



Association between polychlorinated biphenyls in the serum and adipose tissue with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Prevalence of diabetes, especially type 2 diabetes is increasing. One of the environmental risk factors of this disease is persistent organic pollutants. Studies have obtained different results in the field of association of different congeners of persistent organic pollutants such as polychlorinated biphenyls with type 2 diabetes. In this review study (systematic review and meta-analysis), the authors aimed to evaluate the association of different congeners of polychlorinated biphenyls with type 2 diabetes in both prospective and cross-sectional studies. After a systematic review, 6 prospective and 9 cross-sectional studies were evaluated. Mean of odds ratio and heterogeneity for all the studies were $OR=1.97$; $CI(1.57-2.39)$ and $I^2=42.9\%$; $p_{heterogeneity}=0.009$, respectively. Also, mean of odds ratio for the prospective studies ($OR=1.59$; $CI(1.29-1.95)$; $I^2=2.37\%$; $p_{heterogeneity}=0.42$) was less than that of the cross-sectional studies ($OR=2.4$; $CI(1.71-3.36)$; $I^2=49.8\%$; $p_{heterogeneity}=0.025$). Increase in different congeners of PCBs in the serum and adipose tissue can significantly increase the prevalence type 2 diabetes ($p\text{ value}<0.001$). This study supports a positive association of polychlorinated biphenyls in the serum and adipose tissue with type 2 diabetes.

Key words: Polychlorinated biphenyls, Diabetes, systematic review, meta-analysis, serum, adipose tissue.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is worldwide and this disease is becoming a major public health challenge [1, 2]. Usually, in adulthood, high blood glucose level due to insulin resistance and beta cells dysfunction causes this metabolic disease [3, 4]. World Health Organization (WHO) had estimated that in 2008, 347 million people worldwide were living with diabetes [5]. The majority of people with diabetes are in the age range of 40 to 59 years and 80% of them live in countries with low to middle income. Also, the International Diabetes Federation (IDF) has reported that in 2013, 382 million people (8.3%) of the world population suffered from diabetes and 175 million of them have not been diagnosed and has predicted that about 592 million people (10.1%) will be suffering from this disease by 2035 [6]. Diabetes risk factors include obesity, low physical activity level, diet, genetics, race,

age, hypertension, low high-density lipoprotein (low HDL) and high triglycerides [7-9]. Only 6% of T2DM depends on genetic and racial factors [10] and the role of environmental factors in the development of type 2 diabetes is increasing [11]. National Toxicology Program (NTP) of the United States has reported that the role of environmental factors such as arsenic, persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs), other metals, bisphenol A, phthalates and smoking has increased the risk of T2DM [12-14]. PCBs is one of the congeners of persistent organic pollutants that have a long half-life in the human body and also has a damaging and inhibitory effect on the function of endocrine glands [15]. It is said that PCBs can be induced to T2DM by affecting aryl hydrocarbon (Ah) receptor [16]. In addition to diabetes, POPs has harmful effects on the thyroid mechanism [17] and nervous system [18]. Contaminated foods, especially meat and fish are the primary sources of exposure to PCBs [19-22]. Several cross-sectional studies have revealed the association between POPs and T2DM [13, 23-26]. National Health and Nutrition Examination Survey (NHANES) study of the United States showed a strong dose-response association between diabetes and POPs such as polychlorinated biphenyls (PCB-153), dioxins and organochlorine pesticides (OCPs) [13]. Some limited prospective studies have shown that the increase in serum levels of POPs can increase the risk of T2DM [27-30]. But the association of POPs type like PCBs with T2DM has not been specifically studied. In some studies, PCBs are associated with T2DM [31, 32] and in some studies, there is no association [29]. The difference in sample size, exposure level and other errors relating to population studies is mentioned as the cause of this difference. Hence, this study aimed to achieve an accurate assessment of the association between PCBs of serum and adipose tissue with T2DM by a systematic review and meta-analysis.

MATERIALS AND METHODS

Search and selection of studies

First, a list of titles and abstracts of all available articles in the databases including Pubmed, Scopus, Ovid, Embase and ISI Web of Science from 2015.09.06 to 2015.09.27 was prepared by two investigators (YaF and HaK) and evaluated independently in order to determine and select the related titles. Then, the studies relating to the blinding method were primarily evaluated and independently entered for the research process. The studies were evaluated using a check list of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) which is a standard check list. This check list includes 43 various sections and evaluates various aspects of methodology, including sampling methods, measuring variables, statistical analysis and objectives of the study. In the check list, the minimum and maximum attainable rating scores were considered as 40 and 45, respectively. Finally, the best studies with the minimum score of 40 were used for the research and their related data were extracted for meta-analysis process. At the end, prospective (cohort) and cross-sectional (case-control) studies were evaluated for the association of PCBs congener in serum and adipose tissue with the prevalence of T2DM, accurately. Also, the Boolean term "AND" was used for combination of the keywords.

