Exposure to pesticides and overweight - A systematic review

Exposição a agrotóxicos e excesso de peso - Uma revisão sistemática

Exposición a plaguicidas y sobrepeso - Una revisión sistemática

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Calinca Skonieski
ORCID: https://orcid.org/0000-0003-4204-3861
Universidade Federal da Fronteira Sul, Brazil
E-mail: calincasko@gmail.com
Larissa Silva
ORCID: https://orcid.org/0000-0002-2736-538X
Universidade Federal da Fronteira Sul, Brazil
E-mail: 21lariis@gmail.com
Karina Raquel Fagundes
ORCID: https://orcid.org/0000-0003-2818-5601
Universidade Federal da Fronteira Sul, Brazil
E-mail: karinafagundes15@outlook.com
Andresa Talita Nunes
ORCID: https://orcid.org/0000-0002-7028-6441
Universidade Federal da Fronteira Sul, Brazil
E-mail: andressatalita59@gmail.com
Suelen Finhler
ORCID: https://orcid.org/0000-0002-3967-9175
Universidade Federal da Fronteira Sul, Brazil
E-mail: suelenfinhler8@gmail.com
Karine Roversi
ORCID: https://orcid.org/ 0000-0001-5817-8803
Universidade Federal de Santa Maria, Brazil
E-mail: karine.roversi@hotmail.com
André Lazarin Gallina
ORCID: https://orcid.org/ 0000-0002-1535-7980
Universidade Estadual do Centro-Oeste do Paraná, Brazil
E-mail: andregallina@gmail.com
Mario Hiroyuki Hirata
ORCID: https://orcid.org/0000-0002-9521-7979
Universidade de São Paulo, Brazil
E-mail: mhhirata@usp.br
Glaucio Monteiro Ferreira
ORCID: https://orcid.org/0000-0002-1952-9428
Universidade de São Paulo, Brazil
E-mail: glauciom.ferreira@gmail.com
Dalila Moter Benvegnú
ORCID: https://orcid.org/0000-0002-3419-9674
Universidade Federal da Fronteira Sul, Brazil
E-mail: dalilabenvegnu@yahoo.com.br

Abstract
This study results from a systematic review to investigate the possible relationship between pesticide exposure and the induction of body overweight in adult individuals. We used the PICO strategy (Population, Interventions/exposure, Comparisons, Outcomes) and the PUBMED, SCIENCE DIRECT and SCOPUS databases to perform the research. In this review, were included 15 studies, classified as research articles. The data presented demonstrated that 86.66% (13/15) of the studies positively correlated overweight and pesticide exposure. Additionally, we observed exposure to pesticides regarding deregulation mechanism of glucose (increase levels of glucose, insulin and homeostasis model assessment insulin resistance index (HOMA-IR)) and deregulation lipid homeostasis (increase levels of triglycerides and decreased levels of high-density lipoprotein (HDL)). These findings proposed an increase in the risk of cardiac diseases and diabetes. As well, these results show that exposure to pesticides can also increase the risk of overweight development. However, further studies are needed to determine the possible mechanism.
Keywords: Agrochemicals; Endocrine disruptors; Overweight; Associated comorbidities.

Resumo

Este estudo resulta de uma revisão sistemática com objetivo de investigar a possível relação entre a exposição a agrotóxicos e a indução de excesso de peso corporal em indivíduos adultos. Utilizou-se a estratégia PICO (Population, Interventions/exposição, Comparisons, Outcomes) e as bases de dados PUBMED, SCIENCE DIRECT e SCOPUS para realizar a busca. Nesta revisão, foram incluídos 15 estudos. Os dados apresentados demonstraram que 86,66% (13/15) dos estudos correlacionaram positivamente o excesso de peso e a exposição a agrotóxicos. Além disso, observamos relação entre a exposição aos agrotóxicos e o mecanismo de desregulação da glicose (aumento dos níveis de glicose, insulina e índice de resistência à insulina de avaliação do modelo de homeostase (HOMA-IR)) e desregulação da homeostase lipídica (aumento dos níveis de triglicerídeos e diminuição dos níveis de lipoproteína de alta densidade (HDL)). Esses achados propuseram um aumento no risco de doenças cardíacas e diabetes. Além disso, esses resultados mostram que a exposição a agrotóxicos também pode aumentar o risco de desenvolvimento de excesso de peso. No entanto, mais estudos são necessários para determinar o possível mecanismo.

Palavras-chave: Agroquímicos; Disruptores endócrinos; Sobrepeso; Comorbidades associadas.

Resumen

Este estudio es el resultado de una revisión sistemática para investigar la posible relación entre la exposición a plaguicidas y la inducción del sobrepeso corporal en individuos adultos. Se utilizó la estrategia PICO (Population, Interventions/exposure, Comparisons, Outcomes) y las bases de datos PUBMED, SCIENCE DIRECT y SCOPUS para realizar la búsqueda. En esta revisión, se incluyeron 15 estudios. Los datos presentados demostraron que el 86,66% (13/15) de los estudios correlacionaron positivamente el sobrepeso y la exposición a plaguicidas. Además, se observó que la exposición a plaguicidas afectaba al mecanismo de desregulación de la glucosa (aumento de los niveles de glucosa, insulina e índice de resistencia a la insulina del modelo de homeostasis (HOMA-IR)) y a la desregulación de la homeostasis de los lípidos (aumento de los niveles de triglicéridos y disminución de los niveles de lipoproteínas de alta densidad (HDL)). Estos resultados proponen un aumento del riesgo de enfermedades cardíacas y de diabetes. Además, estos resultados muestran que la exposición a los pesticidas también puede aumentar el riesgo de desarrollar sobrepeso. Sin embargo, se necesitan más estudios para determinar el posible mecanismo.

