Review Article

The Risk Factors of Prediabetes in Adolescents: A Systematic Review

Arvida Bar[1], Agusriani[1*], Halimahtussa' diyah[1]

1. Health Polytechnic of Jambi, Sciences Center of Excellence, Health Polytechnic Ministry of Health Jambi, Indonesia.

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ABSTRACT

Background: Pre-diabetes is a risk state for the future development of type 2 diabetes. The risk factors for prediabetes have been categorized as modifiable and non-modifiable. However, conclusive evidence regarding the risk factors associated with pre-diabetes in adolescence is still lacking. This study aims to answer the question of: which risk factors are most associated with the incidence of prediabetes in adolescents?

Methods: This review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A systematic search was conducted in PubMed, ScienceDirect, Scopus and Web of Science electronic databases using the keywords of "modifiable risk factors", "non-modifiable risk factors", "pre-diabetes" and "adolescent" in the time frame of 2010 to 2021. Eligibility criteria were determined based on the (population, intervention, comparison and outcomes) PICOS guidelines. Reference list from identified studies was used to augment the search strategy. Two authors assessed the quality and risk of bias of the studies using National Institute of Health (NIH) Quality assessment tool. Qualitative analysis method was used to review the articles. Based on this, components such as purpose, methodology, risk factors, measurement method and main findings were extracted.

Results: As a result of the initial search, 3982 studies were obtained. All duplicates, case reports, reviews and non-English studies were excluded. A total of ten articles that met the pre-defined eligibility criteria were included in this review. The quality of included studies was mostly in the good category. Overall, the association between risk factors and adolescents' prediabetes appeared to be strongest among modifiable factors such as physical activity, poor diet, smoking, and cardiometabolic factors. The most significant modifiable factor was body mass index (BMI) and the most significant non-modifiable factor was gender.

Conclusion: Considering the prominent role of modifiable risk factors in the occurrence of prediabetes in adolescents, it seems necessary to include lifestyle modification programs for this age group. It is also important to pay attention to gender as a non-modifiable factor in the development of prediabetes in adolescents.

*** Corresponding Author:**
Agusriani
Address: *Health Polytechnic of Jambi, Sciences Center of Excellence, Health Polytechnic Ministry of Health Jambi, Indonesia.*
E-mail: *agusriani180@gmail.com*

Highlights

• Prediabetes is a condition that initiates the occurrence of diabetes in the future.

• Recognizing prediabetes conditions can help control diabetes.

• There are inconsistencies in the results of studies conducted on factors that play a role in the incidence of prediabetes in adolescents.

• Modifiable risk factors are the variables that are strongly related to the incidence of prediabetes in adolescents, and body mass index (BMI) is the most important factor in this category.

• Among non-modifiable factors, gender plays the most important role in the prevalence of prediabetes in adolescents.

Plain Language Summary

Knowing what factors contribute to the occurrence of prediabetes in adolescents is very important, considering the impact that ignoring these factors has on the future of adolescents. In general, the factors that play a role in the occurrence of prediabetes in adolescents are divided into two categories: modifiable and non-modifiable factors. The present study came to the conclusion that the most important factors affecting the incidence of prediabetes in adolescents are modifiable and will be strengthened when combined with other non-modifiable factors. The most important modifiable factor was body mass index (the ratio of weight in kilograms to the square (x^2) of height in meters) and the most important unmodifiable factor was gender.

1. Introduction

Prediabetes is an intermediate glycemic state in which blood glucose concentrations are higher than normal but not of a magnitude that would correspond to the diagnosis of type 2 diabetes (Consortium, 2014). The incidence of prediabetes is increasing globally and is expected to affect 472 million people by the end of 2030 (Tabák et al., 2012). Subjects with prediabetes have a profound risk of developing type 2 diabetes. If prediabetes is not treated, it accounts for 37% of cases of diabetes in succeeding years (Tuso, 2014). Prediabetes also imposes the potential burden of mortality upon the affected individuals due to its association with cardiovascular complications (Siddiqui et al., 2020). However, changes in the lifestyle can reduce or delay the appearance of diabetes among people with prediabetes (Tuomilehto et al., 2001). Thus, it is important to recognize individuals presenting with a higher probability of impaired glucose metabolism and related risk factors to reduce disease progression as well as financial burden on the health care system (Díaz-Redondo et al., 2015).

