekirad et al., 2013) and one in India ($n = 90$) (Patil et al., 2009), found significantly higher mean blood glucose levels in farm workers compared to controls. In contrast, a study of pesticide (DDT, aldrin, β-HCH, malathion, parathion, and/or carbaryl) factory workers in India found that factory workers ($n = 42$) had significantly lower blood glucose levels compared to controls ($n = 15$) (Bhatnagar et al., 1980). Finally, we identified one trial in which subjects were exposed for 8–10 h to either allethrin mosquito coils ($n = 12$), prallethrin-treated mosquito repellent mats ($n = 12$), or no mosquito repellent ($n = 12$) (Narendra et al., 2008). Results indicated that subjects exposed to either allethrin or prallethrin had significantly higher blood glucose levels compared to controls (Narendra et al., 2008).

3.4.2. General population

Two studies evaluated the association of environmental pollutants with blood glucose in the general population. The first, a sample of pregnant women in Taiwan ($n = 40$), found that participants with glucose > 4.66 mmol/l (median) had significantly higher total serum PCDD/F and PCB concentrations compared to participants with glucose ≤ 4.66 mmol/l (Chen et al., 2008). No significant differences were observed when PCDDs, PCDFs, and PCBs were analyzed separately (Chen et al., 2008). The second, a sample selected from 16 regions of Thailand ($n = 1137$; 42.6% male), found that blood glucose was significantly positively associated with serum concentration of p,p′-DDE (Spearman rank correlation coefficient = 0.162), but not p,p′-DDT (Spearman rank correlation coefficient = 0.116) (Teeyapant et al., 2014). Neither study reported on dose–response assessment.

3.5. Outcome: insulin resistance

Three studies evaluated the association of environmental pollutants with insulin resistance, one in a source-related exposure population and two in the general population. Among non-diabetic Taiwanese residents ($n = 1234$) of three municipal districts near a deserted PCP factory and without occupational exposure to PCP byproducts (e.g. PCDD/Fs), those with insulin resistance had significantly higher serum PCDD/F concentrations after adjustment for age, sex, BMI, smoking status, physical activity, body weight control, and family history of diabetes (OR [95% CI], 1.7 [1.2, 2.4]), and a significant ($p < 0.001$) monotonic increase in insulin resistance was observed across serum PCDD/F quartiles in an unadjusted dose–response analysis (Chang et al., 2010a). In the study that measured PCB and organochlorine pesticide concentrations in VAT and SAT, DDTs in VAT, CHLs in VAT and SAT, HCB in VAT, and PCBs with ≤5 chlorides were all significantly correlated with homeostasis model assessment-estimated insulin resistance (HOMA-IR) after adjustment for age, sex, smoking status, alcohol intake, and BMI (Kim et al., 2014). Finally, in the sample of pregnant women in Thailand, serum PCB concentrations, but not serum PCDD/F concentrations, were significantly negatively associated with insulin sensitivity (Pearson correlation coefficient = −0.42) (Chen et al., 2008).

3.6. Outcome: beta-cell function

Only one study evaluated the association between POP exposure and beta-cell function. Among non-diabetic Taiwanese residents ($n = 1234$) of three municipal districts near a deserted PCP factory and without occupational exposure to PCP byproducts (PCDD/Fs), no association was observed between serum PCDD/F concentrations and beta-cell function after adjustment for age, sex, BMI, smoking status, physical activity, body weight control, and family history of diabetes: OR (95% CI), 1.3 (0.9, 1.8) (Chang et al., 2010a). In an unadjusted dose–response analysis, a marginally non-significant association ($p = 0.09$) was observed between serum PCDD/F concentrations and beta-cell function (Chang et al., 2010a).

