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Risk factors for type 2 diabetes mellitus in adolescents: a systematic review and meta-analysis

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ABSTRACT

The prevalence of type 2 diabetes mellitus (T2DM) in adolescents worldwide has increased over the last three decades. Several clinical studies concerning risk factors for T2DM in adolescents were reported, however, the results varied and no systematic review of the studies are reported. This study aimed to systematically review the risk factors for T2DM in adolescents. Publications in English about adolescent with T2DM aged 10-19 yr and coexisting risk factors were searched in Medline and Cochrane. This systematic review and meta-analysis were in-line with MOOSE guidelines. Each publication was assessed the titles, abstracts, and full text, and then extracted the data, and assessed the risk of bias and evidence quality were conducted by 2 independent reviewer. Seven studies involving 52,779 adolescents were included in this review. Meta-analysis using a fixed effect model with the inverse variance method was conducted to calculate the odds ratio with 95% confidence intervals. Adolescents who smoke both actively and passively were at risk of 2.88 times (pooled OR 2.88; 95% CI 1.99-4.17; I^2 = 61%), the male gender was at risk of 1.31 times (pooled OR 1.31; 95% CI 1.09-1.57; I^2 = 0%), having parents with a history of T2DM was at risk of 2.48 times (pooled OR 2.48; 95% CI 1.83-3.36; I^2 = 82%), obesity was at risk of 1.28 times (pooled OR 1.28; 95% CI 1.15-1.43; I^2 = 57%), and hypertension was 1.14 times more likely to get T2DM than those who did not have risk factors. Hypercholesterolemia was not a risk factor for T2DM (pooled OR 1.00; 95% CI 0.95-1.05; I^2 = 0%). In conclusion, the main risk factor for T2DM in adolescents is smoking, followed by parental T2DM, male gender, obesity, and hypertension.

Keywords:
type 2 diabetes mellitus;
risk factors;
smoking;
adolescents;
epidemiology

ABSTRACT

Prevalensi diabetes melitus tipe 2 (DMT2) pada remaja seluruh dunia telah meningkat selama tiga dekade terakhir. Beberapa studi klinis tentang faktor risiko DMT2 pada remaja dilaporkan, namun hasilnya bervariasi dan belum ada kajian sistematik terhadap hasil penelitian tersebut. Kajian ini bertujuan mengkaji secara sistematis faktor risiko yang berpengaruh terhadap DMT2 pada remaja. Publikasi dalam bahasa Inggris tentang DMT2 pada remaja usis 10-19 tahun dan faktor risiko yang menyertai berasal dari Medline dan Cochrane. Kajian sistematik dan meta-analisis disusun berdasarkan panduan MOOSE. Setiap publikasi dinilai judul, abstrak, teks lengkap dan diekstrak datanya, dinilai risiko biasnya dan kualitas buktinya oleh 2 penilai yang independen. Tujuh publikasi hasil penelitian yang melibatkan 52.779 remaja masuk kriteria inklusi. Meta analisis dilakukan menggunakan model efek tetap dengan metode *inverse variance* dalam mengkalkulasi nilai *odds ratio* dengan 95% *confidence intervals*. Remaja perokok baik aktif maupun pasif berisiko 2,88 kali (*pooled* OR=2,88; 95% CI:1,99-4,17; I^2 = 61%), laki-laki berisiko 1,31 kali (*pooled* OR=1,31; 95%CI: 1,09-1,57; I^2 = 0%), memiliki orang tua riwayat DMT2 berisiko 2,48 kali (*pooled* OR=2,48; 95% CI: 1,83-3,36; I^2 = 82%), obesitas berisiko 1,28 kali (*pooled* OR=1,28; 95%CI; 1,15-1,43; I^2 = 57%), dan hipertensi beresiko 1,14 kali lebih besar terkena DMT2 dibanding yang tidak memiliki faktor risiko. Hiperkolestrolemia tidak beresiko terhadap DMT2 (*pooled* OR=1,00; 95% CI;0,95-1,05; I^2 = 0%). Simpulan, faktor risiko utama DMT2 pada remaja adalah merokok, lalu diikuti secara berurutan oleh riwayat parental, jenis kelamin laki-laki, obesitas, dan hipertensi.

