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# Association of hexachlorobenzene in the serum and adipose tissue with type 2 diabetes: a systematic review and meta-analysis and meta-regression

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## ABSTRACT

*The prevalence of metabolic disease type 2 diabetes is increasing. Numerous studies have to take into consideration in addition to the factors such as low mobility, nutrition and inheritance, environmental factors such as hexachlorobenzene in creation of type 2 diabetes. Therefore, it was tried in this study to obtain an exact result regarding the association of hexachlorobenzene with type 2 diabetes by doing a systematic review and meta-analysis of the cross-sectional and prospective studies which were received till 2 March 2016. After searching in the databases SID, Irandoc, Pubmed, Scopus, Ovid, Embase, ISI and Cochrane, 10 studies with 19 subgroups were considered in final assessment. Geometric mean concentration of Hexachlorobenzene was 12.7 ng/ml and 64.77 ng/g lipids in serum and adipose tissues, respectively. The heterogeneity index of* $I^2$*:25.95% (*$I^2$*<50%) and* $t^2$*:0.075 were low and hence fixed model was used for meta-analysis of studies' results. The Pearson correlation coefficient between concentrations of hexachlorobenzene in serum and adipose tissue with the odds ratio of type 2 diabetes were* $R^2$*:0.27, P value=0.57 and* $R^2$*:0.25, P value=0.18, respectively. The highest and lowest odds ratios of type 2 diabetes was [OR:6.2 (0.6-68.1)] and [OR:0.99 (0.3-2.6)], respectively. Overall, the odds ratio for type 2 diabetes induced to hexachlorobenzene was OR:2.33 (1.82-2.74) P value<0.001. Results of this study supported the role of hexachlorobenzene significantly as an environmental risk factor in type 2 diabetes (P<0.001).*

**Keywords:** Type 2 diabetes, hexachlorobenzene, serum tissue, adipose tissue, systematic review

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## INTRODUCTION

High blood glucose levels due to insulin resistance and beta cells dysfunctions are caused by a metabolic disease called type 2 diabetes (T2D)[1,2]. The prevalence of type 2 diabetes mellitus was 2.8% (171 million) in 2000 and it is predicted to reach 4.4% (366 million) by 2030 [3]. The World Health Organization (WHO) has predicted diabetes as the seventh leading cause of death by 2030 [4]. Also, International Diabetes Federation has reported that approximately 592 million people (10.1%) will develop this disease till 2035 [5]. This increasing trend has been attributed to the genetic and environmental factors [6,7]. Diabetes risk factors are include low mobility, obesity, genetics, race, age, high blood pressure and high triglycerides and low amounts of high-density lipoproteins (HDLs) [8,9]. Genetic and racial factors were allocated only 6% of the shares of type 2 diabetes [10]. Although, low mobility is the main cause of obesity and metabolic dysfunction but many evidences were obtained which suggest that environmental factors such as Persistent Organic Pollutants (POPs) [11] are also effective in susceptibility to type 2 diabetes mellitus [12-14]. One of POPs are organo-chlorinated pesticides including Hexachlorobenzene (HCB), 2,2,7,8 tetrachlorodibenzopdioxin (TCDD or dioxin), polychlorinated dibenzofurans (PCDFs), non TCDD polychlorinated dibenzopdioxins (PCDDs), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDD) [15]. Organochlorine pesticides disrupts endocrine function [16], energy production process with impaired glucose uptake [17,18] and dysfunction of adipocyte [19]. Despite use of Hexachlorobenzene (HCB), α- and β-hexachlorocyclohexane and dichlorodiphenyltrichloroethane has been banned in many countries such as India in the late 1990s, China 1983 [20] and US.EPA (1984), but they are still used in some developing countries [21]. Due to the high environmental resistance [22], high atmospheric transfer [23] and heavy use in agriculture, hexachlorobenzene enter the human body through the food chain [24]. Using of foods with animal origin is the main source of human exposure to hexachlorobenzene [25]. Several cross-sectional studies have shown the association of POPs and type 2 diabetes [15, 26-28]. Also some limited prospective studies have shown that the increase in POPs increased the risk of type 2 diabetes [29-31], but the association of hexachlorobenzene with type 2 diabetes have not been specifically studied. In some studies, hexachlorobenzene has been reported as significantly associated with type 2 diabetes [32] but in some other studies, there is no significant associate or this associate is statistically weak. Hence, it was tried in this study to conduct an accurate evaluation of the association of serum and adipose concentrations of hexachlorobenzene with type 2 diabetes by a systematic review and meta-analysis and meta-regression.