Palabras clave: Agroquímicos; Disruptores endocrinos; Sobrepeso; Comorbilidades asociadas.

1. Introduction

At the present moment, the prevalence of diseases related to disrupted metabolism has increased dramatically and continues to grow among adults. One of the diseases caused by disrupted metabolism is obesity. Obesity is considered a metabolic disorder of great concern for the public health system since it contributes to increased healthcare costs once it causes high morbidity and mortality (Aminov and Carpenter 2020). Additionally, obesity is characterized by an abnormal increase in body fat and the body mass index (BMI) > 29.99 kg/m^2 (Elagizi et al., 2018).

Currently, studies in human have associated exposure to various industrial chemicals with obesity (Lee et al. 2007; Dirinck et al. 2011; Lee et al. 2011; Min et al. 2011; Rönn et al. 2011; Lee et al. 2012; Lind et al. 2013; Azandjeme et al. 2014; Dirinck et al. 2014; Henríquez-Hernández et al. 2017; Nonterah et al. 2018; Aminov and Carpenter 2020). Exposure to pesticides promotes disruption of the endocrine system and cause adverse health consequences, such as increased glucose levels and alteration of the lipid profile, which may cause an increase in body weight. Additionally, often referred to as endocrine-disrupting chemicals (EDC), this EDC may be considered an essential contributor to the obesity epidemic (Lee et al., 2012; Monneret, 2017).

Currently, studies reported the relation between organochlorine pesticides (OCPs) and accumulation of body fat (Aminov & Carpenter, 2020; Azandjeme et al., 2014; E. Dirinck et al., 2011; E. L. Dirinck et al., 2014; Henríquez-Hernández et al., 2017; Lee et al., 2007, 2011, 2012; Lind et al., 2013; Min et al., 2011; Rönn et al., 2011). OCPs are highly lipophilic, semi-volatile, resistant to degradation, tending to bioaccumulate in human adipose tissue since their half-life may last years or decades. OCPs could no longer be marketed. In contrast, it is possible to detect in urine and blood samples of the human (Henríquez-Hernández et al., 2017).

Concerning organophosphate pesticides (OP), preadipocytes showed the induction and accumulation of lipid (Smith et al., 2018). Besides, chronic exposure to OP (malathion) promotes insulin resistance in farmers; it was reported a significant increase in OP concentration in blood of farmers. Also, there was a positive correlation between the concentration of malathion in blood, waist circumference, and insulin resistance (Raafat et al., 2012).

The aim of this study was to synthesize the best evidence on the relationship between exposure to pesticides and induction of overweight and comorbidities associated with body weight gain (diabetes, hypertension, metabolic syndrome, cardiovascular diseases, lipid disorders) in adult individuals.

2. Methodology

2.1 Study selection and eligibility criteria

Searches were performed in PubMed, Science Direct and Scopus from March 1, 2020 to March 31, 2020, for conducting the systematic review. The search was limited to research articles published in full-text versions. The descriptors used to conduct the searches in different databases were the following: pesticides and obesity.

Reviewers independently screened the search results and identified studies that were potentially relevant based on their title and abstract. Relevant studies were read in full and selected according to the eligibility criteria. The following elements were used to define eligibility criteria: Individuals exposed to pesticides (population), pesticides (exposure), comparison exposed individuals/unexposed individuals or people with low levels of exposure/people with high levels of exposure (comparisons), obesity (primary outcome) and comorbidities associated with obesity (secondary outcome) (Methley et al., 2014). The PRISMA guidelines used to assemble the article (Main items for Systematic Records and Meta-Analyses) (Moher et al., 2016). A flow diagram of the study selection process is detailed in Figure 1.

Detailing the eligibility criteria:

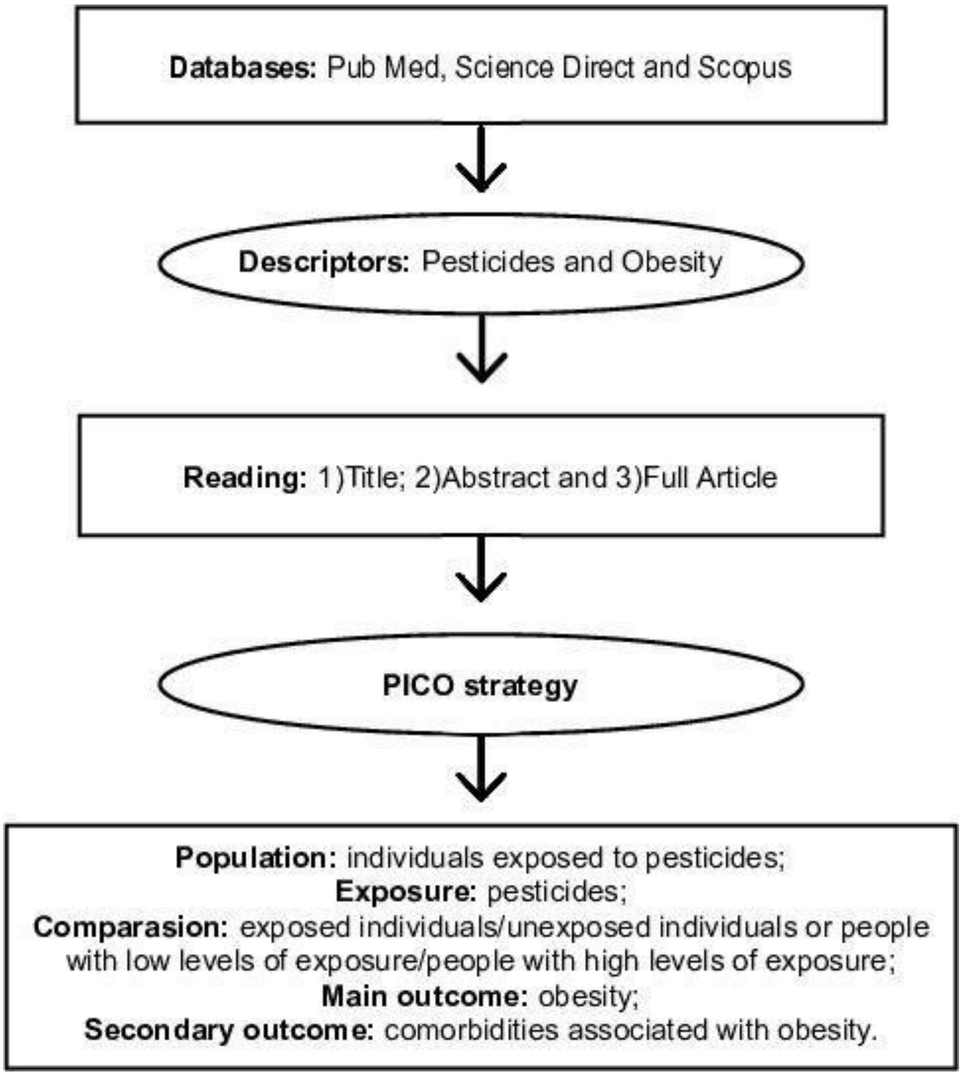
(1) Population: We included studies target human pesticide exposure in subjects of male and female, older than 18 years.

(2**)** Exposure: For the selection of studies, some type of human exposure to pesticides was necessary, besides that, only one study selected for the systematic review presented a group that was not exposed to pesticides, with the purpose of comparison. Additionally, this exposure could be analysed in a biological sample of the subjects (blood, urine and adipose tissue). It could be reported during the interview with the participant (only one study used the questionnaire to determine exposure to pesticides).

(3) Comparison: We included in the review, studies that had any of these comparisons: people with low levels of pesticide metabolites in biological samples/people with high levels of pesticide metabolites in biological samples or people exposed to pesticides/people not exposed to pesticides. In order to observe whether people who had higher levels of pesticide metabolites and were exposed to pesticides had more significant weight gain.

(4) Outcome**:** The main outcome was the relationship between exposure to pesticides and body weight gain in adult individuals of both genders. In order to assess obesity condition, it was performed some measurements as the body mass index (BMI), fat mass index, waist incidence (WC) and waist-hip ratio (WHR). Besides, secondary outcomes could also be included, such as associated comorbidities (hypertension, diabetes, cardiovascular diseases-CVD, peripheral arterial disease-PAD, dyslipidemia, metabolic syndrome) and biochemical analysis (lipid profile, fasting glucose, C-reactive protein, homeostasis model assessment insulin resistance index-HOMA-IR, metabolomics analysis, glycated hemoglobin and A1-HbA1).

Figure 1 - Flow diagram of study selection for the systematic review.