Adolescent is a stage of life between childhood and adulthood, from ages 10 to 19. This evolutionary period may be the right sequence for human progress and the necessary time to create great welfare facilities. The emerging increase in the prevalence of prediabetes in children and adolescents has paralleled the observed increase in childhood obesity over the past three decades. The recorded prevalence of prediabetes depends on the conditions and tools chosen for screening, the population studied, pubertal status, and-importantly-the definitions used. Impaired fasting glucose is defined as above 5·6 mmol/L by the American Diabetes Association (ADA) and above 6·1 mmol/L by the World Health Organization (WHO). As a result, the recorded prevalence of impaired glucose tolerance in obese children and adolescents ranges from 1% to 30%, whereas the prevalence of impaired fasting glucose has a broader range in not only obese children, but also the general adolescent population that is not specifically within at-risk groups. For example, the prevalence of impaired fasting glucose in obese children ranges from 1% in Italy (Brufani et al., 2010) and 4% in Germany, to 17% in Sweden (all with the use of ADA criteria) (Hagman et al., 2014). In the USA, reported prevalence ranges from 2%-9% (WHO criteria) to 15%-47% (ADA criteria) (Di Bonito et al., 2017). Impaired fasting glucose was reported in a small proportion (<5%) of the obese pediatric population in Mexico (Yamamoto-Kimura et al., 2006) India (Narayanappa et al., 2011) and mainland China (Yang et al., 2015) compared with 28% of obese adolescents in Taiwan (Chen et al., 2014). In the

United Arab Emirates, as one of the countries with the highest prevalence of type 2 diabetes in adults worldwide, fasting glucose is impaired in 12% of overweight and obese children (Al Amiri et al., 2015). Several challenges arise when attempting to compare and interpret these prevalence data, since the sample populations have been recruited from different settings (e.g., whole population vs obesity clinic). Additionally, in epidemiological studies involving large samples, some participants might not have truly fasted when fasting glucose is measured, causing an overestimation of the prevalence. Similarly, the presence of impaired glucose tolerance can vary across repeated sampling within a timeframe of weeks (Libman et al., 2008), possibly because whole-body insulin sensitivity can be affected by participant characteristics, such as minor infection or phases of the menstrual cycle. However, arguably, a single detection of impaired glucose tolerance, even if not repeated, already indicates that the β cells of the individual have inadequate function and pronounced insulin resistance.

Several studies have been conducted previously, to investigate the association of these risk factors with the risk of prediabetes (Hadaegh et al., 2015; Lee et al., 2015; Geva et al., 2019); However the findings remained inconsistent. Conclusive evidence to support or refute differences in risk factor association across the wide range of studies is lacking and has never been studied systematically previously. Summarized information is needed because it may help to develop or implement age-appropriate preventive strategies for adolescents that can be used as a key to self-care to improve quality of life among prediabetic individuals. Therefore, this systematic review was conducted to briefly address and summarize the available literature for the evidence of age-specific modifiable and non-modifiable risk factors among adolescent population and answer the question: which risk factors are most associated with the incidence of prediabetes in adolescents?

2. Materials and Methods

We performed a systematic review of the literature consisting of observational or cross-sectional studies, which reported the risk factors of pre-diabetes among adolescent by following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 guidelines (Page et al., 2021).

Information sources and search strategy

We performed a literature search through PubMed, ScienceDirect, Scopus, and Web of Science databases in the time frame of 2010 to 2021. A careful manual search of reference lists of identified papers was also done by all authors to identify studies that were not detected by the database search. All the retrieved articles were then sent to Mendeley to remove duplicates. Screening of titles and abstract based on the pre-defined inclusion and exclusion criteria was done to get relevant citations that were included in the present review. Keywords used were “Modifiable Risk Factors” OR “Non-modifiable Risk Factors” OR “Factors associated” OR “Factors related” AND “Prediabetes” OR “Prediabetic” AND “Adolescent” OR “Youth” OR “Teen” OR “Young people” (Table 1).