## MATERIALS AND METHODS

The present study was a systematic review and meta-analysis and meta-regression of the association of concentration of hexachlorobenzene in the serum and adipose tissues with type 2 diabetes. To find the conducted studies in Iran and the world, were used the databases of SID, Irandoc, Pubmed, Scopus, Ovid, Embase, ISI and Cochrane.

### The criteria of selection and evaluating quality of studies

At first, a list of titles and abstracts of all available studies in databases mentioned by three researchers (Ya.F, Ha.K,Na.A) was developed to avoid biased investigators. Related titles were examined independently then search in studies which were published between the dates 2002 to 2016, was done. Searching was done for two weeks from 18.02.2016 to 02.03.2016, then the related were evaluated initially as blind and independently were entered into the research process. Similar studies were excluded. The main inclusion criteria of different articles to this study was referring to the serum and adipose tissue Hexachlorobenzene and type 2 diabetes mellitus. The researches which were not the primary studies or were about treatment, determining the clinical characteristics, clinical decision making and evaluations not related to type 2 diabetes mellitus were excluded from the study. In the second phase, the abstracts of different selected studies were evaluated by a researcher using Strengthening the reporting of observational studies in epidemiology (STROBE) check list which is a standard check list. This check list contains 43 various sections and aspects of methodology including sampling methods, measuring variables, statistical analysis and evaluates the objectives of study [33]. In this check list, the minimum and maximum scores were considered as 40 and 45, respectively. Finally, the top paper which had been obtained at least 40 score given to the questions of the check list were entered to the study and their data were extracted for meta-analysis process.
To determine sensitivity of study for Publication Bias, Funnel Plot and Begg-Mazumdar test were used as well as meta regression test which was applied to determine the effect of other variables on heterogeneity [34].

### Data extraction

In this study, 10 papers (19 subgroups) which almost a same methodology was used in all of them and were performed from 2007 to 2014, were evaluated. The required important information to analyze data including the information related to the topic, title and methodology such as method of study, type, location of study, odds ratio, gender, concentration of HCB in serum, concentration of HCB in adipose tissue, confidence interval, sample volume and confidence level were gathered.

### Data synthesis and analysis

All statistical analysis was done by comprehensive meta-analysis V.2.2.06 software. The statistics $I^2$ and $T^2$ were calculated using Moment Base Method as an estimator of heterogeneity. After determining the low heterogeneity of studies ($I^2$<50%) based on the fixed effect model, the mean of odds ratio was calculated. The pooled plot in the fixed model was used to evaluate the significance of the association of the HCB in serum and adipose tissue with type 2 diabetes mellitus. Since the number of studies are usually low in the review studies, so the significance level for the odds ratio is P value<0.001 [35]. Using the meta-regression method, the effects of variables including sample volume, study time, concentration of HCB in the serum and adipose tissue which were supposed of causing heterogeneity in the study were studied. The significance level for the covariance of studies was considered as P value<0.05. At the end, concentrations of HCB in the serum and adipose tissue with the prevalence of type 2 diabetes and comparison of the odds ratio of type 2 diabetes were calculated by SPSS 16 software (Independent t test) in the cross-sectional and prospective studies.

## RESULTS

345 studies were searched in the mentioned databases which 179 and 166 of them were considered as irrelevant and related based on title and abstract. Then, 154 review studies, case reports, animal studies or studies with irrelevant results were separated. Of 14 obtained studies, 3 studies which are related to type 1 diabetes and mortality were excluded. Finally, 10 studies [3 prospective studies (4 subgroups) and 7 cross-sectional studies (15 subgroups)] were evaluated (Fig 1).