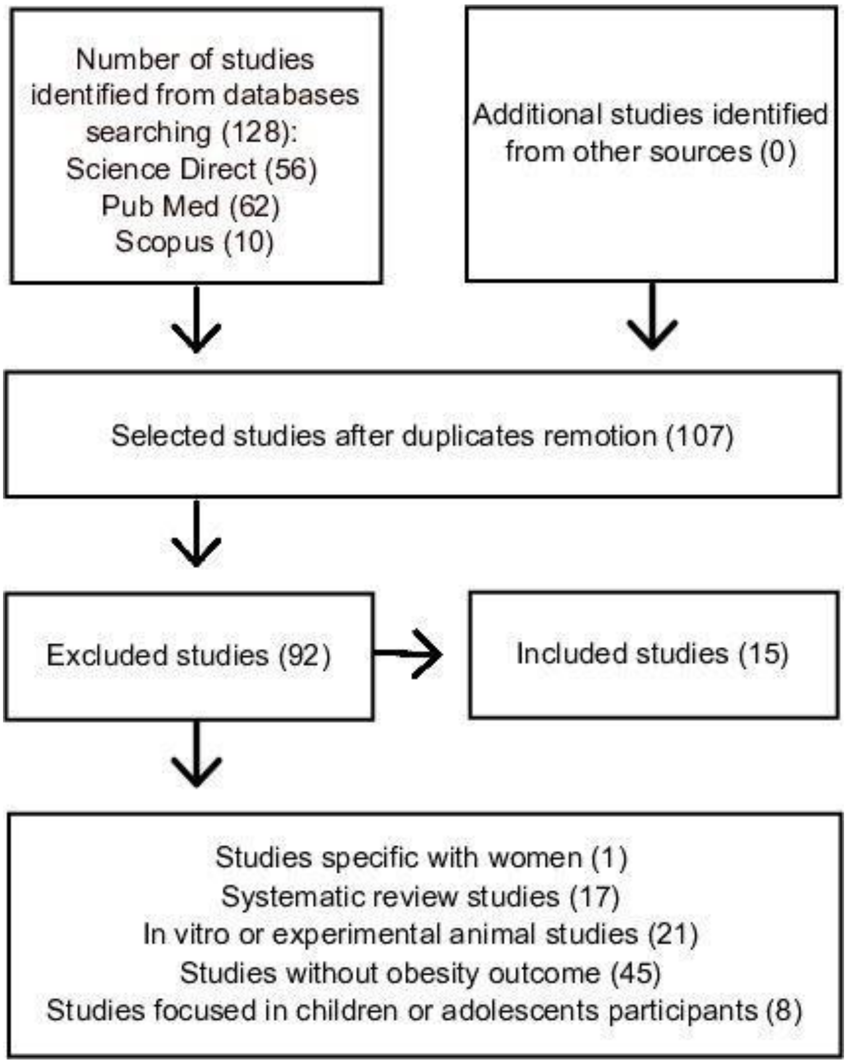


Source: Authors.

3. Results

Initially, 128 studies were identified, and 15 remained following the methodology described in this work. First of all, we read to complete the articles and were removed 92 studies following reasons: 17 of them were systematic reviews; 21 studies were not involving human subjects; 8 studies included children or adolescents as participants; 1 study carried out only by women and for the last 45 studies did not present obesity as an outcome. A flow diagram of specific reasons for exclusion are detailed in Figure 2.

Figure 2 - PRISMA flow diagram. Summarizing the selection of papers included in this review (using the term "pesticides and obesity").



Source: Authors.

3.1 Population

The sample size ranged from 90 (Lee et al., 2011) to 2963 participants (Wei et al., 2014). It was not evaluated the mean age and gender of the individuals in the studies since many did not present information about age and gender. However, all researches included participants from both genders. Regarding the study was conducted in different countries, namely: (33.35%, 5/15) United States of America (America); (26.66%, 4/15) Sweden, (13.33%, 2/15) Belgium, (6.66%, 1/15) Spain, (6.66%, 1/15) Norway (Europe); (6.66%, 1/15) Benin, (6.66%, 1/15) Ghana (Africa).

3.2 Pesticide exposure

The studies were analyzed at least by one of two different indicators: a) exposition through questionnaires (asking if the individual was exposed to pesticides - 6.66%, 1/15), and b) exposure through levels of pesticides in urine, blood or tissues (93.33%, 14/15). Thus, 73.33% (11/15) studies analyzed the presence of pesticides metabolites in serum samples of participants, 13.33% (2/15) in plasma samples and 6.66% (1/15) urine and tissue samples. It was observed that, of the 30 pesticide metabolites analyzed, the most frequent were: dichlorodiphenyldichloroethylene (p,p′-DDE) (12%, 12/15); trans-nonachlor (46.66%, 7/15); hexachlorocyclohexane (β-HCH) and hexachlorobenzene (HCB) (40%. 6/15); dichlorodiphenyltrichloroethane (p,p′-DDT) (33.33%, 5/15); oxychlordane and hexachlorocyclohexane (γ-HCH) (26.66%, 4/15); hexachlorocyclohexane (α-HCH), dieldrin, bromodiphenyl ether (BDE47) and octachlorodibenzo-p-dioxin (OCDD) (20%, 3/15); hexachlorocyclohexane (δ-HCH), mirex, aldrin, and endrin (δ-HCH) (13.33%, 2/15). The frequency with which pesticides or pesticide compounds were analyzed by studies, their chemical class and agrochemical are detailed in Table 1.

Table 1 - Pesticides or pesticide compounds analyzed by studies in blood, urine, or tissue samples of the participants.