Table 1. The syntax of searching on databases

Databases	Keywords
ScienceDirect	Modifiable Risk Factors” OR “Non-Modifiable Risk Factors” AND “Prediabetes” AND “Adolescent” OR “Youth” OR “Young people”. “Factors associated” OR “Factors related” AND “Prediabetes” AND “Adolescent” OR “Youth” OR “Teen” OR “Young people”.
PubMed	Modifiable Risk Factors” OR “Non-Modifiable Risk Factors” OR “Factors associated” OR “Factors related” AND “Prediabetes” OR “Prediabetic” AND “Adolescent” OR “Youth” OR “Teen” OR “Young people”.
Scopus	“Factors associated” OR “Factors related” AND “Prediabetes” OR “Prediabetic” AND “Adolescent” OR “Youth” OR “Teen” OR “Young people” AND NOT Adult
Web of Science	Modifiable Risk Factors” OR “Non-Modifiable Risk Factors” OR “Factors associated” OR “Factors related” AND “Prediabetes” OR “Prediabetic” AND “Adolescent” OR “Youth” OR “Teen” OR “Young people”.

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Eligibility criteria

Eligibility criteria were determined based on the (population, intervention, comparison and outcomes) PICOS guidelines. The participants consisted of adolescent in any age (10-19 years old). No intervention was needed to be considered in this review, but the laboratory tests and diagnostic procedures to identify pre-diabetes were considered as exposure. Comparison was considered as a difference in demographic variables such as age, sex, smoking, race, and family history of diabetes. The outcomes were significant modifiable and non-modifiable factors involved in occurrence of pre-diabetes. In terms of research design, cross-sectional and observational studies were considered and those published in English in the time range of 2010 to 2021 were included in the review. We excluded preprint articles, meta-analytical and systematic reviews, case reports, non-English articles, articles without pertinent data, non-research articles, and articles without full-text availability. In case of duplicate reports from the same study (Díaz-Redondo et al., 2015; Ehrhart et al., 2017), the study which had evaluated the higher number of modifiable and non-modifiable risk factors was included in this review (Díaz-Redondo et al., 2015).

Data extraction and synthesis

Two authors carried out data extraction based on study objectives, design, participants, risk factors, measurement methods, and main findings. A narrative synthesis was done considering the significant levels of the study results. Disagreement between the two reviewers was referred to a third author for final decision.

Quality assessment

The quality of included studies was assessed by using the National Institute of Health (NIH) Quality assessment tool for observational, cohort and cross-sectional studies National Heart, Lung, and Blood Institute (NHLBI). Several reviews have previously used this tool to critically appraise the quality of reviewed studies (Bayfield et al., 2018; Uloko et al., 2018). The related checklist has 14 questions relating to the research question, selection of study subjects, statistical analysis and measurement and selection of timeframe between exposure and outcome to see an effect. The quality of studies was graded as good (G) if the overall score was at least 70%, fair (F) if the article score was at least 50%, and poor (P) if it was less than 50%. (Uloko et al., 2018). We only included studies of Fair and Good quality.

3. Results

The initial search strategy identified 3982 potentially relevant articles, of which 849 remained after removing duplicates and other reasons (Figure 1). After abstract and title screening, 815 studies were excluded because the sample used did not include adolescents. A total of 34 articles remained for full text screening, of which 10 articles were included in this review that met the predefined eligibility criteria.

Table 2. Summary of risk of bias assessment using axis tool

Studies & Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Mamtani	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ratliff	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sylvia	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Casapulla	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Propst	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Nagarajan	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Taranikanti	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Al amiri	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Luo	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Duke	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