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INTRODUCTION

Diabetes mellitus (DM) refers to the condition of hyperglycemia.[1] Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance leading to the failure of pancreatic beta cells to compensate.[2] In adolescents, symptoms are often asymptomatic or only minimally typical symptoms such as polyuria, polydipsia, polyphagia, and weight loss and are often detected during routine lab tests or when severe complications arise.[3] The most common sign of insulin resistance is the appearance of thickened and black skin patches in the body folds, such as the neck and armpit folds called acanthosis nigricans.[4] In diagnosing T2DM in adolescents, the criteria used are the same as adults, namely, fasting blood sugar ≥126 mg/dL (7.0 mmol/L), HbA1C ≥6.5%, or 2 hr postprandial blood sugar ≥200 mg/dL (11.1 mmol/L).[5,6] The condition of T2DM in adolescents is very dangerous because it more aggressively risks various other health problems, such as nonalcoholic fatty liver disease, depression, eating disorders, and possible future complications such as angiopathy, neuropathy, nephropathy, retinopathy, and heart problems.[1,3] Adolescents who develop T2DM will also lose approximately 15 yr of life expectancy.[7]

Initially, T2DM occurred only in adults (age >19 yr), hence the term adult-onset diabetes. However, over the past three decades, there has been a global increase in the incidence of T2DM within the pediatric population, encompassing the adolescent group (ages 10-19 yr).[1,3,4,8–10] The latest data from the Centers for Disease Control and Prevention show that as of 2019, 35 out of 10,000 adolescents had DM, with one-third (20-33%) having T2DM.[2,11] In 2021, there were approximately 41,600 new cases of T2DM in the pediatric population worldwide, 30-40% of which were in the West Pacific region and middle-income countries.[12]

In adults, risk factors for T2DM include age, obesity, physical inactivity, hypertension, dyslipidemia, heredity, and ethnicity,[13] and a review explained that obesity is a major risk factor.[14] In the pediatric population, there are several clinical studies that discuss risk factors for T2DM[15-17] but have varying results, and there is no systematic review that scientifically summarizes these results; therefore, systematic review and meta-analysis are needed that can make a conclusion on risk factors for T2DM in adolescents.

MATERIAL AND METHODS

This meta-analysis was based on the MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines.[18] The data sources used in this systematic review and meta-analysis were studies from the Medline and Cochrane databases, which were published in English within the last 10 yr from 2013 to 2023. The last search was conducted on September 30, 2023. The keywords used in the search included “type 2 diabetes mellitus”, “adolescent”, “risk factor”, “obesity”, “hypertension”, “family”, “hypercholesterolemia”, “smoking”, “gender”, “skin color”, “risk ratio”, “hazard ratio”, and “odds ratio”. The detailed search query utilized for our two selected databases would be provided as supplementary data.

The studies included in this systematic review and meta-analysis are studies conducted on adolescents aged 10 - 19 yr who have T2DM with various accompanying risk factors and are observational study designs. In contrast, our exclusion criteria were carefully defined to maintain methodological rigor, relevance, and ethical considerations. We excluded studies beyond the adolescent age range (10 - 19 yr) to ensure homogeneity in the study population, concentrating on developmental periods associated with the onset of T2DM. In addition, the exclusion of studies that did not assess individuals with identifiable risk factors aimed to increase the specificity of our

analysis. Ethical considerations guided our decision to exclusively include observational studies, aligning with the principles of participant well-being by minimizing potential risks. This non-interventional approach prioritized participant autonomy and upheld ethical considerations, which contributed to the credibility and ethical integrity of our meta-analysis.

After study selection was carried out, a data extraction TABLE was prepared and used to collect data from each study. Two reviewers independently extracted the data, including study title, author name, year of publication, country of study, measured risk factors, outcome, estimated risk values (risk ratio, hazard ratio, odds ratio), confidence intervals (CIs), and conclusions. In cases of unclear and ambiguous data, the reviewer would contact the author via email or phone. Differences of opinion in data extraction were resolved by discussion.