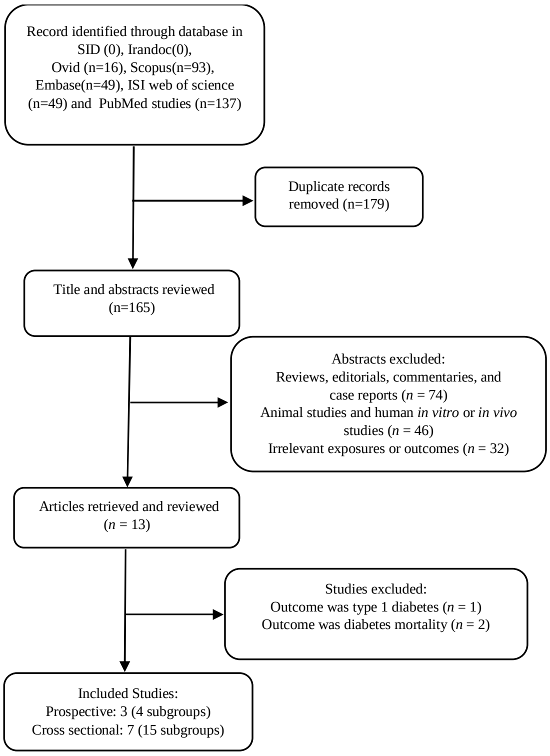


**Figure 1. Studies selection process for meta-analysis**

After the primary analysis, since the heterogeneity indices including $I^2$=25.95 (I2<50%) and $t^2$=0.075 were low (Table 2) so, there is not a huge difference between studies hence Fixed Effect Model was used for meta-analysis of the studies' results. $I^2$=25.95 showed that 25.95% of the observed differences between the studies indices is due to the heterogeneity of studies.

The total number of people in 10 studies was 5449 people that the geometric mean and HCB concentration in their serum and adipose tissue were 12.7 ng/ml and 64.77 ng/g lipids, respectively. In some studies, HCB unit was different therefore after making the units identical, the mean was calculated. The maximum and minimum odds ratios were related to Son et al study [OR=6.2 (0.6-68.1)] and Codru et al study [OR=0.99 (0.3-2.6)] (Table 1). The total odds ratios in the cross-sectional and prospective studies were OR=2.12 (1.7-2.63), P value<0.001 and OR=3.35 (1.83-6.11), P value<0.001 respectively and generally OR=2.33 (1.82-2.74), P value<0.001 (Fig 2).

**Table 2. Overall results of meta-analysis odds ratio diabetes mellitus type 2 induced by HCB**

| | | | | Heterogeneity | | |
|---|---|---|---|---|---|---|
| **Model** | **Mean odds ratio** | **Z-value** | **P-value** | **P-value** | **$I^2$** | **$t^2$** |
| Fixed | 2.23 | 7.66 | <0.000 | 0.14 | 25.95 | 0.075 |

Despite the low heterogeneity, the effective variable in heterogeneity of studies was identified by the meta-regression model. So, the covariance of the study location, study time, HCB concentration in the adipose tissue, HCB concentration in the serum, type of study and sample volume were entered to the meta-regression analysis in moment base. Since in most studies, a detailed breakdown was not done between the genders men and women, so entering the covariance of gender was neglected.