4. Discussion

4.1. Overview

We do not fully understand what is causing the rapid rise in diabetes in Asia. This systematic review sought to evaluate the scientific literature regarding the novel diabetes risk factors related to exposure to POPs and non-persistent pesticides. To date, the evidence linking POPs and non-persistent pesticides to diabetes and diabetes-related health outcomes in Asian populations is equivocal. PCDD/Fs and PCBs were by far the most common exposures evaluated: 8 (42%) out of the 19 articles evaluated PCDD/Fs or populations thought to be exposed to high concentrations of PCDD/Fs (for example, contaminated rice oil cohorts and PCP factory workers), and 6 (32%) out of the 19 articles evaluated

PCBs or populations thought to be exposed to high concentrations of PCBs (for example, contaminated rice oil cohorts). Seven articles evaluated pesticide exposures, three of persistent pesticides (organochlorines such as DDT and DDE) and four of non-persistent pesticides (pyrethroids and organophosphates). Prospective studies conducted in Asian populations are urgently needed as levels of diabetes and pollution continue to increase rapidly in this region of the world.

4.2. Relevance and importance for Asian populations

To our knowledge, no studies of large cohorts in the United States (e.g. NHANES) or elsewhere have evaluated modification of the effect of POPs on diabetes risk by Asian race/ethnicity. However, there is some evidence that non-Hispanic white race/ethnicity in NHANES is significantly associated with lower concentrations of octa-chlorodibenzo-p-dioxin (OCDD), oxychlordane, DDE, and *trans*-nonachlor (Lee et al., 2006). One study included in this review, Son et al., 2010, concluded that "Asians may be more susceptible to adverse effects of organochlorine pesticides than other races," given the average serum concentrations and magnitude of effect observed relative to studies conducted in the United States. In this study of the general Korean population, the 3rd tertile of p,p′-DDE (median concentration of 667.4 ng/g lipid) had an adjusted OR of 12.7 compared to the 1st tertile (median concentration of 162.2 ng/g lipid) (Son et al., 2010), markedly higher than the OR of 4.3 comparing those ≥90th percentile (3700 ng/g lipid) to those <25th percentile (112 ng/g lipid) in the general U.S. population (Lee et al., 2006). However, the 95% CI around the Korean point estimate was exceptionally wide (1.9 to 83.7) (Son et al., 2010) and therefore the estimate was not reliable and difficult to compare to the U.S. estimate (95% CI for U.S. study was 1.8 to 10.2) (Lee et al., 2006). Future research should explore this potential effect modification by Asian race/ethnicity in a larger sample population.

Few studies have examined the association between POP exposure and organophosphate exposure and the pathogenic processes that lead to diabetes, such as insulin resistance and beta-cell function. Only one study identified in this review assessed both of these processes, using fasting insulin and glucose measures, and found that only insulin resistance and not beta-cell function was associated with high PCDD/F concentrations (Chang et al., 2010a). In contrast to this, epidemiological studies and animal studies support reductions in beta-cell function associated with POP exposure (Piaggi et al., 2007; Jørgensen, 2008; Hectors, 2011). Longitudinal studies are needed to confirm the impact of POP exposure on mechanisms leading to diabetes specifically within Asian populations.

4.3. Comparison to literature outside of Asian populations

In light of the limited evidence currently available in Asian populations, it is worth mentioning the results of similar work in U.S. and European populations. Consistent with studies of U.S. Vietnam veterans (Kang et al., 2006; Michalek and Pavuk, 2008), two studies included in this review also found significantly increased risk of diabetes with exposure to Agent Orange among Korean Vietnam veterans (Kim et al., 2003; Yi et al., 2014). However, the first of these studies may have been subject to selection bias: of 4432 Vietnam veterans contacted, only 1224 (27.6%) completed the study and of 2682 non-Vietnam veterans contacted, only 154 (5.7%) completed the study (Kim et al., 2003). The authors speculate that Vietnam veterans experiencing symptomatic medical problems may have been more motivated to participate in order to receive compensation from the Korean Ministry of Patriots and Veterans Affairs (Kim et al., 2003). Compared to non-participants, Vietnam veterans who participated were older and served in Vietnam earlier and longer (Kim et al., 2003). One may therefore predict that the effect estimate is biased away from the null given the higher exposure level (from longer service) and higher outcome prevalence among participants.