In evaluating the quality of each included study, the Newcastle–Ottawa quality assessment scale (NOS) was employed, utilizing the NOS-for case–control studies tool for case–control study designs and the NOS-modified for cross-sectional studies tool for cross-sectional study designs. The NOS has three assessment domains, namely, the selection, comparability, and outcome domains. For case–control studies, the Selection domain encompasses the Adequacy of case definition, Representativeness of cases, Selection of Controls, and Definition of Controls. The Comparability domain focuses on the comparability of cases and controls based on the study design or analysis, while the Outcome domain assesses Ascertainment of outcome, the Consistency of ascertainment methods for cases and controls, and the Non-Response rate. Similarly, for cross-sectional studies, the Selection domain evaluates Representativeness of the sample, Sample size, Non-respondents, and Ascertainment of the exposure. The Comparability domain assesses the comparability of subjects in different outcome groups, controlling for confounding factors. The Outcome domain evaluates the Assessment of outcome and the application of Statistical tests. The assessment in each domain was converted into conclusions of good quality (3 or 4 stars in Selection, 1 or 2 stars in Comparability, and 2 or 3 stars in Outcome), fair quality (2 stars in Selection, 1 or 2 stars in Comparability, and 2 or 3 stars in Outcome), and poor quality (0 or 1 star in Selection, 0 stars in Comparability, or 0 or 1 stars in Outcome), based on the number of stars achieved in each respective domain.[19] To further gauge the certainty of the evidence for each outcome, a GRADE (Grading of Recommendations Assessment, Development, and Evaluation) assessment was carried out with the help of the GRADE Pro tool.[20] This assessment considered parameters such as risk of bias, inconsistency, indirectness, imprecision, publication bias, large size, plausible confounding, and dose-response gradient. The results were automatically converted into conclusions of high, moderate, low, or very low certainty of the evidence.

This meta-analysis was conducted using RevMan (Review Manager) software version 5.4.[21] To assess the pooled odds ratio (OR)/pooled hazard ratio (HR), each OR/HR value along with its 95%CI were calculated by the inverse variance method. The heterogeneity of each outcome was assessed based on I^2, with I^2 values >75% - 100% interpreted as high heterogeneity, but this result considered the strength of evidence of heterogeneity (p value of chi-square) with $p \leq 0.05$ as statistically significant heterogeneity.[22] The random effects model was used when there was significant high heterogeneity, while the fixed effects model was used when there was no heterogeneity. The meta-analysis results will be condensed and displayed in a comprehensive TABLE, offering a clear and organized summary of the findings.

Small-study effects, such as publication bias of each study on each outcome, were visually assessed using funnel plots when the number of studies on each outcome is ≥10 studies, as recommended by the Cochrane Handbook.[22] Additional subgroup analysis of risk factors for parents with T2DM (parental T2DM) were divided into paternal T2DM and maternal T2DM according to data availability.

RESULTS

Study selection

The search results from the Medline and Cochrane databases yielded 2963 studies, but only 7 studies met the eligibility criteria and were included in the systematic review and meta-analysis. The results of the study selection process are shown in the flowchart in FIGURE 1.

The 7 included studies were from China, Arabia, Iran, Canada, Brazil, and Mexico. All studies used adolescent participants ≤ 19 y.o. and had various associated risk factors (n= 52,779), with an outcome of T2DM. Additional subgroup analyses could not be performed due to the unavailability of paternal T2DM data in the parental T2DM outcome. A summary of the characteristics of each study is shown in TABLE 1.

