

ASSOCIATION BETWEEN POLYCHLORINATED BIPHENYL (PCB) AND DIOXIN WITH METABOLIC SYNDROME (METS): A SYSTEMATIC REVIEW AND META-ANALYSIS

INPLASY202450047

doi: 10.37766/inplasy2024.5.0047

Received: 10 May 2024

Published: 10 May 2024

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ADMINISTRATIVE INFORMATION

Support - Ministry of Energy and Natural Resources, the government of Malaysia through the National Water Research Institute of Malaysia (NAHRIM) [grant number: 100-TNCPI/GOV 16/6/2 (019/2021)].

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202450047

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 May 2024 and was last updated on 10 May 2024.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis was to assess the associations of PCBs and dioxin with MetS and its risk factors, including obesity, hypertriglyceridaemia (HTG), hypertension (HTN) and diabetes mellitus (DM).

Rationale Although many studies have been performed on in vitro and in vivo models, the negative effects of EDC exposure on humans and the risk of developing MetS are still not well understood. While some meta-analyses have assessed the relationship between the incidence of diabetes and polychlorinated biphenyl (PCB) and its congener dioxin (Goodman et al., 2015; Gang et al., 2022), data on the relationship between these contaminants and the burden of MetS itself are lacking primarily among human population studies

that were exposed to these persistent organic pollutants (POP); hence, they were reviewed in the present systematic review and meta-analysis.

Condition being studied MetS and its risk factors, including obesity, hypertriglyceridaemia (HTG), hypertension (HTN) and diabetes mellitus (DM).

METHODS

Search strategy A literature search was performed by two researchers independently using three online databases, SCOPUS, Web of Science (WoS) and PubMed, on articles related to polychlorinated biphenyl (PCB) and its congeners dioxin and furans with the outcome of metabolic syndrome (MetS).

Participant or population MetS is defined based on the criteria established by the World Health Organization (WHO) (2), European Group for the

Study of Insulin Resistance (EGIR) criteria (Balkau & Charles, 1999), National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (Expert Panel on Detection, 2001) and International Diabetes Foundation (IDF) (Zimmet et al., 2007). The criteria established by the WHO needed impaired fasting glucose (> 100 mg/dl) to be the main criterion for diagnosis, followed by the presence of any two diseases, including obesity (BMI > 30 kg/m²), elevated arterial pressure (> 160/90 mmHg), elevated plasma triglycerides (> 1.7 mmol/l), low HDL (< 20 mg/dl). The EGIR criteria were a modification of the WHO criteria, where the presence of insulin resistance (fasting plasma insulin value > 75th percentile) is the main diagnostic criterion and supported by two diseases, including obesity, hypertension or dyslipidemia. The ATP III criteria needed three out of five criteria to be fulfilled to establish MetS in a patient. The five criteria are waist circumference above 40 inches for men and 35 inches for women, blood pressure above 130/85 mmHg, fasting triglyceride level above 150 mg/dl, fasting HDL < 40 mg/dl for men and 50 mg/dl for women and fasting blood glucose level over 100 mg/dl. Last, the IDF criteria described that obesity is needed as the main diagnosis, and this disease is measured by population-specific cut points with additional requirements of two of the four criteria, including fasting glucose above 100 mg/dl, plasma triglyceride level above 150 mg/dl, HDL level below 40 mg/dl for men and 50 mg/dl for women and blood pressure above 130/80 mmHg. Studies that utilized any of the definitions and criteria established by these groups to diagnose the studied population with MetS were included in the present study.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included The study design of the included studies consisted of three prospective studies, three cross-sectional studies, two cohort studies and two case-control studies.

Eligibility criteria The inclusion criteria of the articles for the present systematic review and meta-analysis were original studies involving humans and observational studies such as prospective, case-control, cohort, and cross-sectional studies. The studies involved participants who were diagnosed with metabolic syndrome or at risk of the syndrome, including having the risk factors for the syndrome, which are obesity, hypertension, hypertriglyceridaemia, low high-density lipoprotein and diabetes mellitus. The

studies used human biological samples such as blood and tissues to assess the level of PCBs and their congeners dioxin and furans. The outcome of the studies presented with either MetS or its risk factors. Studies that were included must contain quantitative assessment of the risk, such as odds ratio (OR), hazard ratio (HR) and relative risk (RR) with 95% confidence intervals (CI), mean and standard deviation (SD), mean difference as well as combination of OR with mean and SD. Studies containing in vitro or in vivo studies, review and meta-analysis articles, studies not containing quantitative assessment, studies not related to PCB and its congeners, dioxin and furans and metabolic syndrome were excluded from the selection. The articles identified were independently screened based on the inclusion and exclusion criteria by two researchers. The final list of eligible articles was discussed by the two researchers and finalized for the present systematic review and meta-analysis.