The keywords used in the research include the following: type 2 diabetes mellitus and diabetes mellitus, insulin resistance and polychlorinated biphenyls, adipose tissue, prospective and cross-sectional studies, adult male, adult men aged, chemically induced, health surveys, middle aged and male, polychlorinated biphenyls, toxicity and polychlorinated biphenyl, prevalence, diabetes and humans, epidemiology and diabetes, polychlorinated biphenyls and serum levels, cholesterol and type 2 diabetes and polychlorinated biphenyl, high density lipoprotein, lipid, polychlorinated biphenyl, prevalence and type 2 diabetes, triacylglycerol, disease association and diabetes, environmental exposure and polychlorinated biphenyls, health survey and diabetes mellitus, prevalence and polychlorinated biphenyl, priority journal, questionnaire on cholesterol, glucose and T2DM, lipid and type 2 diabetes, low density lipoprotein and T2DM and environmental exposure, pesticide and polychlorinated biphenyls, accumulation of polychlorinated biphenyls, beta-cell function and polychlorinated biphenyls and type 2 diabetes.

Data extraction

According to the standard method for data extraction, three independent investigators (YaF, HaK and AbB) extracted and shape of the table all data. Disagreements points about studies were resolved by consensus between three investigators. Information extracted included first author, publication year, study design, concentration of PCBs in serum and adipose tissue, sample size, type PCBs, odds ratio and confidence interval.

Assessment of heterogeneity and data synthesis

All the statistical analyses were done by Comprehensive Meta-Analysis V2.0 software. Heterogeneity (I^2) was determined by Q tests. If significant heterogeneity was observed ($I^2 > 50\%$), the meta-analyses were conducted using a random effect model. A fixed effect model was used for the meta-analysis where heterogeneity was acceptable ($I^2 < 50\%$). $P < 0.05$ was considered significant for tests heterogeneity. To assess the presence of publication bias, funnel plots were used, where $\ln(OR)$ values were plotted against their corresponding CIs. The authors also used cumulative meta-analysis with studies sorted in the sequence from most to least precise to assess the effect of studies with less precision on the OR estimates and to estimate and adjust for the numbers and outcomes of missing studies.

Since, the number of prospective and cross-sectional studies was low, the significance level was p value < 0.001 [33]. Egger's test and Funnel Plot were used to determine Publication Bias.

RESULTS

From the 770 articles (Ovid: 31, Scopus: 69, Embase: 57, ISI: 289 and Pubmed: 324), the 475 articles excluded were duplicated records and the remaining 295 were reviewed abstract. Then, reviews, editorials, commentaries, case reports ($n=79$), animal studies, human *in vitro* or *in vivo* (93) and irrelevant exposures or outcomes studies were excluded (25). From the remaining 98 studies that were excluded from the review, Non-humans articles ($n=81$), outcome was type 1 diabetes ($n=2$) and diabetes mortality ($n=1$). Finally, 6 prospective and 9 cross-sectional articles were remaining for evaluation (Figure 1).