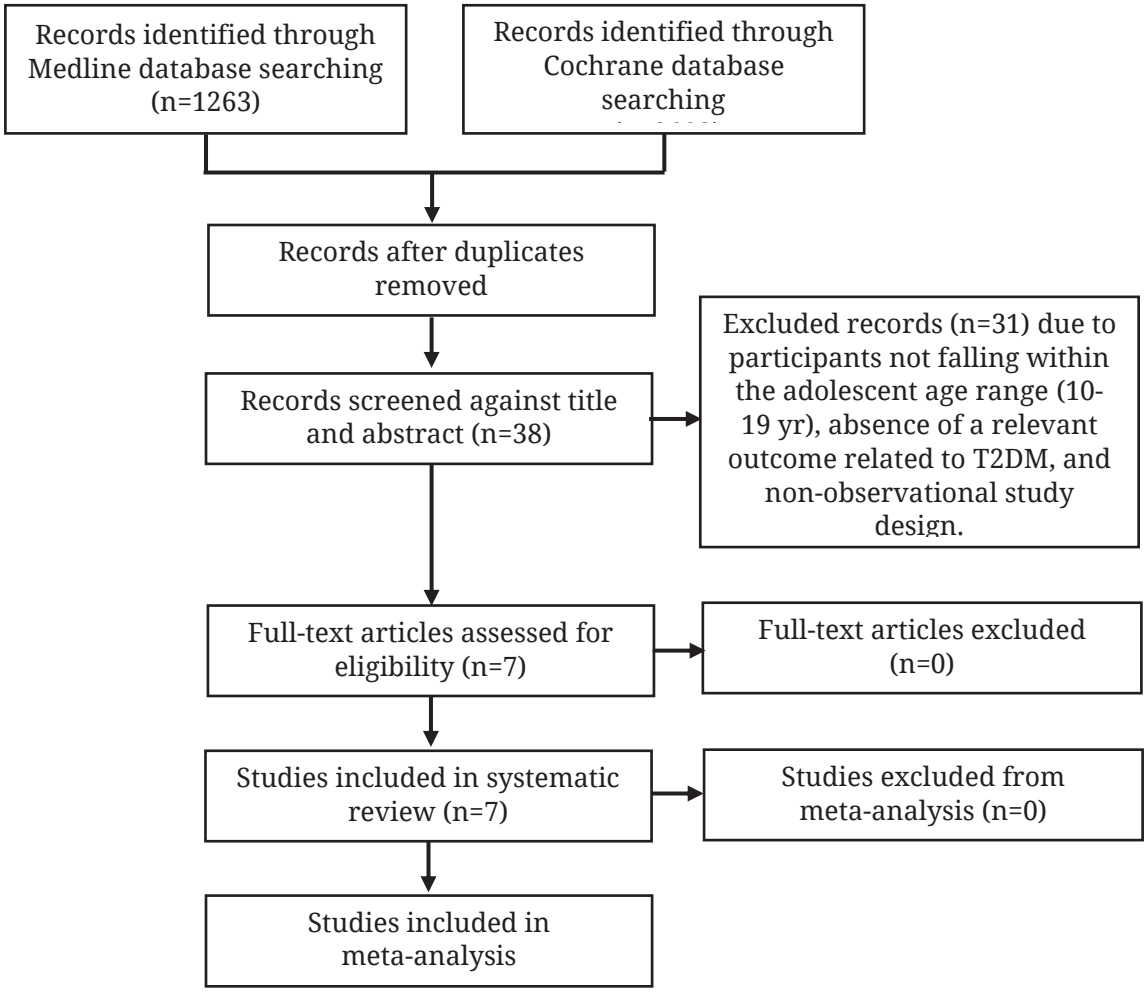

FIGURE 1. Flowchart of study selection

TABLE 1. Study characteristics

References	Location	Study Design	Participants aged (yr)	Sample size (n)		Outcome
				Incidence T2DM	Total Sample	
Al Amiri *et al.*[15]	Saudi Arabia	Cross-sectional	11-17	9	1032	Gender, parental T2DM, obesity, hypertension, hypercholestrolemia
Miranda *et al.*[16]	Mexico	Case–control	≤18	97	181	Gender, obesity, parental T2DM
Zhu *et al.*[17]	China	Cross-sectional	10-18	26	3173	Smoking, high birth weight
Mirbolouk *et al.*[23]	Iran	Cross-sectional	10-19	208	2563	Gender, parental T2DM, obesity, hypertension, hypercholestrolemia
Halipchuk *et al.*[24]	Canada	Case–control	10-17	270	1611	Parental T2DM
Telo *et al.*[25]	Brazil	Cross-sectional	12-17	1233	37.854	Gender, skipping breakfast, obesity, urban residence
Barakat *et al.*[26]	Saudi Arabia	Cross-sectional	≤19	55	6365	Gender, smoking