The results of the Wang et al., 2011 study of pyrethroid factory workers are particularly disturbing as pyrethroids are commonly used throughout Asia. Indeed, pyrethroids are the third most commonly used insecticide in China and the fourth most commonly used in India (China Chemicals Market (CCM), 2011; Bhushan et al., 2013). A small trial conducted in India also found that exposure to the pyrethroids, allethrin and prallethrin (mosquito repellents), resulted in a significant increase in fasting blood glucose (Narendra et al., 2008). To date, most research on the health effects of pyrethroids has focused on male reproductive health outcomes (Kolaczinski and Curtis, 2004; Koureas et al., 2012; Thatheyus and Gnana Selvam, 2013). More research is needed to improve our understanding of the effects of pyrethroids on glucose metabolism and diabetes.

Females had higher serum concentrations of environmental pollutants compared to males in several of the studies identified in this review (Chen et al., 2006; Kanagawa et al., 2008; Wang et al., 2008; Chang et al., 2010a). Furthermore, in one study, a significant association between prior exposure to high levels of POPs and diabetes was seen in women, but not in men (Wang et al., 2008). These sex differences have also been reported in the literature (Bertazzi et al., 2001; Vasiliu et al., 2006), and several reasons have been hypothesized including differences in adiposity (Mullerova and Kopecky, 2007) and differences in estrogen status (Wang et al., 2006).

BMI status may also modify the effect of POPs on diabetes risk. For example, an analysis of the Helsinki Birth Cohort Study in Finland found a significant effect of organochlorine pesticides on diabetes risk among overweight participants but not among normal weight participants (Airaksinen et al., 2011). Future studies could address this limitation by stratifying analyses by BMI status or prospectively controlling for BMI or weight trajectory.

4.4. Limitations of current literature and suggested future directions

There were four key limitations of the current literature on this topic worth highlighting: 1) cross-sectional study designs, 2) lack of dose–response assessment, 3) variability in exposure assessment, and 4) variability in outcome assessment. Additional limitations of the current literature include: effect estimates were imprecise; few studies were conducted in Southern or South-Eastern Asia; and no studies included nationally representative samples. Furthermore, there were limitations to our review methodology. In particular, we excluded studies not published in English. Given that our target populations were in predominantly non-English speaking countries, this may have resulted in the exclusion of studies conducted on this topic in Asian populations.

4.4.1. Cross-sectional study designs

Most of the studies identified in this systematic review were cross-sectional. None of the prospective studies evaluated the association between measured values of pollutants and diabetes/diabetes-related health outcomes; rather, they compared individuals exposed to high doses of pollutants at some earlier time point (e.g. Vietnam veterans and "oil disease" incidents) to unexposed individuals, without accounting for selection biases. A major limitation of these analyses was that individuals with pre-diabetes or diabetes are advised to lose weight or can lose weight with disease progression. Indeed, one of the studies included in this review was nested in a larger weight loss trial (Tanaka et al., 2011). Because POPs are fat-soluble, weight loss increases serum POP concentrations (Walford et al., 1999; Lim et al., 2011). Consequently, associations of POPs with diabetes may vary depending on state of energy balance.

Diabetes itself may also modify POP metabolism resulting in reverse causality, but the evidence is mixed with animal models supporting a potential mechanism (Pass et al., 2002) while an epidemiological study in U.S. Vietnam veterans did not find differences in the metabolism of TCDD between individuals with and without diabetes (Michalek et al., 2003). Future studies should prospectively measure incident diabetes and weight status in order to address these issues of temporality and improve causal inferences.