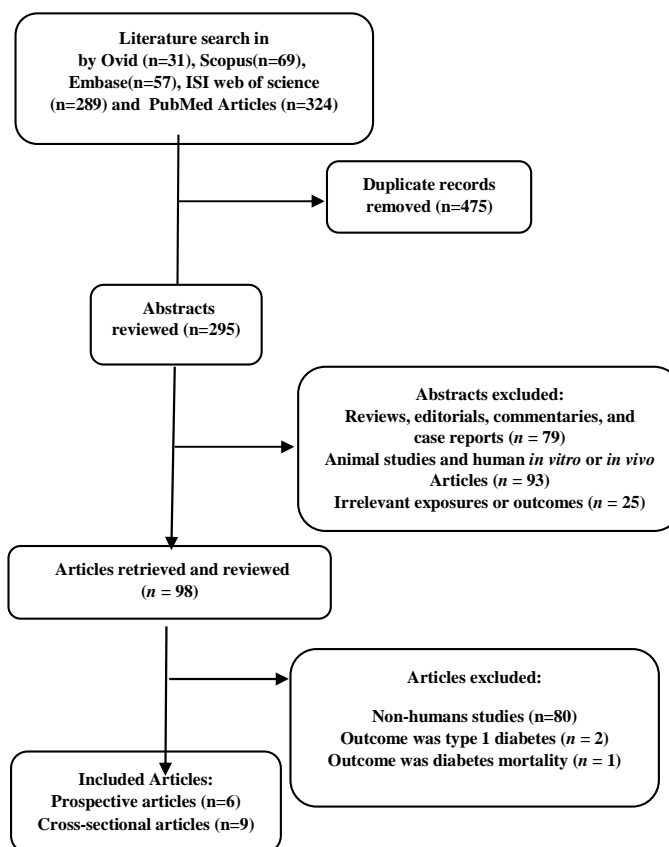


Figure1. Results of literature review following the description of the full search process.

Mean of odds ratio and heterogeneity for all the studies was (OR=1.979; CI (1.57-2.39); $I^2=42.9\%$; $\rho_{\text{heterogeneity}}=0.009$). Mean of odds ratio for the prospective studies (OR=1.59; CI (1.29-1.95); $I^2=2.37\%$; $\rho_{\text{heterogeneity}}=0.42$) was less than that of the cross-sectional studies (OR=2.4; CI(1.71-3.36); $I^2=49.8\%$; $\rho_{\text{heterogeneity}}=0.025$). According to Cochrane classification, I^2 for the prospective and cross-sectional studies has 30-60% moderate I^2 and 50-90% substantial, respectively [34]. Since in most of the review studies, the number of studies under review is low, to compensate for the low power, the significance level in I^2 test and OR and the relative risk was considered as p value < 0.001.

In the prospective studies, lowest and highest OR was observed in Silverstone et al (TPCBs) and Lee et al (PCB-74) studies and in the cross-sectional studies of Tanaka et al (PCB 163/164) and Longnecker et al ($>=5$ $\mu\text{g/l}$, TPCBs), respectively. In all the studies (prospective and cross-sectional), lowest and highest OR were observed in the study of Tanaka et al (PCB 163/164) and Lee et al (PCB-74), respectively (Table 1).

Table1. Characteristics of prospective and cross-sectional studies included in the systemic review and meta-analysis.

Type study	First Author (Year)	Study population	Sample size	Type PCBs	Odd Ratio (Confidence Interval)	Reference
Prospective	Lee et al (2011)	PIVUS (5-year follow-up)	725	TPCBs	7.5 (1.4-38.8)	[27]
				PCB 74	9 (1-78)	
				PCB 153	1.7 (0.5-6.2)	
	Wu et al (2013)	Nurses' Health Study–Breast Cancer Study (18-year follow-up)	673	PCB 118	0.98 (0.26-4.2)	[35]
	Wang ¹ et al (2008)	Victims in the Yucheng registry (24-year follow-up)	747	TPCBs	1 (0.5-1.9)	[29]
	Wang ² et al (2008)			TPCBs	2.1 (1-4.5)	
	Vasiliu ¹ et al (2008)	Michigan PBB Cohort (25-year follow-up)	1384	TPCBs	0.5 (0.23-1.12)	[31]
	Vasiliu ² et al (2008)			TPCBs	1.52 (0.74-3.14)	
	Turyk et al (2015)	Great Lakes sport fish consumers (8.4 y follow-up)	471	TPCBs	2.43 (0.96-6.12)	[36]
Arrebola et al (2013)	Non-cancer surgery patients	386	PCB 118	2.83 (1.35-5.9)	[37]	
			PCB 138	1.53 (0.5-4.3)		
			PCB 180	1.04 (0.35-3.09)		
Cross Sectional	Tanaka et al (2011)	Participant ; 59 (50.4%) were male and 58 (49.6%) were female	117	PCB 163/164	0.14 (0.03-0.58)	[38]
				PCB 182/187	1.15 (0.36-3.64)	
	Airaksinen et al (2012)	Birth cohort in Helsinki	1988	PCB 153	1.64 (0.92-2.93)	[23]
	Silverstone et al (2012)	Birth cohort in Helsinki	1988	TPCBs	1.21 (0.87-1.69)	[39]
	Gasull et al (2012)	Catalan Health Interview Survey in Catalonia	684	TPCBs	2.4 (1.1-5.4)	[40]
				PCB 118	2.1 (1-4.4)	
				TPCBs	1.7 (1.1-2.6)	
	Everett et al (2012)	NHANES 1999–2004	2245	PCB 118	3.53(1.64-7.58)	[41]
	Persky et al (2012)	women were post-menopausal	118	TPCBs	3 (1.3-7)	[42]
				Total Lipid PCBs	3 (1.3-7.2)	
				TPCBs	3 (1.2-7.5)	
				Estrogenic PCBs	2.4 (1.2-4.9)	
	Rignell-Hydbom (2009)	WHILA (7–11-year follow-up)	78	PCB-153	0.99 (0.71-1.4)	[28]
Ukropec et al (2010)	Recruited by physicians from the heavily polluted districts	2047	TPCBs	2.74 (1.92-3.9)	[43]	
Longnecker (2001) et al	Pregnant women	2245	TPCBs (>=5 µg/l)	5.1 (1.9-13.8)	[44]	
			TPCBs (3.75-5 µg/l)	4.4 (1.6-12.5)		
			TPCBs(2.5-5 µg/l)	2.9 (1.1-7.3)		