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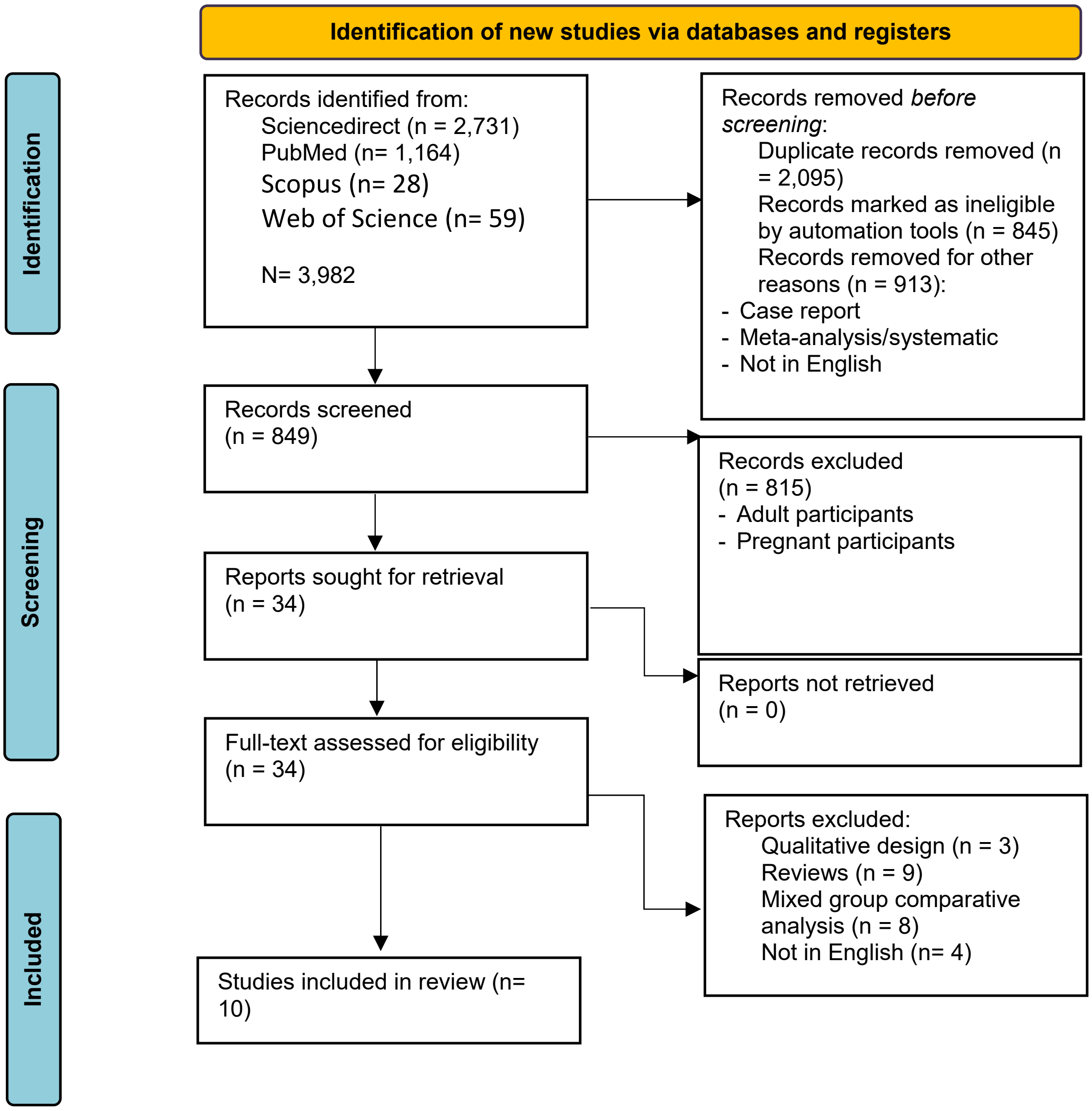

Figure 1. PRISMA flowchart of literature search

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Study characteristics

The major characteristics of 10 studies were summarized in chronological order in Table 2. The studies included in this review came from a number of countries in various parts of the world, including the US (n=4), and one study each from Qatar, Ecuador, Indonesia, India, China, and UAE. The number of subjects who participated in the reviewed studies ranged from 131 to 125,375 adolescent. All the studies utilized cross-sectional design except one study which used retrospective study design (Propst et al., 2015).

