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Exposure to pesticides and diabetes: A systematic review and meta-analysis

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ABSTRACT

Background: Diabetes mellitus has a multifactorial pathogenesis with a strong genetic component as well as many environmental and lifestyle influences. Emerging evidence suggests that environmental contaminants, including pesticides, might play an important role in the pathogenesis of diabetes.
Objectives: We performed a systematic review and meta-analysis of observational studies that assessed the association between exposure to pesticides and diabetes and we examined the presence of heterogeneity and biases across available studies.
Methods: A comprehensive literature search of peer-reviewed original research pertaining to pesticide exposure and diabetes, published until 30st May 2015, with no language restriction, was conducted. Eligible studies were those that investigated potential associations between pesticides and diabetes without restrictions on diabetes type. We included cohort studies, case–control studies and cross-sectional studies. We extracted information on study characteristics, type of pesticide assessed, exposure assessment, outcome definition, effect estimate and sample size.
Results: We identified 22 studies assessing the association between pesticides and diabetes. The summary OR for the association of top vs. bottom tertile of exposure to any type of pesticide and diabetes was 1.58 (95% CI: 1.32–1.90, $p = 1.21 \times 10^{-6}$), with large heterogeneity ($I^2 = 66.8\%$). Studies evaluating Type 2 diabetes in particular ($n = 13$ studies), showed a similar summary effect comparing top vs. bottom tertiles of exposure: 1.61 (95% CI 1.37–1.88, $p = 3.51 \times 10^{-9}$) with no heterogeneity ($I^2 = 0\%$). Analysis by type of pesticide yielded an increased risk of diabetes for DDE, heptachlor, HCB, DDT, and *trans*-nonachlor or chlordane.
Conclusions: The epidemiological evidence, supported by mechanistic studies, suggests an association between exposure to organochlorine pesticides and Type 2 diabetes.

1. Introduction

Diabetes mellitus encompasses a group of diseases characterized by hyperglycaemia due to reduced insulin production, insulin action, or both. Type 2 diabetes (T2D) accounts for the vast majority of cases (approximately 90% of all cases) (Nolan et al., 2011). Diabetes is a world-wide epidemic, currently affecting more than 350 million people and expected to reach 550 million by 2050 (Whiting et al., 2011). It represents a major public health challenge across the globe, due to the immediate cost of treatment but also the burden of diabetes-associated morbidity and mortality.

Diabetes mellitus has a multifactorial pathogenesis with a strong genetic component (Bradfield et al., 2011; Morris et al., 2012) as well as many lifestyle influences. The increasing incidence of diabetes, in particular T2D, has been mainly attributed to lifestyle factors, including westernization of diet and obesity. Over the last few years, emerging evidence suggests that environmental contaminants may also play an important role. Pesticides represent an increasingly widespread environmental exposure today and some of them (e.g. organochlorine [OC]) have the potential to accumulate in human tissues either through direct exposure or through the food chain. Different types of pesticides including OC compounds have been directly associated with increased

Abbreviations: OR, Odds ratio; CI, Confidence interval; DDE, Dichlorodiphenyl dichloroethylene; HCB, Hexachlorobenzene; DDT, Dichlorodiphenyltrichloroethane.

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T2D risk in a dose-response way (Lee et al., 2006) as well as with diabetes risk factors including adiposity, insulin resistance and dyslipidaemia (Lee et al., 2011b). However, evidence to date has been inconsistent.

In this report, we performed the first systematic review of observational studies that assess the association between exposure to a wide range of pesticides and different types of diabetes including T2D, Type 1 diabetes (T1D) and gestational diabetes. We performed quantitative synthesis to calculate a summary effect size when data were available and we assessed the presence of heterogeneity and biases across available studies.

2. Materials and methods

2.1. Data sources and searches

We conducted a comprehensive literature search of peer-reviewed original research pertaining to pesticide exposure and diabetes. We have updated a systematic literature search published by the European Food and Safety Authority, which only included studies published within January 2006 to September 2012, to include studies published before and after those dates (Ntzani et al., 2013), using the same search strategy and inclusion criteria. The review highlighted a potential association between diabetes and pesticides but concluded that evidence beyond the timeline examined needs to be gathered to support this observation along with more thorough examination of individual study characteristics and individual pesticides (Ntzani et al., 2013). The search strategy was designed so as to identify observational epidemiologic studies which examined the relationship between any pesticide exposure and any type of diabetes. The last search was performed on 30st May 2015. Two reviewers (GN, MC) independently searched MEDLINE (through PubMed) and EMBASE (See Fig. A.1 in Supplemental Material for search algorithm) without any language restrictions to identify eligible articles. In case of inconsistencies, consensus was reached with a third experienced reviewer (EE, IT, EEN). Studies were first screened at the title only level as previously suggested (Mateen et al., 2013) followed by abstract and tile screening.