TABLE 2. Newcastle–Ottawa quality assessment scale (NOS) – modified for cross-sectional study design

References	Selection			Comparability#		Outcome		Result
	Sample representativeness	Sample size	Non respondents	Ascertainment of risk factor	Comparable & controlled	Assessment	Statistic analysis	
Zhu *et al.*[17]	*	*	*	**	**	*	*	Good quality
Al Amiri *et al.*[15]	*	*	*	**	**	*	*	Good quality
Mirbolouk *et al.*[23]	*	*	*	**	**	**	*	Good quality
Telo *et al.*[25]	*	*	*	**	**	*	*	Good quality
Barakat *et al.*[26]	*	*	*	**	**	*	*	Good quality

#The subjects in different outcome groups are comparable, based on the study design or analysis. confounding factors are controlled */** = fulfilled

Study quality assessment

In assessing the risk of bias in each study, 5 cross-sectional studies by Al Amiri *et al.*,[15] Zhu *et al.*,[17] Mirbolouk *et al.*,[23] Telo *et al.*,[25] and Barakat *et al.*[26] showed good quality results in the NOS-modified for cross-sectional studies, although the studies by Zhu *et al.*,[17] Al Amiri *et al.*,[15] Telo *et al.*,[25] and Barakat *et al.*[26] have weakness in the domain of assessment of outcomes due to the diagnosis of T2DM not being measured by researchers but being self-reported. Two case–control studies by Halipchuk *et al.*[24] and Miranda-Lora *et al.*[16] also showed good quality results in all domains in the NOS for case–control studies. The risk of bias assessment for each study is listed in TABLE 2 and TABLE 3.

Analysis results

There were 3 outcomes, namely, the risk factors for high birth weight, skipping breakfast, and urban residence, that could not be included in the meta-analysis due to insufficient studies that could be used as comparative analysis. The study by Zhu *et al.*[17] showed that adolescents with a history of high birth weight had a 1.92 times higher risk of developing T2DM compared to normal birth weight (OR=1.92; 95%CI:1.06-3.49). The study by Telo *et al.*[25] explained the risk factors for skipping breakfast and urban residence to the incidence of T2DM. Adolescents with risk factors for skipping breakfast and living in urban areas were at 1.48 times (OR=1.48; 95% CI: 1.21-1.81) and 1.76 times (OR=1.76; 95% CI: 1.27-2.43) higher risk than those without risk factors, respectively.

After meta-analysis, the results showed that adolescents who smoked both actively and passively had a 2.88 times greater risk (pooled OR=2.88; 95%CI: 1.99 to 4.17; I^2 = 61%), male gender had a 1.31 times greater risk (pooled OR=1.31; 95%CI:1.09 to 1.57; I^2 = 0%), having a parent with T2DM had a 2.48 times greater risk (pooled OR=2.48; 95%CI: 1.83 to 3.36; I^2 = 82%), obesity had a 1.28 times greater risk (pooled OR=1.28; 95%CI:1.15 to 1.43; I^2 = 57%), and hypertension was 1.14 times more likely (pooled OR=1.14; 95%CI :1.00 to 1.29; I^2 = 0%) to develop T2DM than those without these risk factors. The risk factor hypercholesterolemia did not affect the risk of T2DM (pooled OR=1.00; 95% CI:0.95 to 1.05; I^2 = 0%). The majority of outcomes had low heterogeneity ≤75%, but the parental T2DM risk factor outcome had significantly high heterogeneity, which was due to the lack of paternal T2DM and maternal T2DM subgroups in the analysis. In analyzing the strength of evidence with the GRADE approach, high-quality results were obtained. A summary of the meta-analysis results is shown in TABLE 4.