Risk of bias

The quality of included studies was evaluated by using appraisal tool for observational cross-sectional studies (AXIS) (Young & Solomon, 2009). This assessment tool has 20 questions and sections to record answers as "yes", "no" or "don't know" (Table 3). Based on the result of risk of bias assessment, all of the studies included were in the moderate to low risk of bias category.

Table 3. Characteristics of the included studies

Author, Year, Country	Aim of the Study	Study Design	Participants	Risk Factors	Measurement Methods	Main Findings	Quality
Mamtani et al., 2014, Qatar	To investigate risk factors associated with prediabetes in students aged 11–18 at four schools	Cross-sectional	1694 students, aged 11-18 years old	Gender, family history of diabetes, daily exercise, anthropometric factors such as weight, BMI z-score, waist-to-height ratio, waist z-score, and obesity.	Questionnaire, WHO AnthroPlus soft-ware, the national cholesterol education program adult treatment panel (NCEP ATP), random blood sugar or a fasting blood sugar	Most associated factors of prediabetes including Gender (OR 3.2, P=0.0005), family history of DM (OR 1.9 P=0.025), and waist-to-height ratio (OR 1.8, P.016)	Good
Ratliff et al., 2019, US	To evaluate possible associations between LCSB and water consumption with nutrient intake and prediabetes criteria among adolescents who were free of diabetes	Cross-sectional	8868 adolescents 12 to 18 year of age who were free of diabetes	Low-calorie sweetened beverage (LCSB), water consumption patterns	National health and nutrition examination survey NHANES questionnaire, what we eat in America (WWEIA), homeostasis model assessment of insulin resistance (HOMA-IR)	Based on the prediabetes criteria, there are no significant associations between consumption of either beverage with measures of glycemic control, water consumption was not associated with any measures of lipid metabolism	Good
Sylvia & Ardiyani, 2019, Indonesia	To determine the risk factors of pre-diabetes among senior high school students	Cross-sectional	Students aged 14-19 years old, male (n=53) or female (n=78) students	Smoking, BMI , physical activity, family history of diabetes	Questionnaire, BMI calculation, fasting plasma glucose level	Smokers have a higher risk 1.9 times of having prediabetes compared to non-smokers ($P<0.05$). Physical activity<3 times a week, tend to experience prediabetes 1.9 times compared to physical activity ≥3 times ($P<0.05$). Low BMIs were not at risk of having Impaired Glucose Tolerance (IGT) levels of 0.9 times compared to normal BMI.	Fair
Casapulla et al., 2017, Ecuador	To identify and better understand the prevalence of overweight and obesity, cardio-metabolic risk factors, prevalence of type 2 diabetes, prediabetes and metabolic syndrome	Cross-sectional	Adolescents ages 13–18 (N=433) were recruited from two schools	Gender	Tension-regulated tape, sphygmomanometer, blood glucose level, sex-specific growth charts	Girls had higher BMI compared to boys ($P<0.001$). Boys had higher systolic blood pressure SBP (P=0.003) and diastolic blood pressure DBP (P=0.05) than girls. Girls had higher total cholesterol (TC) ($P<0.001$), low density lipoprotein (LDL) ($P<0.001$), high density lipoprotein (HDL) (P=0.01), very low density lipoprotein (VLDL) (P=0.01) and Triglyceride (TG) (P=0.009) than boys. There were no significant sex differences in HbA1c (P=0.32).	Fair