Pesticide	Frequency	Chemical Class	Agrochemical Class	Reference
2,4- DCP	1	Chlorophenols	Herbicide	Wei et al. (2014)
2,5-DCP	1	Chlorophenols	Herbicide	Wei et al. (2014)
Ortho-phenylphenol	1	-	Fungicide	ChEBI (2020)
2,4,5-trichlorophenol	1	Chlorophenols	Herbicide	CAMEO Chemicals (2020h)
2,4,6-trichlorophenol	1	Chlorophenols	Herbicide	ChEBI (2018)
p, p′-DDE	12	Organochlorine	Insecticide	ChEBI (2015)
p, p′-DDT	5	Organochlorine	Insecticide	ChEBI (2015)
o, p′-DDT	1	Organochlorine	Insecticide	ChEBI (2015)
p,p′-DDD	1	Organochlorine	Insecticide	ChEBI (2015)
Oxychlordane	4	Organochlorine	Insecticide	ChEBI (2014)
Trans-nonachlor	7	Organochlorine	Insecticide	ChEBI (2014)
Mirex	2	Organochlorine	Insecticide	ChEBI (2015a)
HCB	6	Organochlorine	Fungicide	ChEBI (2015b)
Aldrin	2	Organochlorine	Insecticide	ChEBI (2018a)
Dieldrin	3	Organochlorine	Insecticide	ChEBI (2018a)
Endrin	2	Organochlorine	Insecticide	ChEBI (2021)
α-Endosulfan I	1	Organochlorine	Insecticide	ChEBI (2014a)
β-Endosulfan II	1	Organochlorine	Insecticide	ChEBI (2014a)
α-chlordane	1	Organochlorine	Insecticide	ChEBI (2014)
γ-chlordane	1	Organochlorine	Insecticide	ChEBI (2014)
α-HCH	3	Organochlorine	Insecticide	CAMEO Chemicals (2021e)
β-HCH	6	Organochlorine	Insecticide	CAMEO Chemicals (2021e)
γ-HCH	4	Organochlorine	Insecticide	CAMEO Chemicals (2021e)
δ-HCH	2	Organochlorine	Insecticide	CAMEO Chemicals (2021e)
Cis-nonachlor	1	Organochlorine	Insecticide	ChEBI (2014)
PeCB	1	Chlorobenzenes	-	Dusanov et al. (2018)
OCDD	3	Organochlorine	Fungicide	Rönn et al. (2011)
BDE47	3	Organochlorine	-	Rönn et al. (2011)
TNK	1	Organochlorine	-	Rönn et al. (2011)

Abbreviations: (DCP) dichlorophenol; (DDE) dichlorodiphenyldichloroethylene; (DDT) dichlorodiphenyltrichloroethane; (DDD) dichlorodiphenyldichloroethane; (HCB) hexachlorobenzene; (HCH) hexachlorocyclohexane; (PeCB) pentachlorobenzene; (OCDD) octachlorodibenzo-p-dioxin; (BDE47) bromodiphenyl ether and (TNK) transnonachlordane. Source: Authors.

3.3 Main outcome

We assessed the primary outcome (overweight) through different methods in the studies. 93.33% (14/15) of the studies used the BMI, (40%, 6/15) waist circumference, (26.66%, 4/15) waist-to-hip ratio, (13.33%, 2/15) bioimpedance analysis and finally (6.66%, 1/15) used Dual-energy X-ray absorptiometry (DXA). The primary and secondary outcomes assessed by the studies included in our systematic review are detailed in Table 2.

Table 2 - Assessment of primary and secondary outcomes studied due to participants' exposure to pesticides.

Reference	Mean Outcome	Secondary Outcome
Lee et al. (2007)	BMI and WC.	Glucose; insulin; HOMA-IR.
Dirinck et al. (2010)	BMI, WC, WHR and bioimpedance analysis.	Glucose; insulin; HOMA-IR.
Lee et al. (2011)	BMI.	TG; HDL; LDL; glucose; insulin; HOMA-IR.
Min et al. (2011)	BMI.	Presence of DM; serum cotinine levels; TC; TG; PAD.
Rönn et al. (2011)	DXA and BMI.	-
Lee et al. (2012)	WC.	TC; TG.
Lind et al. (2013)	BMI, WC and WHR.	Blood pressure; TC; LDL; HDL; TG; glucose.
Azandjeme et al. (2014)	BMI.	Glucose.
Dirinck et al. (2014)	BMI, WC, WHR and bioimpedance analysis.	Glucose; the presence of DM; insulin; HOMA-IR; HbA1.
Wei et al. (2014)	BMI.	-
Salihovic et al. (2016)	BMI.	TC; TG; glucose; CRP; blood pressure; metabolomics analysis.
Henríquez-hernández et al. (2017)	BMI and WHR.	Glucose; the presence of DM; insulin; HOMA-IR; TG; HDL; LDL; TC.
Dusanov et al. (2018)	BMI and WC.	TC; HDL; TG; glucose; CRP; HOMA-IR; blood pressure; metabolic syndrome.
Nonterah et al. (2018)	BMI.	-

Source: Authors.

Regarding obesity and its relationship with pesticide exposure, the 15 studies evaluated in this systematic review (86.66%, 13/15) presented a positive correlation between weight gain and pesticide exposure and only (13.33%, 2/15) of the studies demonstrated no correlation. In addition, the pesticide metabolites that showed a positive correlation with the obesity profile were: 2.5 DCP, TNK, DDE, dieldrin, HCB, HCH, trans-nonachlor, DDT, OCDD and oxychlordane. The main results found in the studies in our systematic review are detailed in Table 3.

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Table 3 - Characteristics and results of studies evaluated in this systematic review.