Information sources A literature search was performed by two researchers independently using three online databases, SCOPUS, Web of Science (WoS) and PubMed, on articles related to polychlorinated biphenyl (PCB) and its congeners dioxin and furans with the outcome of metabolic syndrome (MetS). The year of the articles was limited between 2017 and 2023. We focused only on the more recent evidence because it has been suggested that the current information on the relationship between EDC exposure and metabolic abnormalities is heterogeneous and fragmented (Haverinen et al., 2021). The articles were identified using the string method in each database, which included the keywords “persistent organic pollutant” OR dioxin OR “dioxin-like polychlorinated biphenyl” OR “dioxin-like compound” OR “polychlorinated dibenzodioxin” OR “polychlorinated dibenzo-p-dioxin” OR “polychlorodibenzo-4-dioxin” OR PCDD OR TCDD OR tetrachlorodibenzodioxin OR tetrachlorodibenzodioxin OR chlorodibenzofuran OR “polychlorinated dibenzofuran” OR “chlorinated dibenzofuran” OR “polychlorinated biphenyl” OR PCB OR “polychlorobiphenyl compound” AND “metabolic syndrome”. Independent research for each risk factor for MetS in the databases was not performed because those risks were analysed as separate outcomes instead, where articles that fell under the ‘metabolic syndrome’ keyword only will be considered for the analyses. The searches were performed within topics (article title, abstract and keywords), and the articles included were limited only to English articles and human studies. The articles identified using the keywords were further

assessed manually by two researchers to further identify the articles to be included in the systematic review for meta-analysis.

Main outcome(s) Eleven studies were included from three databases up to 2021. The meta-analysis results showed a strong association between PCB exposure and diabetes mellitus (OR = 3.593, 95% CI: 2.566, 5.031), while most of the risk factors for MetS, including obesity (OR = 1.875, 95% CI: 0.883, 3.979), hypertension (OR = 1.335, 95% CI: 0.902, 1.976) and hypertriglyceridaemia (OR = 1.611, 95% CI: 0.981, 2.643), were weakly associated with PCB. Furthermore, both PCBs (OR = 1.162, 95% CI: 0.994, 1.357) and dioxin (OR = 2.742, 95% CI: 1.936, 3.883) were found to be weakly and strongly associated with MetS, respectively.

Data management The articles identified using the keywords during the search stage were assessed manually by two researchers to identify the articles to be included in the systematic review for meta-analysis. Then, the articles identified were independently screened based on the inclusion and exclusion criteria by two researchers. The final list of eligible articles was discussed by the two researchers and finalized for the present systematic review and meta-analysis.

Quality assessment / Risk of bias analysis Funnel plot and Egger's Regression Test were employed to mitigate publication bias and address asymmetry in the research. Publication bias is shown by an asymmetric funnel plot or a p-value < 0.05 in the Egger's Test.

Strategy of data synthesis Meta-analysis was conducted using a random-effects model on the Comprehensive Meta-Analysis V3 platform (Higgins & Thompson, 2002) to assess the pooled effect estimates to evaluate the association between PCB and its congeners' exposure with compose the risk of developing each risk factor for MetS and MetS and dioxin exposure with the risk of developing MetS. Meta-regression analysis was performed to assess the subgroup heterogeneity between moderators. The moderators included in the present meta-regression analysis were countries and years of studies conducted before or after 2015. Funnel plot and Egger's Regression Test were employed to mitigate publication bias and address asymmetry in the research. Publication bias is shown by an asymmetric funnel plot or a p-value < 0.05 in the Egger's Test. The year 2015 was chosen due to the sudden surge of articles being reported in online article databases,

which reflects an increase in awareness of the danger of EDC exposure.

Subgroup analysis Meta-regression analysis was performed to assess the subgroup heterogeneity between moderators. The moderators included in the present meta-regression analysis were countries and years of studies conducted before or after 2015.

Sensitivity analysis Funnel plot and Egger's Regression Test were employed to mitigate publication bias and address asymmetry in the research. Publication bias is shown by an asymmetric funnel plot or a p-value < 0.05 in the Egger's Test.

Language restriction Articles included were limited only to English articles.

Country(ies) involved Malaysia.

Keywords polychlorinated biphenyl, dioxin, obesity, hypercholesterolemia, hypertension, diabetes mellitus, metabolic syndrome.

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