Author, Year, Country	Aim of the Study	Study Design	Participants	Risk Factors	Measurement Methods	Main Findings	Quality
Propst et al., 2015, Alabama (US)	To examine the prevalence and characteristics of co-morbidities in obese and morbidly obese children with a comparison between the 2 sets of children.	Retrospective	1,111 obese children and adolescents	Medical history of co-morbid conditions, medication use, and cardiovascular risk markers	Observation forms, blood glucose, sphygmomanometer, vitros 5.1 fs chemistry system, direct coupling analysis DCA2000 assay	BMI was positively associated with SBP in African American (AA) subjects ($r=0.079$; $P=0.04$). BMI was inversely associated with HDL in the overall group ($r=-0.102$; $P=0.0006$) and also specifically in AA ($r=-0.08$; $P=0.04$) and non-hispanic white (NHW) ($r=-0.17$; $P=0.001$) subjects.	Good
Nagarajan et al., 2017, US	To examine the association between family consumer behaviors (healthy food availability and supermarket spending) and adolescent prediabetes and diabetes	Cross-sectional	National health and nutrition examination survey NHANES subjects from 2007 to 2010 who were 12–19 years old and from households where an eligible person had administered the consumer behavior questionnaire (CBQ)	House-hold healthy food availability, and supermarket spending on food	Blood glucose, (CBQ)	Adolescents with healthier household food availability had a significant and negative odds of adolescent prediabetes/diabetes (OR=0.74). Adolescents with higher log supermarket spending had a significantly protective odds of adolescent prediabetes/diabetes (OR=0.69).	Fair
Taranikanti, et al., 2014, India	To see the prevalence of prediabetes if any in school students between 14-18 year of age.	Cross-sectional	140 students of both sexes between ages 14-18 years	Obesity, family history of DM, Physical activity	Predesigned questionnaire	There was no correlation between plasma glucose and BMI. Relation between prediabetes and waist-hip-Ratio (WHR) was not significant ($P>0.05$).	Fair
Al Amiri et al., 2015, UEA	to compare the prevalence of prediabetes and type 2 diabetes (T2D) among overweight/ obese children and adolescents using different diagnostic/ screening methods	Cross-sectional	1034 participants (45% females) median age 14.7 years	Obesity, overweight	Questionnaire, blood pressure, biochemical measurements, BMI	No significant correlation was seen between glycemic status and level of physical activity, presence of prediabetes symptoms ($P=0.032$) Family history of diabetes, parents being unemployed and high levels of TG were independent risk factors for abnormal glycemic testing ($P<0.05$) Family history of T2D first-degree relatives ($P=0.028$) and high levels of TG ($P=0.019$) were statistically correlated with abnormal glycemic testing based on fasting blood glucose	Fair

Author, Year, Country	Aim of the Study	Study Design	Participants	Risk Factors	Measurement Methods	Main Findings	Quality
Luo et al., 2020, China	To evaluate whether urinary organophosphate esters (OPEs) metabolites were associated with prediabetes and glucose homeostasis	National survey with a multi-stage complex sampling design (Cross sectional)	349 adolescents (12-19-year old)	Urinary (OPE)	Urine specimen	bis (1,3-dichloro-2-propyl) phosphate BDCIPP was significantly associated with elevated odds of prediabetes (OR 1.49); di(2-propylheptyl) phthalate DPHP was positively associated with HbA1c (β= 0.05); detectable BCIPP was negatively associated with 2 h-oral glucose tolerance test OGTT (β-0.07) Detectable DNBP was negatively associated with Fasting plasma glucose (FPG) (β-2.53) and 2 h- OGTT (β-0.11)	Good
Duke, 2020, US	To examine relationship between Sugar sweetened beverage SSB intake and reported prediabetes	Cross-sectional	125,375 students 5th, 8th, 9th, and 11th grade in regular public elementary and secondary schools, charter schools, and tribal schools	SSB Intake	Beverage intake questions	SSB intake frequencies were significantly associated with increased odds of reported prediabetes. (OR 1.37)	Fair

Pre-diabetes reports

Assessment of prediabetes in the participants of included studies was carried out using Fasting Blood Glucose (Al Amiri et al., 2015; Casapulla et al., 2017; Mamtani et al., 2014; Propst et al., 2015; Nagarajan et al., 2017), glycated hemoglobin (HbA1c) (Al Amiri et al., 2015; Casapulla et al., 2017), fasting plasma glucose (Ratliff et al., 2019; Sylvia & Ardiyani, 2019; Taranikanti, Khan & Tabassum, 2014; Luo et al., 2020) and sweetened beverage (SSB) intake (Duke, 2021).