| Type of Study | First name | Odds ratio | Lower | Upper | Z-Value | P-Value |
|---|---|---|---|---|---|---|
| Cross-Sectional | Gasull et al | 1.70 | 0.98 | 2.94 | 1.89 | 0.06 |
| Cross-Sectional | Gasull et al | 1.90 | 1.02 | 3.55 | 2.01 | 0.04 |
| Cross-Sectional | Gasull et al | 1.60 | 0.72 | 3.58 | 1.14 | 0.25 |
| Cross-Sectional | Arrebola et al | 2.30 | 0.68 | 7.75 | 1.34 | 0.18 |
| Cross-Sectional | Arrebola et al | 5.27 | 1.61 | 17.25 | 2.75 | 0.01 |
| Cross-Sectional | Al-Othman et al | 3.00 | 1.22 | 7.35 | 2.40 | 0.02 |
| Cross-Sectional | Al-Othman et al | 4.30 | 2.16 | 8.55 | 4.16 | 0.00 |
| Cross-Sectional | Ukropec et al | 1.25 | 0.64 | 2.44 | 0.66 | 0.51 |
| Cross-Sectional | Codru et al | 2.50 | 0.91 | 6.87 | 1.78 | 0.08 |
| Cross-Sectional | Codru et al | 4.80 | 1.68 | 13.73 | 2.93 | 0.00 |
| Cross-Sectional | Codru et al | 0.90 | 0.31 | 2.65 | -0.19 | 0.85 |
| Cross-Sectional | Codru et al | 4.50 | 1.41 | 14.38 | 2.54 | 0.01 |
| Cross-Sectional | Cox et al | 1.30 | 0.70 | 2.41 | 0.83 | 0.40 |
| Cross-Sectional | Son et al | 6.20 | 0.58 | 66.05 | 1.51 | 0.13 |
| Cross-Sectional | Son et al | 6.10 | 1.01 | 36.90 | 1.97 | 0.05 |
| Cross-Sectional | | 2.12 | 1.70 | 2.63 | 6.73 | 0.00 |
| Prospective | Lee et al | 2.10 | 0.61 | 7.22 | 1.18 | 0.24 |
| Prospective | Wu et al | 3.73 | 1.05 | 13.28 | 2.03 | 0.04 |
| Prospective | Wu et al | 3.46 | 1.02 | 11.72 | 1.99 | 0.05 |
| Prospective | Burns et al | 4.37 | 1.44 | 13.27 | 2.60 | 0.01 |
| Prospective | | 3.35 | 1.83 | 6.11 | 3.93 | 0.00 |
| Overall | | 2.23 | 1.82 | 2.74 | 7.67 | 0.00 |