Reference	Country	Age of subjects	Sample (n)	Exposure assessment	Main outcome	Secondary outcome
Lee et al. (2007)	United States of America	> 20 years	749	Analysis of Oxychlordane and Trans-nonachlor in serum samples	A positive correlation between pesticide concentrations and BMI	A positive correlation between oxyclordane and trans-nonaclor concentrations and HOMA-IR.
Dirinck et al. (2010)	Belgium	> 18 years	145	Analysis of p,p′-DDE and β-HCH in serum samples	A positive correlation between β-HCH concentration and: WC; subcutaneous and visceral abdominal fat and BMI	A positive correlation between β-HCH: HOMA IR, fasting insulin, and 2 hours of glucose and postprandial insulin
Lee et al. (2011)	United States of America	18-30 years	90	Analysis of oxychlordane, trans-nonachlor, HCB, β-HCH, γ-HCH, p,p′-DDE, p,p′-DDT and Mirex in serum samples	The concentrations of p, p'-DDE most consistently predicted higher BMI after 20 years	The p,p'-DDE predicted higher triglycerides and HOMA-IR and lower HDL cholesterol after 20 years. Oxiclordane, trans-nonachlor and HCB also significantly predicted higher levels of triglycerides
Min et al. (2011)	United States of America	> 40 years	2032	Analysis of β-HCH, p,p′-DDE, oxychlordane, trans-nonachlor, dieldrin in serum samples	Positive correlation of the concentrations of p, p-DDE, trans-nonachlor, oxychlordane, dieldrin, and the sum of the five pesticides between obese individuals with PAD	Positive correlation between PAD and levels of all OC pesticides in obese patients
Rönn et al. (2011)	Sweden	70 years	890	Analysis of HCB, TNK, and the breakdown product of DDT, DDE, OCDD; BDE47 in plasma samples	Positive correlation between HCB, TNK concentrations and the decomposition product of DDT, DDE with the total fat mass	Secondary outcomes were not evaluated, as they were not collected
Lee et al. (2012)	Sweden	70 years	511	Analysis of trans-nonachlor, p,p′-DDE, HCB, OCDD and BDE47 in serum samples	A positive correlation between p,p'-DDE, trans-nonaclor OCDD and HCB concentrations with abdominal obesity	Statistical analysis was no performed between the quantification of pesticides and possible secondary outcomes
Lind et al. (2013)	Sweden	70 years	1016	Analysis of OCDD, trans-	The sum of the concentrations of	Statistical analysis was no performed

				nonachlor, p,p′-DDE, HCB and bromodiphenyl ether in serum samples	the analyzed pesticides was positively related to weight gain over the years	between the quantification of pesticides and possible secondary outcomes
Azandjeme et al. (2014)	Benin	18-65 years	118	Analysis of aldrin, dieldrin; endrin, α-endosulfan I, β-endosulfan II, α-chlordane, γ-chlordane, α-HCH, β-HCH, γ-HCH, cis-nonachlor, trans-nonachlor, p,p′-DDE and p,p′-DDT in serum samples	A positive correlation between p,p'-DDT and β-HCH concentrations and obesity	Statistical analysis was no performed between the quantification of pesticides and possible secondary outcomes
Dirinck et al. (2014)	Belgium	> 18 years	195	Analysis of p,p′-DDE in serum and tissue samples	A positive correlation between p,p'-DDE concentrations and BMI	A positive correlation between the levels of p,p'-DDE and HbA1c and glucose tolerance
Wei et al. (2014)	United States of America	20-85 years	2963	Analysis of 2,4-DCP; 2,5-DCP, ortho-phenylphenol, 2,4,5-trichlorophenol and 2,4,6-trichlorophenol in urine samples	A positive correlation between 2,5-DCP concentrations and obesity	Secondary outcomes were no evaluated, as they were not collected
Salihovic et al. (2016)	Sweden	70 years	965	Analysis of p,p′-DDE and HCB in plasma samples	There was no positive correlation between p,p'-DDE and HCB concentrations with obesity	The levels p,p′-DDE and HCB are linked to a set of lipid-related metabolites that are involved in important metabolic processes
Henríquez-hernández et al. (2017)	Spain	> 18 years	429	Analysis of p,p′-DDT, p,p′-DDE, p,p′-DDD, aldrin, dieldrin, endrin HCH isomers α, β, δ, and γ in serum samples	A positive correlation between p,p'-DDE concentrations and obesity	A positive correlation between p,p'-DDE levels glucose levels and HOMA-IR
Dusanov et al. (2018)	Norway	18-78 years	431	Analysis of p,p′DDT, p,p′DDE, α-HCH, β-HCH, γ-HCH, PeCB, HCB, trans-nonachlor, and oxychlordane in serum samples	There was no positive correlation between pesticide concentrations and BMI and WC	A positive correlation between HCB and β-HCH concentrations and fasting blood glucose. Trans-nonaclor and MS and triglycerides. Negative

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						correlations between pesticide concentrations and HDL
Nonterah et al. (2018)	Ghana	40-60 years	2014	Asked if he uses pesticide	Participants exposed to pesticides had a higher prevalence of overweight and obesity compared to those not exposed	Secondary outcomes were no evaluated, as they were not collected
Aminov and Carpenter (2020)	United States of America	> 18 years	601	Analysis of HCB, DDE and Mirex in serum samples	A positive correlation between serum concentrations of total pesticides and obesity. However, there was a positive association between HCB concentrations and obesity risk. But, Mirex, showed a significant inverse association with obesity	A positive correlation between higher pesticide concentrations and BPH, DM, CVD, elevated serum lipids and MS

Abbreviations: (BMI) body mass index; (WC) waist incidence; (WHR) waist-hip ratio; (TC) total cholesterol; (TG) triglycerides; (DM) diabetes mellitus; (CRP) C-reactive protein; (HOMA-IR) homeostasis model assessment insulin resistance index; (PAD) peripheral arterial disease; (CVD) cardiovascular diseases; (HDL) high-density lipoprotein; (LDL) low-density lipoprotein and (HbA1) glycated hemoglobin A1. Source: Authors.