4.4.2. Lack of dose–response assessment

For many of the environmental pollutants evaluated in this review, the relationship with diabetes may not be monotonic, thus traditional toxicology approaches would not be appropriate in this context (United Nations Environment Programme and World Health Organization, 2013). Few of the studies identified in this review formally evaluated dose–response relationships, likely because of small sample sizes. A study conducted in Korean Vietnam veterans did not find a difference in diabetes prevalence across categories of estimated Agent Orange exposure (Kim et al., 2003), while a study conducted in Yucheng "oil disease" cohort members found that within the exposed group, women with higher mean serum PCBs were significantly more likely to report having diabetes compared to women with lower mean serum PCBs, suggesting a potential dose–response effect (Wang et al., 2008). Two studies reported adjusted p-values for trends across tertiles (Son et al., 2010; Kim et al., 2014). The first found significant trends for serum concentrations of oxychlordane, *trans*-nonachlor, HCB, β-HCH, p,p′-DDE, p,p′-DDT, and o,p′-DDT (Son et al., 2010), and the second found a marginally significant trend for PCBs with ≤5 chlorides in SAT and a significant trend for DDTs in VAT (Kim et al., 2014). Finally, Chang et al. (2010a) reported unadjusted p-values for trends in insulin resistance and beta-cell function, and found a significant monotonic increase in insulin resistance across quartiles of serum PCDD/F concentrations.

4.4.3. Variability in exposure assessment

Only half of the articles included in this review measured levels of the exposure directly in human samples. The remaining articles relied on employee rosters, cohort registries (for the "oil disease" studies), military records, or residential area, all of which could have led to measurement error. Among those that directly quantified serum or VAT/SAT concentrations of POPs, most used high-resolution gas chromatography (HRGC)/high-resolution mass spectrometry (HRMS), which provides the most accurate measurement available for these exposures. Results of these studies are therefore less likely to be biased as a result of exposure misclassification, though are still subject to confounding as discussed previously.

4.4.4. Variability in outcome assessment

A key limitation of the current literature is that many of the studies used self-reported history of diabetes to define the outcome, and thus were not able to differentiate between type 1 diabetes and type 2 diabetes; disorders having very different etiologies. Furthermore, in the sample of Taiwanese residents living near municipal waste incinerators, while serum PCDD/F concentrations were strongly associated with measured blood glucose, the association between serum PCDD/F concentrations and self-reported history of physician-diagnosed diabetes was only marginally significant ($p = 0.07$) in the unadjusted analysis and non-significant ($p = 0.49$) in the adjusted analysis (Chen et al., 2006). These results exemplify that the choice of diabetes definition can lead to different exposure–disease associations. Future research should evaluate multiple outcome definitions in order to improve our understanding of potential causal pathways.

Taking all of these limitations into account, ideally, future epidemiological studies should prospectively follow large, randomly selected and nationally representative samples. Exposure to POPs and non-persistent pesticides should be directly measured in appropriate biological specimens (blood or urine) at multiple time points throughout follow-up, as should multiple indicators of impaired glucose metabolism (e.g. fasting plasma insulin and glucose). Information on key confounders, particularly adiposity as measured by dual-energy X-ray absorptiometry (DXA), should also be collected concurrent with the exposure measures.

5. Conclusions

There are several substantial gaps in our knowledge of the impact of POPs and pesticides on diabetes risk in Asia, especially South and South-Eastern Asia. Gaps include differences by disease outcomes; how POP exposure varies by sex and race/ethnicity, especially when considering varying levels of adiposity, insulin resistance, and beta-cell function; and which POPs may be most feasible/effective to intervene upon in Asia with the goal of reducing the prevalence of diabetes. Given that the burden of diabetes in this part of the world is already significant and expected to increase, well-conducted research that begins to answer these questions is urgently needed.

Acknowledgments

This work was unfunded.

Appendix A. Supplementary material

Supplementary material to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.12.001.

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