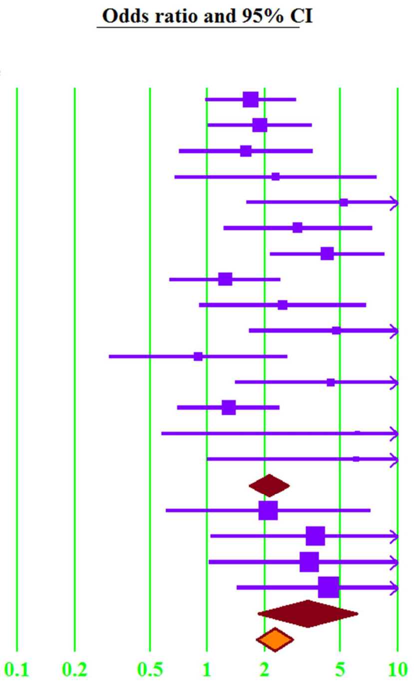


**Figure 2.forest plot of odds ratio diabetes mellitus type 2 in the prospective and cross sectional study**

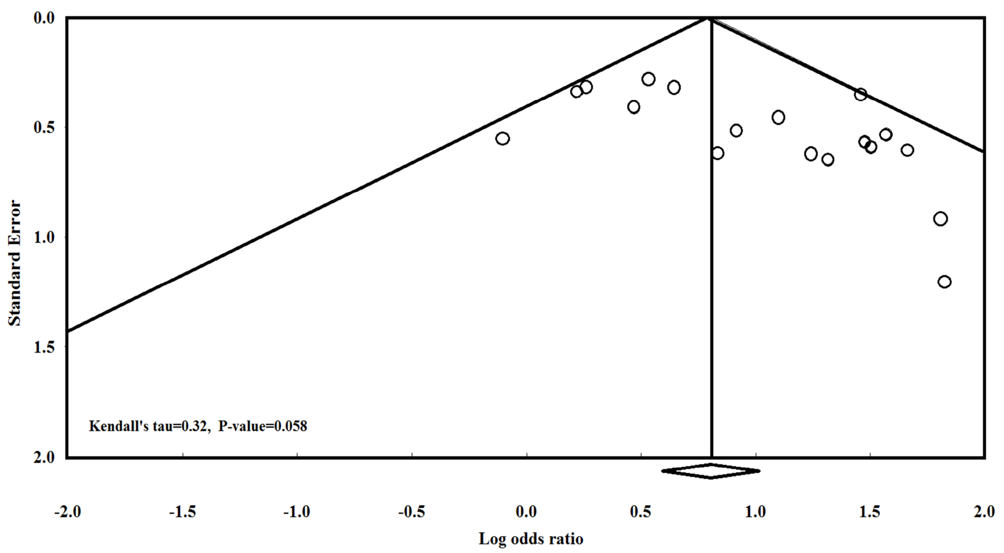


**Figure 3. Funnel plot of standard error by log adds ratio**

**TABLE 1. Cross-sectional and prospective studies of Hexachlorobenzene and type 2 diabetes risk**

| First Author | Year | Type study | OR | 95% CI | | Number samples | Concentration | Serum/ Lipids | Location | Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gasull et al | 2012 | Cross-Sectional | 1.70 | 1.00 | 3.00 | 360 | 0.510 −1.193 ng/ml | Serum | Spain (Catalonia) | Male and Female | Concentrations of p,p′-DDT, p,p′-DDE and β-HCH were not associated with diabetes or prediabetes. Increasing concentrations of PCBs and HCB were positively associated with diabetes and prediabete | [35] |
| | | | 1.90 | 1.00 | 3.40 | | 1.194 −2.610 ng/ml | Serum | | | | |
| | | | 1.60 | 0.70 | 3.50 | | >2.61 ng/ml | Serum | | | | |
| Lee et al | 2011 | Prospective | 2.10 | 0.60 | 7.10 | 725 | Not mentioned | Serum | Sweden | Male and Female | Exposure to some POPs substantially increased risk of future type 2 diabetes in an elderly population. | [36] |
| Arrebola et al | 2013 | Cross-Sectional | 2.30 | 0.68 | 7.73 | 386 | 7.37–30.07 ng/g lipid | Lipids | Spain (Southern) | Male and Female | A statistically significant interaction was observed between p,p 0-DDE and body mass index, such that the risk of diabetes increased with tertiles of exposure in a linear manner in non-obese subjects but not in the obese, in whom an inverted U-shape pattern was observed | [29] |
| | 2013 | Cross-Sectional | 2.27 | 1.62 | 17.14 | | > 30.07 ng/g lipid | Lipids | | | | |
| Wu et al | 2012 | Prospective | 3.73 | 1.05 | 13.30 | 1095 | 34.1 ng/ml | Serum | Usa | Female | Support an association between POP exposure and the risk of T2D | [37] |
| | | | 3.46 | 1.02 | 11.70 | | 41.6 ng/ml | | | | | |
| Al-Othman et al | 2014 | Cross-Sectional | 3.00 | 1.20 | 7.20 | 60 | 8.8 ng/ml | Serum | Saudis Arabic | Male | Diabetes associated with HCH pesticide exposure and proposes possible hormonal pathways worthy of further investigation | [38] |
| | | | 3.30 | 1.90 | 7.60 | 76 | 8.8 ng/ml | Serum | | Female | | |
| Ukropec et al | 2010 | Cross-Sectional | 1.86 | 1.17 | 3.57 | 410 | 1364–17927 ln ng/g lipid (mean:9.17 ng/g lipid) | Lipids | Slovakia | Male and Female | Interestingly, unlike PCBs, DDT and DDE, increased levels of HCB and β-HCH seemed not to be associated with increased prevalence of diabetes. | [39] |
| Codru et al | 2007 | Cross-Sectional | 2.50 | 0.90 | 6.80 | 352 | 12.1± 6.5 ng/g lipid | Lipids | American (Mohawk) | Male and Female | Elevated serum PCBs, DDE, and HCB were positively associated with diabetes after controlling for potential confounders, whereas a negative association was observed for mirex. | [40] |
| | | | 4.80 | 1.70 | 13.90 | | 12.1± 6.5 ng/g lipid | Lipids | | | | |
| | | | 0.9 | 0.30 | 2.60 | | 0.08 ± 0.04 ppb | Serum | | | | |
| | | | 4.5 | 1.4 | 14.3 | | 0.08 ± 0.04 ppb | Serum | | | | |
| Cox et al | 2007 | Cross-Sectional | 1.3 | 0.7 | 2.4 | 1303 | 1.63 ppb | Serum | Mexico | Male and Female | Higher serum levels of certain organochlorine pesticides may be associated with increased prevalence of diabetes. Additional studies with more extensive clinical assessment are needed to confirm this association. | [41] |
| Son et al | 2010 | Cross-Sectional | 6.2 | 0.60 | 68.10 | 80 | 149.3 ± 92.8 pg/g | Serum | South Korea | Male and Female | Low-dose background exposure to OC pesticides was strongly associated with prevalent type 2 diabetes in Koreans even though absolute concentrations of OC pesticides were no higher than in other populations. Asians may be more susceptible to adverse effects of OC pesticides than other races | [42] |
| | | Cross-Sectional | 1.90 | 0.30 | 10.00 | | 24.2 ± 13.0 ng/g lipid | Lipids | | | | |
| Burns et al | 2014 | Prospective | 4.37 | 1.44 | 13.28 | 602 | 770 ng/g lipid | Lipids | Russian | Male and Female | Higher hexachlorobenzene (tertile 3 vs. tertile 1) was associated with higher odds of IR in models adjusted for BMI (odds ratio = 4.37, 95% confidence interval: 1.44, 13.28) | [43] |