3.4 Secondary outcomes

In addition to the main outcome (overweight), the studies evaluated other outcomes. Of the 15 studies evaluated, (66.66%, 10/15) evaluated serum glucose; (53.33%, 8/15) triglycerides; (46.66%, 7/15) total cholesterol; (40%, 6/15) homeostasis model assessment insulin resistance index (HOMA-IR); (33.33%, 5/15) insulin, (26.66%, 4/15) high-density lipoprotein (HDL), high blood pressure (HBP) and presence of diabetes mellitus (DM) (through the questionnaire), (20%, 3/15) low-density lipoprotein (LDL); (13.33%, 2/15) CRP and metabolic syndrome; (6.66%, 1/15) serum cotinine levels, peripheral arterial disease (PAD), prevalence of cardiovascular diseases (CVD), metabolomics analysis and HbA1 (Table 2).

Regarding the comorbidities mentioned above, some were correlated with exposure to pesticides. We observed the positive correlation between exposure to pesticides and increased glucose levels, HOMA-IR, TRI levels and insulin levels; and presence of metabolic syndrome, PAD, HBP, DM, CVD, and HbA1. While negative correlation, we compared to decrease in HDL levels (Table 3).

4. Discussion

In our study, it was observed that 86.66% (13/15) of the studies correlated overweight and exposure to pesticides. In addition, we observed exposure to pesticides regarding the mechanism of glucose dysregulation (increased levels of glucose, insulin and HOMA-IR) and disrupted lipid homeostasis (increased levels of triglycerides and decreased levels of HDL).

The BMI was the most used methodology to quantify the excess body weight. This fact is attributed to BMI being easy to work (kg/m^2) and useful in most populations, being used worldwide. However, BMI may not be such an accurate method because it does not measure adipose tissue because people with large amounts of lean mass can be classified as overweight, even if fat is reduced (Nuttall, 2015).

Additionally, BMI doesn't measure the physical distribution of adipose tissue (Nuttall, 2015). This may explain the fact that some studies use other methodologies besides BMI, such as waist circumference and waist-to-hip ratio. Since waist circumference is linked to central obesity and is thus related to central adiposity, which is one of the factors linked to metabolic syndrome, BMI and waist circumference predict health risk better than just BMI (Janssen et al., 2004). The waist-to-hip ratio is the best predictor of cardiometabolic risk and is also associated with central adiposity (Dhaliwal and Welborn 2009).

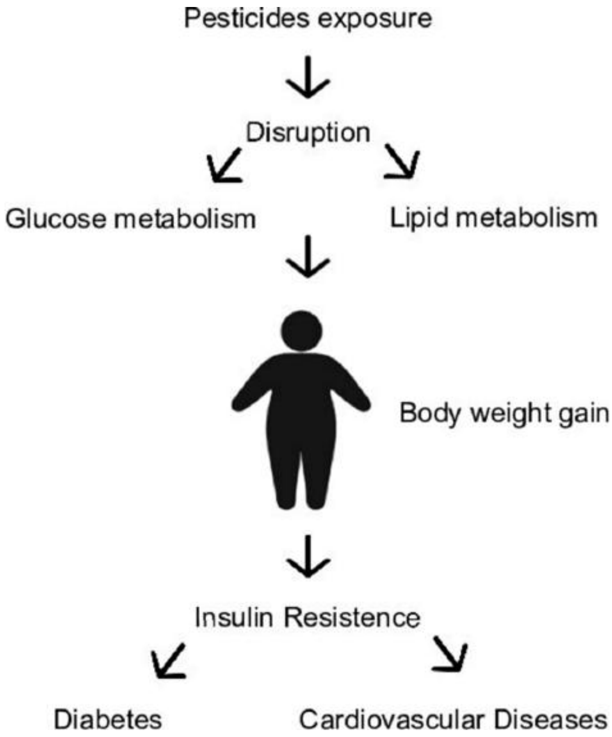
There are several mechanisms that pesticides are reported in the literature as body weight gain inductors. The literature described that pesticides might dysregulate the absorption of nutrients in the intestine (Liang et al., 2020), change the storage of energy in the liver (Liu et al., 2017), adipose tissue (Kim et al., 2014) and muscle (Singh et al., 2019) and thereby, to interfere in the regulation of energy metabolism by the pancreas (Pakzad et al., 2013) and the immune system (Mangum et al., 2016). Consequently, these energy disorders caused by pesticides result in imbalances in energy metabolism, which cause an increase in body weight, deregulation of the lipid profile and an increase in blood glucose (He et al., 2020).

Additionally to weight gain, other comorbidities were related to pesticide metabolites such as oxychlordane, trans-nonachlor, β-HCH and p,p'-DDE. In this way, we observed that pesticides might be deregulation mechanism of glucose (increase levels of glucose, insulin and HOMA-IR) and deregulation lipid homeostasis (increase levels of triglycerides and decreased levels of HDL). As well, these findings proposed an increase in the risk of cardiac diseases and diabetes.

HOMA-IR method is one of the most used epidemiological studies techniques due to its ease and very useful in evaluating insulin resistance (Katsuki et al., 2001). This method aims to assess homeostasis of insulin resistance through a mathematical model that relates interactions between fasting plasma insulin and fasting plasma glucose concentrations (Matthews et al., 1985).