2.2. Study selection

Eligible studies were those that investigated potential associations between pesticide exposure and diabetes without restrictions on diabetes type. We included cohort studies, case–control studies, and cross-sectional studies and we excluded reviews, case reports, conference abstracts and ecological studies. Studies or analyses on arsenic, α, β, hexachlorocyclohexane (HCH), lead, dioxins (and dioxin-like compounds), polychlorinated biphenyls (PCBs), and polychlorinated dibenzofurans PCDFs) were excluded as they are not strictly classified as pesticides. Also, studies on poisoning and Agent Orange studies on very high exposure doses were excluded.

2.3. Data extraction

From each eligible study, two independent reviewers extracted information on the first author; the journal and the year of publication; the type and name of pesticide assessed; how exposure was assessed (questionnaire/biomarker); the outcome definition; the effect estimate and its uncertainty; the comparison level; origin of the population; total sample size and number of cases and controls; and the study design.

2.4. Data synthesis and analysis

We defined three groups of studies based on their definition of the outcome examined: studies with no clear reported definition of diabetes type (not specific statement about type of diabetes) which according to the age range of the population could be assumed to be predominately T2D studies (nonspecific definition); and studies with a clear statement in their methods that they studied T2D type (specific definition); studies of T1D; and studies of gestational diabetes. Our main analyses focused on the association of T2D (either nonspecific or specific) with the exposure to i) any pesticide and ii) OC pesticides only. We also performed a sensitivity analysis including only the studies that provide estimates adjusted for BMI and/or smoking habits. Eligible studies often reported more than one analysis using different types of pesticides in the same article. For the analysis on any pesticide, we included in the main analysis the reported comparison with the largest sample size opting for maximal precision. Whenever two or more eligible articles studied the same population, pesticide and examined the same exposure period, the most recent publication was included in the analysis. Additionally, we performed meta-analyses for specific types of pesticides whenever data were available in more than 3 studies. We calculated summary ORs by pooling the study-specific estimates using fixed and random-effects models (DerSimonian and Laird, 1986; Lau et al., 1997). The presence and extent of heterogeneity was assessed by the I^2 (ranging from 0% to 100%) (Higgins et al., 2003; Ioannidis et al., 2007). We assessed 95% predictive intervals (PI) to display the confidence interval of the approximate predictive distribution of a future trial, based on the extent of heterogeneity (Higgins et al., 2009; Riley et al., 2011).

Different effect estimates were often used for the association between pesticides exposure and diabetes across studies (such as per-unit change or per–1-SD change or comparisons of the extremes of quintiles, quartiles, tertiles or other groupings). To enable a consistent and comparable approach to meta-analysis, estimates were transformed and harmonized to represent top and bottom tertiles using previously described and widely used methods. Harmonization to unit increase changes was not possible as most studies reported categorical and not continuous exposure estimates. For example, log risk estimates were transformed with the comparison between the top and the bottom thirds being equal to 2.18 times the log risk estimate for one SD increase, 2.54 times for a comparison of the top vs. bottom quartiles and 2.78 for the top vs. bottom quintiles (Chene and Thompson, 1996).

We assessed small study effects (an indication of publication bias) by visual inspection of funnel plots and the Egger test (Egger et al., 1997). To assess possible sources of heterogeneity we performed a meta-regression according to pre-specified study-level characteristics: exposure assessment; exposure type (occupational vs. non-occupational); and median sample sizes (above vs. below). All analyses were performed with Stata (version 10; StataCorp, College Station, TX, USA) and p-values < 0.05 were deemed significant.

3. Results

Fig. 1 shows the flow chart for the study selection process; nine new studies updated the systematic review prepared for and published by EFSA (Ntzani et al., 2013). In total, 25 studies assessing diabetes were deemed eligible with a total sample size of 80,161 participants (5841 cases/74,320 controls) and median sample size of 725 participants (interquantile range [IQR]: 352 to 2047) per study. Table 1 provides an overview of the main study characteristics. The majority of the studies were cross-sectional ($N = 12$ studies) but there was also data from 8 prospective cohort studies. Ten studies were based in North-America, 8 in Europe, 4 in Asia-Pacific region. The majority ($N = 21$) of studies assessed organochlorine exposure using biomarker measurements of various metabolites. Overall, 22 studies were either assumed to examined T2D due to study age range or clearly defined in their methods that examined T2D only, 1 study examined T1D only and 2 focused on gestational diabetes. All studies reported age-adjusted effects.

3.1. Type 2 diabetes

The summary OR for the association of the top vs. bottom tertile of exposure to any type of pesticide and T2D (nonspecific definition)