DISCUSSION

From the meta-analysis-data of the two prospective and cross-sectional studies, it was found that PCBs in the serum and adipose tissue were associated with increased risk of developing T2DM. In the prospective studies, the lowest and highest percentage of weight was in Lee et al (PCB-74) [27] and Wang et al (men, PCBs) [29] studies and in the cross-sectional studies of Tanaka et al (PCB 163/164) [38] and Silverstone et al, (TPCBs) [39], respectively. This difference in weight percentage was due to the difference in the confidence interval. Difference in confidence interval resulted from the difference in the kind of study, the population and number of measurements [45]. Since in the prospective studies, three congeners of PCBs (Lee et al ; TPCB, PCB 174 and PCB-118) had a high confidence interval, the mean of OR was not significant (p value>0.001). But in the cross-sectional studies, only one congener of PCBs (Tanaka PCB 163/164) had a high confidence interval, so the OR was significant (p value<0.001). In Song et al study, the mean of OR for the prospective and cross-sectional studies was 1.63 (1.15-2.33) and 2.92 (2.14-3.92), respectively, which were almost close to that of the present study [46], but the total OR in Song et al study is 2.39 which is higher than that of the present study (Figures 3 and 4).

¹Male
²Female

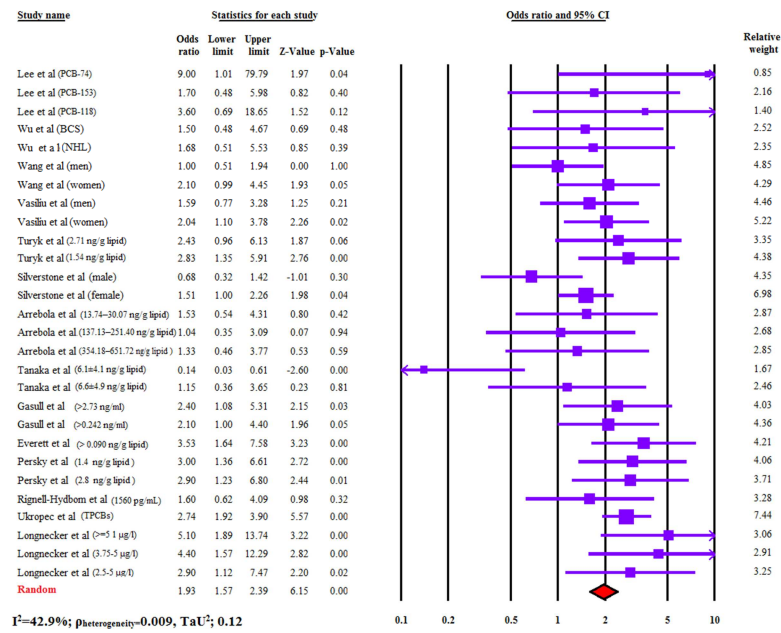


Figure 2. Forest plot showing the effect of PCBs on T2DM in all the articles

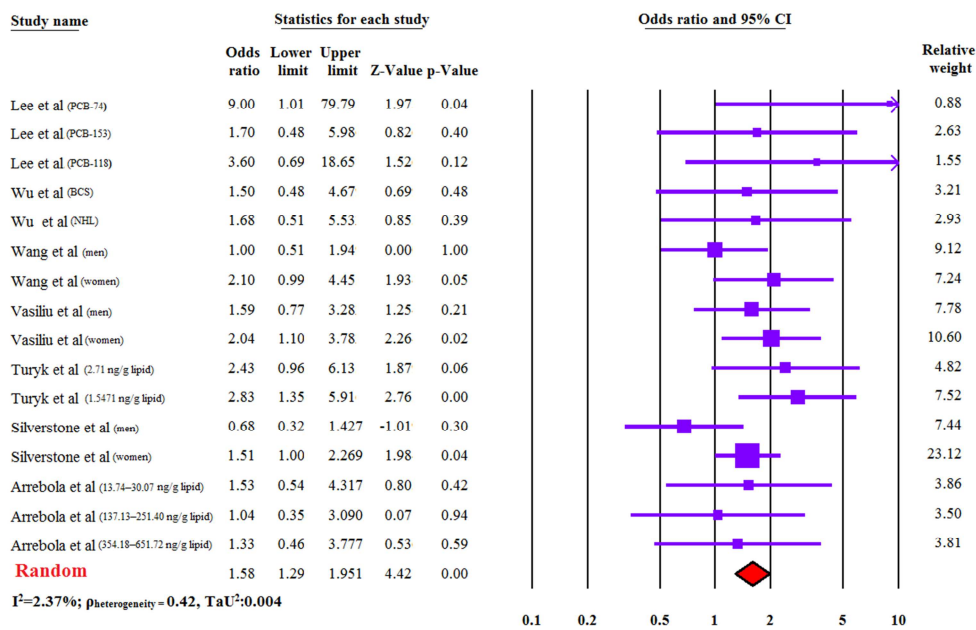