TABLE 3. Newcastle–Ottawa quality assessment scale (NOS) – for case-control study design

References	Selection				Comparability#	Outcome			Result
	Case adequate	Sample representa-tiveness	Control selection	Control definition	Comparable & controlled	Exposure ascertain-ment	Case/ control ascertain-ment	Non response rate	
Halipchuk *et al.*[24]	*	*	*	*	**	*	*	*	Good quality
Miranda-Lora *et al.*[16]	*	*	*	*	**	*	*	*	Good quality

*/** = fulfilled

TABLE 4. Synthesis summary of T2DM risk factors

Risk factors	Number of studies	POR (95% CI)	Heterogeneity (p; I^2 %)	Strength of evidence (GRADE)
Smoking	2	2.88 (1.99 to 4.17)	(0.11; 61)	⊕⊕⊕⊕High
Male Gender	4	1.31 (1.09 to 1.57)	(0.73; 0)	⊕⊕⊕⊕High
Parental T2DM	4	2.48 (1.83 to 3.36)	(0.0009; 82)	⊕⊕⊕⊕High
Obesity	4	1.28 (1.15 to 1.43)	(0.07; 57)	⊕⊕⊕⊕High
Hypertension	2	1.14 (1.00 to 1.29)	(0.65; 0)	⊕⊕⊕⊕High
Hypercholestrolemia	2	1.00 (0.95 to 1.05)	(0.87; 0)	⊕⊕⊕⊕High

POR: pooled OR

DISCUSSION

Based on this systematic review and meta-analysis, smoking emerges as the primary risk factor for T2DM in adolescents, followed by parental history of T2DM, male gender, obesity, and hypertension. Additionally, factors such as high birth weight, skipping breakfast, and urban residence are associated with the risk of T2DM. In contrast to the adolescent population, a review of 86 meta-analyses involving adult participants indicates that the primary risk factor for the development of T2DM is overweight to obesity, encompassing both metabolically healthy and unhealthy obesity. Smoking, encompassing both current and former use, retains its status as a risk factor, albeit with diminished significance compared to obesity.[14] Furthermore, our findings align with other studies,[27] suggesting that hypercholesterolemia does not contribute as a risk factor for T2DM.

Adolescents who smoke both actively and passively have a 2.88 times greater risk than nonsmokers. According to the Centers of Disease Control and Prevention, the nicotine content in cigarettes can change the cell's response to insulin and induce proinflammatory metabolic conditions in cells so that cell sensitivity to insulin is reduced and glucose cannot be carried into cells. Smokers are also at risk of having higher abdominal fat than nonsmokers even though they are not overweight, which is why smoking is a stronger risk factor than obesity in developing T2DM.[28] Another study explains that smoking can affect insulin sensitivity by epigenetic mechanisms. There are 95 DNA methylation sites in 66 chromosomal regions that undergo methylation processes differently than nonsmokers. These DNA sites are related to "insulin receptor binding" and "negative regulation of glucose import".[29,30] In addition, nicotine in cigarettes can interfere with insulin secretion by binding to *n*euronal nicotinic acetylcholine receptors (nAChRs) in pancreatic beta cells and stimulating apoptosis of pancreatic beta cells.[31]

Adolescents who have parents with T2DM are at 2.48 times greater risk of developing T2DM. A study showed that more than 90 genes inherited from parents are associated with T2DM. These genes do not act alone but involve environmental or lifestyle factors to cause T2DM. These genes are responsible for controlling insulin secretion, insulin regulation in the blood, and glucose uptake into cells.[32,33] In terms of psychology, adolescents tend to mimic the habits of their parents, including parents with T2DM, so that the diet and physical activity patterns of parents will also be adopted by their children.[34]

Obesity is one of the risk factors for T2DM in adolescents. Obesity puts adolescents at 1.28 times greater risk of developing T2DM than nonobese adolescents. Adipose tissue can affect glucose metabolism by releasing nonesterified fatty acids (NEFAs), retinol-binding protein-4 (RBP4), and proinflammatory cytokines, which are increased in obese conditions. NEFAs can cause insulin resistance by inhibiting insulin-stimulated peripheral glucose uptake and insulin signaling to its receptor. RBP4 decreases phosphatidylinositol-3-OH kinase (PI(3)K) signaling, which plays a role in GLUT 4 translocation and glycogen synthesis in muscle and increases the gluconeogenesis process by inducing the expression of phosphoenolpyruvate carboxykinase enzyme in the liver. Proinflammatory cytokines in obesity are associated with chronic low-level inflammatory conditions. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) overexpression can cause insulin resistance by inhibiting insulin signaling to the insulin receptor.[35]