On the other hand, obesity (visceral obesity) was linked to insulin resistance since it is an essential factor in DM and CVD development. It was explained by the fact that glucose intolerance, caused by insulin resistance, can contribute to changes in the function of endothelial cells, macrophages and smooth muscle that can promote atherosclerosis (Peppa et al., 2003). In addition, insulin resistance is related to an increase in triglyceride and LDL concentrations, decreased HDL, and consequently deregulation of the lipid profile that can contribute to CVD (Grundy, 1998). Therefore, in Figure 3, we observe how weight gain leads to a metabolic disorder.

Figure 3 - Mechanism responsible for pesticides leading to metabolic disorders.



Source: Authors.

Based on data from the World Health Organization (WHO), obesity worldwide has almost tripled since 1975. The most recent data available showed that in 2016, more than 1.9 billion adults (aged 18 years and over) were overweight. Of these, more than 650 million were obese. These numbers result in 39% of adults worldwide with overweight and 13% of these with obesity in 2016 (WHO 2020). In addition, obesity is considered a multifactorial pathology, and many factors can interfere in this situation, besides increased energy consumption and decreased physical activities, such as the shortness of sleep (Cappuccio et al., 2008), gut bacterial overgrowth (Turnbaugh et al., 2009) and also the so-called environmental factors or EDC that can affect the organism and cause changes in fat mass and consequently obesity induction (Trasande & Blumberg, 2018). According to the WHO the definition for EDC is "An endocrine disruptor is an exogenous substance or mixture that alters function (s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" (Combarnous, 2017). In our study, it was possible to observe that most studies showed a relationship between exposure to pesticides and body weight gain.

Moreover, pesticides are substances or mixtures of substances used to control or prevent pests, such as insects, herbicides, fungi or rodents. Besides that, pesticides were classified according to several criteria, such as origin (organic sources, inorganic sources, biological); target pest species (feeding deterrents, ovipositor deterrent, repellents, attractants, fumigants, insect growth regulator, synergist); and function (fungicides, herbicides, insecticides, among others) (Abubakar et al., 2020)

In our study, it was possible to observe that most of the analyzed pesticides were organochlorines. Organochlorines are part of the organic source class (according to origin) and synthetic subclass. They can also be designated chlorinated hydrocarbons and are considered one of the first categories of pesticides produced in the world, used in agriculture since most of them are used as an insecticide to have a tremendous residual effect on the environment (Abubakar et al., 2020).

Although many of these pesticide organochlorines were banned in most developed countries, they are still current because of their characteristics that promote persistence (Henríquez-Hernández et al., 2017). It is still possible to find concentrations of this class in blood and urine samples from populations in different countries (Azandjeme et al., 2014; Dusanov et al., 2018; Henríquez-Hernández et al., 2017).

Exposure to pesticides can occur in several ways, such as inhalation, water consumption, and contaminated food. Although many of the pesticides reported in our study are not used due to the ban, several of them may be detected in soil and rivers (Aminov and Carpenter 2020). Besides that, most studies have analyzed the concentration of pesticides in samples such as blood, urine and adipose tissue. It is essential to note that the pesticide metabolites that were related to weight gain are considered to be practically insoluble in water (DDT, DDE, dieldrin, oxychlordane, OCDD, HCH, 2,5-DCP and HCB) (CAMEO Chemicals 2021, 2021a, 2021b, 2021c, 2021d, 2021e, 2021g). In this way, they are preferably stored in the adipose tissue of individuals and, therefore, a higher percentage of fat may be related to a higher content of these substances that they are preferably stored in adipose tissue and consequently have lower serum levels (E. L. Dirinck et al., 2014; Hue et al., 2007). Besides that, there has been an increase in the plasma levels of organochlorine pesticides in individuals with a bodyweight loss (Chevrier et al., 2000).

An example would be patients who experienced significant weight loss in a short period after bariatric surgery and consequently increased these substances in the blood (Jansen et al., 2018). However, it is essential to mention that pesticide metabolites with a more hydrophilic could be more easily detected in the blood (E. Dirinck et al., 2011). On the other hand, because organochloride levels in the blood are not a reliable representation of the levels of pesticides stored in adipose tissue, authors recommend measurement in the adipose tissue when possible (Kohlmeier and Kohlmeier 1995; Aronson et al. 2000; Botella et al. 2004).

Despite limited knowledge of the relationship between serum concentrations and adipose tissue (Arrebola et al., 2012), researchers report that pesticides in these two biological samples (blood and adipose tissue) have different biological meanings. While adipose tissue would be better related to long-term exposure/accumulation, blood levels would be more linked to current exposure and mobilization of persistent organic pollutants from adipose tissue (Archibeque-Engle et al., 1997; Arrebola et al., 2012).

5. Conclusion

Although there is no doubt that factors such as caloric diet and lack of exercise contribute to overweight and subsequent related illnesses, these results show that exposure to pesticides can also increase the risk of developing overweight. In summary, through these findings, our study raises the hypothesis that pesticides, mainly from the class of organochlorines, may be involved in the pathogenesis of obesity. Thus, it may partly explain the increase in insulin resistance, disruption of glucose metabolism, and lipids related to an increased risk of developing DM and CVD.

However, further studies are needed using other pesticides without being organochlorine since data regarding different classes of pesticides are scarce in the literature.

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Disclosure of interest

The authors report no conflicts of interest.

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