Figure 3. Forest plot showing the effect of PCBs on T2DM in the prospective studies.

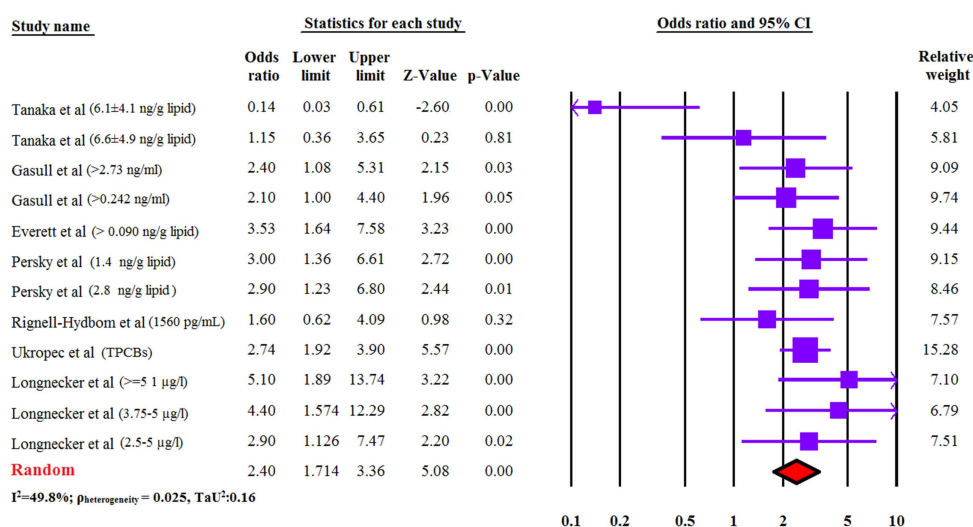


Figure 4. Forest plot showing the effect of PCBs on T2DM in the cross-sectional studies.

Although, the type of study and sample size in both Lee et al. and Wu et al [35] studies were almost the same, the OR for Lee et al [27] study (PCB-118) was more than that of Wu et al study (PCB-118). This high difference is due to the errors in Lee et al study, and Wu et al study did not have heterogeneity with the other studies which were investigated in the field of PCB-118 (Figures 3 and 4).

In Rignell-Hydbom et al [28] study and 7 years after the baseline examination, the increase in PCB-153 (OR=1.6 (0.6-4)) increased the risk of T2DM [28]. This is why Wu et al cited wrongly in his article that Rignell-Hydbom reported that only p,p-DDE increases the risk of T2DM [35].

During the late 1970s, a number of people in Taiwan were poisoned due to the consumption of rice contaminated with paints containing PCBs. 24 years later, a prospective study showed that the prevalence of T2DM in men who were exposed to PCBs, was 2 times more than that of other individuals [29]. Longnecker et al study showed that the serum level of PCBs in diabetic pregnant women is 30% higher than that of non-diabetic pregnant women [44].

In Lee et al study, OR for fourteen congeners of PCBs in 5 quintiles (OR;7.5 (1.4-38.8)) was more than that of other studies [32]. This high OR can be induced to elderly studied groups (aged 70 years) [47].