Male adolescents with T2DM were more prevalent than females.[26] This is in line with the findings in this study, where male adolescents are 1.31 times more likely to have T2DM than females. There is no clear explanation for this, but a study by Nordström *et al.*[36] suggests that this could be due to higher visceral fat in males compared to females. Another study explains the role of body iron (Fe) levels on the incidence of T2DM. Serum ferritin (sF), which is a marker of body iron storage, has a greater amount in men, where iron can suppress the transcription process of adiponectin mRNA so that the amount of adiponectin, which acts as an insulin sensitizer, is reduced and leads to insulin resistance.[37]

Adolescents with hypertension often show insulin resistance and have a 1.14 times greater risk of developing diabetes than individuals with normal blood pressure.[38] These results are in line with other studies, where hypertension can be a significant predictor of the development of T2DM.[39] The study by Kim *et al*.[39] showed that uncontrolled hypertension is more at risk of developing T2DM than controlled hypertension. In hypertension, mechanical changes occur, including loss of effectiveness of microvascular perfusion units, arterioles or capillaries, which leads to a decrease in blood flow to peripheral areas such as skeletal muscles. Insulin resistance occurs as a direct effect of this decreased perfusion.[41]

Hypercholesterolemia has no association with the incidence of T2DM. A study by Xu *et al*.[42] explained that the lower the LDL level in the blood, the higher the risk of T2DM. This is because the measured LDL level is the blood LDL level, while the LDL that can trigger insulin insensitivity in peripheral tissues is intracellular LDL. The appropriate measurement of LDL levels to see its relationship with T2DM is the intracellular LDL concentration. Besseling *et al.*[42] explained that the administration of statin drugs can increase cholesterol uptake into cells, thereby increasing the risk of T2DM.

High birth weight is linked to an increased risk of T2DM, indicating intrauterine growth influenced by maternal factors like gestational diabetes. This factor is interrelated with parental history risk factors.[17] Skipping breakfast is also associated with a higher risk of T2DM through mechanisms involving prolonged fasting, leading to increased free fatty acids and disruptions in circadian rhythms.[43] Urban residence contributes to the risk of T2DM by fostering a sedentary lifestyle and unhealthy dietary patterns, creating an obesogenic environment for adolescents.[44]

Based on the insights gained from the findings of this systematic review and meta-analysis, it is clear that adolescent lifestyle choices have a significant influence on the incidence of T2DM. It is critical to recognize that adolescents who develop T2DM may, in turn, pass on the high risk of the condition to their offspring, thus perpetuating the intergenerational cycle of diabetes vulnerability. Given these intergenerational implications, preventive measures that focus on lifestyle behavior modification during adolescence are particularly important. Breaking the transmission of diabetes risk factors from one generation to the next is emerging as a strategic imperative. Therefore, cessation of unhealthy lifestyles in adolescents is not only an important intervention for their immediate health, but also decisive in breaking the chain of T2DM incidence for future generations. Strong prevention efforts are favored over curative efforts, given their far-reaching impact on family and community health.

The studies included in this meta-analysis were from both developed and developing countries, so the results of this analysis can be generalized to

adolescents around the world. The strength of evidence for each risk factor outcome using the GRADE approach showed high-quality results, so we can ensure that this systematic review and meta-analysis can be used as a reference and recommendation in handling cases of T2DM in adolescents. This review has some weaknesses, as we only used studies from two databases and those published in English, so although the search strategy was systematic and comprehensive, some studies may have been overlooked.

CONCLUSION

In conclusion, smoking emerges as a main risk factor for T2DM in adolescents, with parental T2DM, male gender, obesity, and hypertension following suit, while hypercholesterolemia does not contribute as a risk factor.

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