Type and time of study did not have a significant effect on heterogeneity of studies (p value>0.05) but the difference in HCB concentration in adipose tissue and serum, study location and number of samples were significantly effective on heterogeneity of studies (Table 3). Being reverse of the funnel chart, logarithmic pooled of the studies odds ratios were not significant and on top of the funnel. Begg-Mazumdar test (p value=0.058) showed a general lack of biases in studies (Fig 3).

## DISCUSSION

The meta-analysis results of 10 studies with low heterogeneity ($I^2$<50%) in fixed model showed that an increase concentrations of HCB in the serum and adipose tissue increased the risk of type 2 diabetes significantly (p value<0.001).

### Meta-Analysis and Meta-Regression

Pearson correlation coefficient between the concentration of HCB in adipose tissue and serum with the odds ratio of type 2 diabetes was $R^2$=0.27, P value<0.57 and $R^2$=0.25, P value<0.18, respectively. Due to the difference in the selected studies such as sample volume, concentration of HCB, study location and etc., a significant Pearson correlation coefficient was not achieved but with the increase in concentration of HCB in the adipose tissue and serum, the risk of type 2 diabetes was increased (Fig 4, 5).

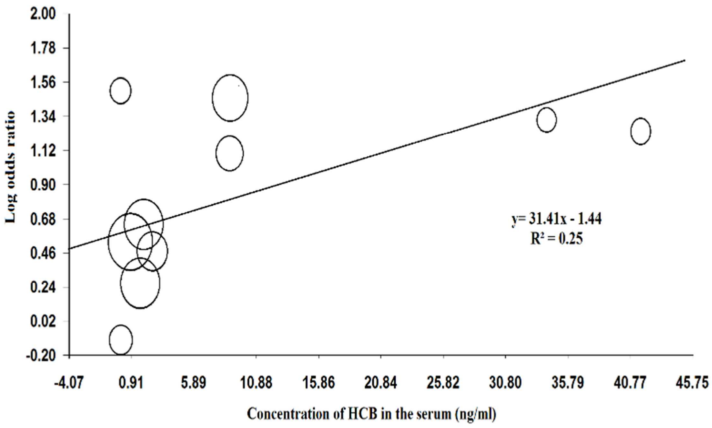


**Figure 4. Correlation on HCB in the serum with log odds ratio type 2 diabetes**

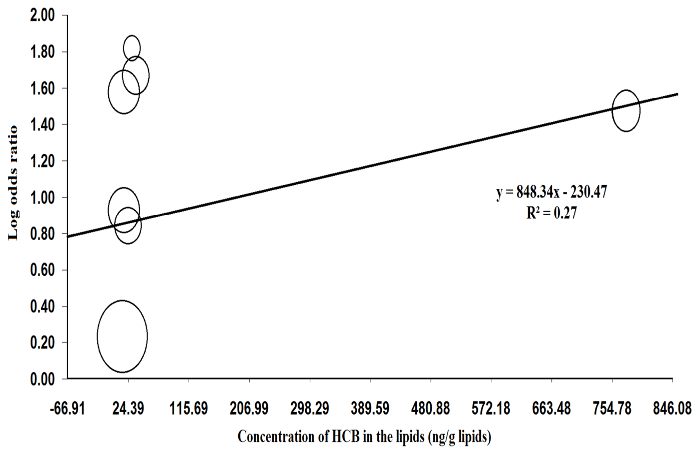


**Figure 5. Correlation on HCB in the lipids with log odds ratio type 2 diabetes**

Concentration of HCB in the adipose tissue and serum, date study, number samples and location study in meta-regression analysis were known as the significant factors of heterogeneity creation (Table 3).