In the Longnecker et al study, OR was higher than that of some of studies because of high concentration of PCBs and more sensitive (women) population study (Figure 4).

Tanaka et al [38] study on the obese and very obese people in Japan who were exposed to PCBs, showed that an increase in the serum level of PCB-180 can increase the risk of T2DM, but PCB-163/164 did not cause a decrease in this risk. Thirteen congeners of PCBs were tested and it was found that PCB-180 is the most congener of PCBs [38]. This study showed that PCBs were positively associated with T2DM in women which is similar to studies of Wang et al on cohorts exposed to PCBs and furans in contaminated rice oil in Taiwan [29] and Vasiliu et al on women exposed to polybrominated biphenyls (PBBs) and PCBs through contaminated milk and animal feed in Michigan [31]. Surplus T2DM risk in exposed women may be due to higher body fat, allowing for greater accumulation and retention of lipophilic compounds [48]. Other mechanisms including estrogenic activities found in PCB congeners and their metabolites possibly affect glucose metabolism [16].

Serum levels of PCBs of former male employees in a capacitor plant were significantly associated with T2DM. In this study, insulin resistance was not associated with PCBs level [42]. Another study showed that male employees in capacitor plant have the serum levels of PCBs which were associated with T2DM [16].

Hofe et al study on adults who had a high serum level of dioxins similar to PCBs, showed that consumption of fruits and vegetables can reduce the risk of T2DM (Three congeners of PCBs were associated with T2DM) [49].

Since, CI range is passed zero in Egger test, so in general there is no considerable publication bias in the prospective [Egger test; intercept=1.28 CI (-0.18, 3.48)] and cross-sectional studies [Egger test; intercept=0.98 CI (-0.21,

1.34)]. Also, as it is observed in figure 5, the reverse funnel plot shows the lack of the publication bias in the prospective and cross-sectional studies.

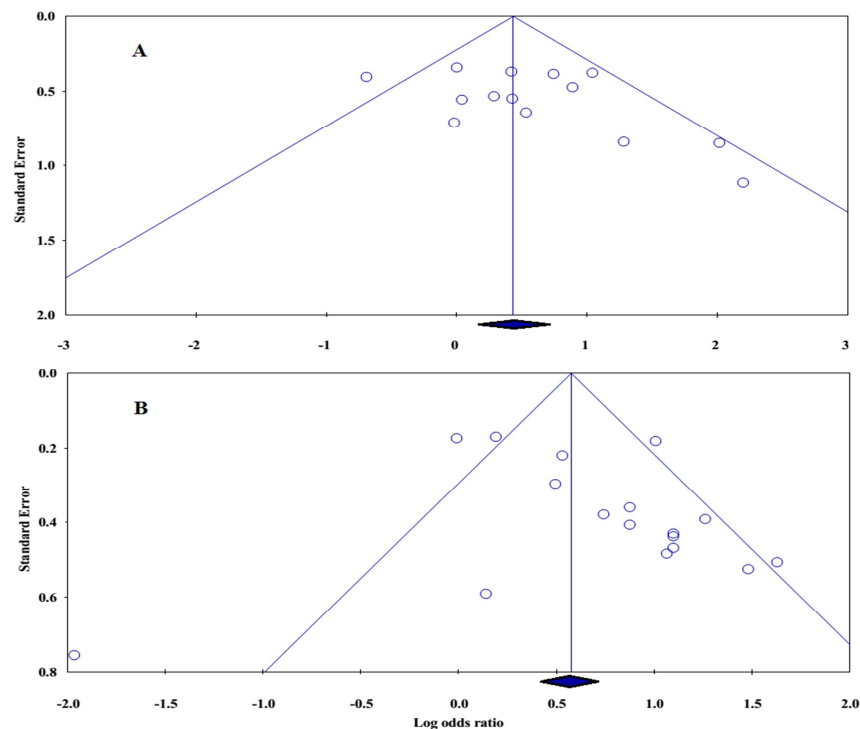


Figure 5. Funnel plot for the prospective (A) cross sectional (B) studies

There are limitations in this study. First, bias may exist for published data, non-English except Persian language studies were not included. Second, some studies without sufficient data to calculate the OR and CI were excluded. Third, time range of research was between 2000 and 2016.

CONCLUSION

Systematic review and Meta-analysis of 15 articles (31 studies) showed that the increase concentration of PCBs in the serum and adipose tissue can increase the risk of T2DM significantly ($P < 0.001$). Results of this study support the effective role of PCBs as an environmental risk factor for T2DM.

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REFERENCES

- [1] Guo YL. Increased Risk of Diabetes and Polychlorinated Biphenyls and Dioxins. *Diabetes Care*. 2008;31(8):1574-9.
- [2] Hu FB. Globalization of Diabetes The role of diet, lifestyle, and genes. *Diabetes care*. 2011;34(6):1249-57.
- [3] CDC. Surveillance for dental caries, dental sealants, tooth retention, edentulism, and enamel fluorosis: United States, 1988-1994 and 1999-2002: Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
- [4] Mohan M, Deshmukh H, Baig F, Lynn R, Elder D, Lang C. Insulin resistance is associated with all-cause mortality and accelerates the risk of progression to diabetes in non diabetic heart failure patients. *Journal of the American College of Cardiology*. 2014;63(12_S).
- [5] World Health Organization (WHO). *Diabetes*. 2013.
- [6] Federation ID. *IDF diabetes atlas: International Diabetes Federation, Executive Office*; 2011.
- [7] Tuomi T. Type 1 and Type 2 Diabetes What Do They Have in Common? *Diabetes*. 2005;54(suppl 2):S40-S5.
- [8] Dey L, Attele A. Type 2 diabetes. *Traditional Chinese Medicine*. 2011:231.
- [9] Katzmarzyk PT. Obesity and physical activity among Aboriginal Canadians. *Obesity*. 2008;16(1):184-90.

- [10] Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nature Reviews Genetics*. 2010;11(6):446-50.
- [11] Patel CJ, Bhattacharya J, Butte AJ. An environment-wide association study (EWAS) on type 2 diabetes mellitus. *PLoS one*. 2010;5(5):e10746.
- [12] Gray SL, Shaw AC, Gagne AX, Chan HM. Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in mice. *Journal of Toxicology and Environmental Health, Part A*. 2013;76(12):701-15.
- [13] Lee D-H, Lee I-K, Song K, Steffes M, Toscano W, Baker BA, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes results from the National Health and Examination Survey 1999–2002. *Diabetes Care*. 2006;29(7):1638-44.
- [14] Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environ Health Perspect*. 2012;120(6):779-89.
- [15] Mullerova D, Kopecky J. White adipose tissue: storage and effector site for environmental pollutants. *Physiological Research*. 2007;56(4):375.
- [16] Persky V, Piorkowski J, Turyk M, Freels S, Chatterton Jr R, Dimos J, et al. Polychlorinated biphenyl exposure, diabetes and endogenous hormones: a cross-sectional study in men previously employed at a capacitor manufacturing plant. *Environ Health*. 2012;11(1):57.
- [17] El Majidi N, Bouchard M, Carrier G. Systematic analysis of the relationship between standardized biological levels of polychlorinated biphenyls and thyroid function in pregnant women and newborns. *Chemosphere*. 2014;98:1-17.
- [18] Longnecker MP, Wolff MS, Gladen BC, Brock JW, Grandjean P, Jacobson JL, et al. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. *Environmental health perspectives*. 2003;111(1):65.
- [19] Harrad S, Ibarra C, Robson M, Melymuk L, Zhang X, Diamond M, et al. Polychlorinated biphenyls in domestic dust from Canada, New Zealand, United Kingdom and United States: implications for human exposure. *Chemosphere*. 2009;76(2):232-8.
- [20] Milbrath M, Wenger Y, Chang C-W, Emond C, Garabrant D, Gillespie BW, et al. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. *Environ Health Perspect*. 2009;117(3):417-25.
- [21] Fierens S, Mairesse H, Heilier J-f, De Burbure C, Focant J-f, Eppe G, et al. Dioxin/polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. *Biomarkers*. 2003;8(6):529-34.
- [22] Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, et al. Health effects of dioxin exposure: a 20-year mortality study. *American Journal of Epidemiology*. 2001;153(11):1031-44.
- [23] Airaksinen R, Rantakokko P, Eriksson JG, Blomstedt P, Kajantie E, Kiviranta H. Association between type 2 diabetes and exposure to persistent organic pollutants. *Diabetes Care*. 2011;34(9):1972-9.
- [24] Codru N, Schymura MJ, Negoita S, Environment ATFot, Rej R, Carpenter DO. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. *Environmental health perspectives*. 2007;114:2-7.
- [25] Jørgensen ME, Borch-Johnsen K, Bjerregaard P. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. *Diabetologia*. 2008;51(8):1416-22.
- [26] Lars R, Anna R-H, Lars H. A cross-sectional study of the association between persistent organochlorine pollutants and diabetes. 2005.
- [27] Lee D-H, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. *Environmental health perspectives*. 2010;118(9):1235-42.
- [28] Rignell-Hydbom A, Lidfeldt J, Kiviranta H, Rantakokko P, Samsioe G, Agardh C-D, et al. Exposure to p, p'-DDE: a risk factor for type 2 diabetes. *PLoS one*. 2009;4(10):e7503.
- [29] Wang S-L, Tsai P-C, Yang C-Y, Guo YL. Increased Risk of Diabetes and Polychlorinated Biphenyls and Dioxins A 24-year follow-up study of the Yucheng cohort. *Diabetes Care*. 2008;31(8):1574-9.
- [30] Turyk M, Anderson H, Knobeloch L, Imm P, Persky V. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. *Environ Health Perspect*. 2009;117(7):1076-82.
- [31] Vasiliu O, Cameron L, Gardiner J, DeGuire P, Karmaus W. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. *Epidemiology*. 2006;17(4):352-9.
- [32] Lee D-H, Lind PM, Jacobs DR, Salihovic S, van Bavel B, Lind L. Polychlorinated Biphenyls and Organochlorine Pesticides in Plasma Predict Development of Type 2 Diabetes in the Elderly The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care*. 2011;34(8):1778-84.
- [33] Durand CP, Promotion TUoTSoPHH, Management BS. A Systematic Review and Meta-analysis of Diabetes Disease Management Programs: University of Texas School of Public Health; 2008.
- [34] Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*: Wiley Online Library; 2008.