**Table 3. Meta-regression analysis of Covariance in the studies**

| | Crude | | Adjusted | |
|---|---|---|---|---|
| **Covariance** | **Coefficient** | **P value** | **Coefficient** | **P value** |
| Date study | 0. 71 | 0.12 | 2.1 | 0.39 |
| Concentration in serum | 0. 24 | 0.032 | 0.92 | 0.015 |
| Concentration in lipids | 0.048 | 0.043 | 1.4 | 0.011 |
| Type study | 0.41 | 0.24 | 2.6 | 0.7 |
| Number samples | -0.004 | 0.001 | -0.064 | 0.001 |
| Location study | 0.038 | 0.029 | 0.069 | 0.014 |

Despite the lack of significant difference between the prevalence of type 2 diabetes in cross-sectional and prospective studies (p value=0.62), because of more credit of prospective studies, they were separated in meta-analysis. The mean of odds ratio in cross-sectional and prospective studies were observed as 2.12 (95%CI:1.7-2.63) and 3.35 (95%CI 1.83-6.11), respectively (Fig 2). Despite the prevalence of type 2 diabetes was not significantly increased from 2007 to 2014 ($R^2$:0.014, P value=0.06), but the studies showed that over time, the prevalence of type 2 diabetes was significantly increased due to changes in nutrition, decreased mobility and increased environmental pollutants [3,44]. One of the lack of significance in the increased prevalence of type 2 diabetes can be the short range of studies years.

**Environmental and genetic differences**

Although the World Health Organization (WHO) has announced, the prevalence of type 2 diabetes does not have a significant difference between men and women in general and only is higher in men lower than 60 years old and women upper than 65 years old [45]. But the genetic differences between man and woman have made women more sensitive to organochlorine pesticides [46]. First, due to the higher body fat and then, accumulation of more HCB and secondly, HCB could disrupt estrogenic activity of women and following that, glucose metabolism [47]. POPs such as organochlorine pesticides cause diabetes through different mechanisms. The most important of these mechanisms include altered gene transcription, lipid metabolism, insulin production, changes in insulin signaling pathway [48] and altered glucose transport [49]. On the other hand, consumption of contaminated food caused by environmental pollution increased concentration of HCB in the body and would be followed by an increase in the prevalence of type 2 diabetes.

It should be noted that the exposure rate has the leading role in the increased prevalence of type 2 diabetes because some studies showed that concentration of POPs such as p,p-DDE were higher in serum and adipose tissues of men than women due to the more exposure [50].

In Glynn et al study, the concentrations of organochlorine pesticides were measured in 205 women who had consumed contaminated fish. The results showed that the mean concentration of HCB in 7 women with diabetes (85 ng/g lipid; 95% CI 66-109) was significantly higher than 198 women without diabetes (60 ng/g lipid; 95% CI 58-63) (p value=0.008) [51].

In Verhulst et al prospective study among mothers and their children (n=138) in Flanders of Belgium who were exposed to environmental pollutants of hexachlorobenzene, dichlorodiphenyldichloroethylene (DDE), dioxin-like compounds and polychlorinated biphenyls (PCBs), BMI between children's with DDE and PCBs especially among children's with mothers who smoker, a positive and significant association was observed. Although, a significant association was not observed between HCB with BMI in this study, but some of POPs cause an increase in adipose tissue production through genetic changes (damage to the gene). Increased adipose tissue accumulation also provides the condition for more POPs accumulation due to these compounds accumulate more in adipose tissue. Of course, Verhulst et al study was the first research in this regard and more research are required to be conducted in this field [52].