- [35] Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, et al. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. *Environmental health perspectives*. 2012;121(2):153-61.
- [36] Turyk M, Fantuzzi G, Persky V, Freels S, Lambertino A, Pini M, et al. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers. *Environmental research*. 2015;140:335-44.
- [37] Arrebola JP, Pumarega J, Gasull M, Fernandez MF, Martin-Olmedo P, Molina-Molina JM, et al. Adipose tissue concentrations of persistent organic pollutants and prevalence of type 2 diabetes in adults from Southern Spain. *Environmental research*. 2013;122:31-7.
- [38] Tanaka T, Morita A, Kato M, Hirai T, Mizoue T, Terauchi Y, et al. Congener-specific polychlorinated biphenyls and the prevalence of diabetes in the Saku Control Obesity Program (SCOP). *Endocrine journal*. 2011;58(7):589-96.
- [39] Silverstone AE, Rosenbaum PF, Weinstock RS, Bartell SM, Foushee HR, Shelton C, et al. Polychlorinated biphenyl (PCB) exposure and diabetes: results from the Anniston Community Health Survey. *Environmental health perspectives*. 2012;120(5).
- [40] Gasull M, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, et al. Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia. *Environmental science & technology*. 2012;46(14):7799-810.
- [41] Everett CJ, Thompson OM. Associations of dioxins, furans and dioxin-like PCBs with diabetes and pre-diabetes: Is the toxic equivalency approach useful? *Environmental research*. 2012;118:107-11.
- [42] Persky V, Piorkowski J, Turyk M, Freels S, Chatterton R, Dimos J, et al. Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant. *Environmental research*. 2011;111(6):817-24.
- [43] Ukropec J, Radikova Z, Huckova M, Koska J, Kocan A, Sebkova E, et al. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. *Diabetologia*. 2010;53(5):899-906.
- [44] Longnecker MP, Klebanoff MA, Brock JW, Zhou H. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. *Diabetes Care*. 2001;24(6):1099-101.
- [45] Egger M, Davey-Smith G, Altman D. *Systematic Reviews in Health Care: Meta-Analysis in Context*: Wiley; 2008.
- [46] Song Y, Chou EL, Baecker A, You NCY, Song Y, Sun Q, et al. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. *Journal of diabetes*. 2015.
- [47] Scherthaner G, Durán-García S, Hanefeld M, Langslet G, Niskanen L, Östgren CJ, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes, Obesity and Metabolism*. 2015;17(7):630-8.
- [48] Zeliger HI. Lipophilic chemical exposure as a cause of type 2 diabetes (T2D). *Reviews on environmental health*. 2013;28(1):9-20.
- [49] Hofe CR, Feng L, Zephyr D, Stromberg AJ, Hennig B, Gaetke LM. Fruit and vegetable intake, as reflected by serum carotenoid concentrations, predicts reduced probability of polychlorinated biphenyl-associated risk for type 2 diabetes: National Health and Nutrition Examination Survey 2003-2004. *Nutrition Research*. 2014;34(4):285-93.