**Comparison studies**

In contrast to our study, the results of Ukropec et al study showed that unlike HCB and β-HCH, increasing concentration of DDT, PCBs and DDE in lipid increase the prevalence of pre-diabetes and type 2 diabetes. Of course, it was mentioned in this study that HCB (1.86, 95%CI :1.7-2.9) and β-HCH (1.97, 95%CI 1.28-3.04) adopted to the age, sex and BMI in $5^{th}$ quintile, pre-diabetes and type 2 diabetes were six times more in 1th quintile [39].

Also, in Cox et al study which was among 1303 people from Mexican America aged 20 to 74 from 1982 to 1984, a significant positive relationship was not observed between HCB and the prevalence of type 2 diabetes (self-reported) [41].

Lee et al study, the prevalence of type 2 diabetes in 90 cases and 90 controls showed that there is not a significant association of HCB and type 2 diabetes [53] or among 725 residents in Uppsala, Sweden that 36 cases of diabetes were diagnosed after 5 years following-up, but a significant positive association of was no observed between HCB and type 2 diabetes (self-reported) [36].

The results of Arrebola et al study showed that unlike HCB, increased concentration of p,p-dichlorodiphenyldichloroethylene [OR: 3.6 (0.8-17.3) ]and p-hexachlorocyclohexane [OR: 3.3 (1.0-10.4) ]prevalence of type 2 diabetes was significantly increased [29].
Unlike Ukropec et al study, in Cordu et al study, HCB similar to PCBs and DDE had a significant positive with symptoms of diabetes (serum fasting glucose values>125 mg/dl and/or use of antidiabetic medication).

One of the reasons of significant association of HCB in Codru et al study higher concentration of HCB (12.1±6.5 ng/g lipid) compared to Ukropec et al study (9.17 ng/g lipid) [40].

A significant positive association was observed between concentration HCB in the serum with type 2 diabetes in a group of 1095 women (48 cases of diabetes and 1,047 controls) in Wu et al study like Glynn et al study. Since in Glynn et al and Wu et al studies, was measured concentration of HCB in the adipose tissue and serum respectively, the comparison between HCB concentrations was not performed [51].

In Burns et al study, concentration of HCB was measured in 318 Russian boys (8-9 years of pre pubertal age at baseline; 10-13 years of pubertal age at follow up). There is a significant positive association of concentration of HCB and the risk of insulin resistance (OR 4.37; 95% CI 1.44-13.28). The important point is that concentration HCB in the adipose tissue was very higher in Burns et al study compared to the other studies (770 ng/g lipid). This difference in concentration due to the difference in nutritional pattern of residents especially children's or a source of contamination in the environment [43].

Studies have shown that fish consumption especially which are living in contaminated water increased organochlorine pesticides such as HCB in serum and adipose tissue as well as the risk of type 2 diabetes[51,54-56].
In a community-based health interview survey which was conducted by Gasull et al among 886 participants in Catalonia of Spain, the concentration of HCB serum in prediabetes (202 cases) and diabetes (143 cases) were higher than other groups. Odds ratios for patients with prediabetes and diabetes were 2.1 (95% CI 1.0-4.4) and 3.2 (95% CI 1.3-8.1), respectively. The risk of diabetes in both groups with increased concentration of HCB was significantly higher [35].

In another community-based health interview survey which was conducted by Son et al in 40 cases of type 2 diabetes and 40 controls in Uljin County of South Korea, the results showed that by the increased concentration of HCB in serum and adipose tissue, the risk of type 2 diabetes was significantly increased (p value=0.03) [42].

**Limitations of the study**

The limitations of this study include time limitations of date studies (2002 to 2016), language limitation (except the published studies in English and Persian languages), lack of separation between women and men in some of studies, using small groups (low number of samples), presence of the other organochlorine pesticides in adipose tissue and serum and not to mention the heritance and genetics effects of humans on the prevalence of type 2 diabetes.

## CONCLUSION

The results of the systematic review and meta-analysis and meta-regression of 10 selected studies from different countries showed that the prevalence of type 2 diabetes increased significantly with concentration of HCB in the serum and adipose tissue (P value<0.001). The results of this study supports HCB as a risk factor of type 2 diabetes mellitus.

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