The standard criteria for prediabetes based on the measurement results of fasting blood glucose is 5.5 mmol/L (Mamtani et al., 2014). The standard percentage of HbA1c is 5.7% to 6.4% (Luo et al., 2020; Propst et al., 2015), 5.7% (39 mmol/L) (Nagarajan et al., 2017). While indications of prediabetes through Fasting plasma glucose (FPG) examination are 100-125mg/dl, and/or 2-h plasma glucose from OGTT at 140-199mg/dl (Sylvia & Ardiyani, 2019), 140 to 126 mg/dl (Taranikanti et al., 2014), 100 mg/dl and less than 125 mg/dl (Luo et al., 2020). One study did not report standard criteria for prediabetes (Casapulla et al., 2017).

Modifiable factors

Modifiable factors included in the reviewed studies were BMI, smoking, physical inactivity, poor diet, and cardio-metabolic factors. Some studies analyzed the physical activity of the participants which was considered to have a relationship with prediabetes. Daily exercise, when compared with less than daily exercise, had a significant beneficial effect on several key anthropometric factors such as weight (P=0.003), BMI z –score (P=0.02), waist-to-height ratio (P=0.0003), waist z-score (P=0.0004) and obesity (P=0.003) (Mamtani et al., 2014). In Indonesia, students who had physical activity<3 times a week were 1.9 times at risk of prediabetes than students who engaged in physical activity ≥3 times in a week. Although, the risk is not proven statistically (P>0.05) (Sylvia & Ardiyani, 2019). A study in US showed that adolescents with vigorous physical activity had a significant and negative odds of prediabetes/diabetes (OR=0.74) (Nagarajan et al., 2017). In UEA, no significant correlation was found between glycemic status and level of physical activity, presence of acanthosis nigricans or symptoms of diabetes, except for weight loss (P=0.032) (Al Amiri et al., 2015). In Duke's study, it was found that for each additional day of being physically active for at least 60 min, the odds of student reported prediabetes was significantly decreased, by approximately 7%-8% (OR: 0.93-OR: 0.92) (Duke, 2021).

A study in the United States by Ratliff and colleagues concluded that consuming 1 serving/d of either low-calorie sweetened beverage (LCSB) or water is not associated with an increased risk for prediabetes (Ratliff et al., 2019). Another study found that households with high levels of healthy food access had a lower prevalence of prediabetes or diabetes in adolescents compared to those with low healthy food availability (4.05% vs 3.69%, P=0.08). However, the prevalence of adolescent prediabetes or diabetes was not significantly lower in households with high vs low supermarket spending proportion (3.77 vs 3.97%, p=0.46). The association of higher healthy food availability showed negative odds of adolescent prediabetes/diabetes (OR=0.78) (Nagarajan et al., 2017). Luo et al., in their study of analyzing the urine of adolescents found that urinary organophosphate esters (OPEs) metabolites were associated with prediabetes and indices of glucose homeostasis (Luo et al., 2020). Another study on adolescent consumption patterns stated that increasing frequency of SSB intake was significantly associated with the odds of youth reported diagnosis of prediabetes (Duke, 2021).

Duke and colleagues in the United States reported that for each additional hour of sleep, the odds of reported prediabetes were significantly reduced, by approximately 14%-15% (OR:0.86—OR:0.85) (Duke, 2021).

Cardiometabolic factors such as obesity, hypertension, and dyslipidemia were also reported in several studies included in this review. Mamtani et al. reported that an elevated waist-to-height ratio were each independently predictive of prediabetes (P=0.03) (Mamtani et al., 2014). Meanwhile, a study in Indonesia reported that thinner students have 0.9 times at risk of having high impaired glucose tolerance levels compared to students with normal BMI (95% CI:0.3-2.4). Meanwhile, obese students had a 2.2 times higher risk of developing prediabetes than students with normal BMI (95% CI:0.7-6.8). However, it was not proven statistically (P>0.05) (Sylvia & Ardiyani, 2019). Studies in Ecuador also prove that waist circumference, BMI, as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly affect the condition of prediabetes (Casapulla et al., 2017). In Alabama, morbidly obese adolescents had a higher prevalence of pre-diabetes (19.5% of obese versus 27.3% of morbidly obese; P<0.0001) and type 2 diabetes (39.8% of obese versus 52.4% of morbidly obese; P<0.0001) (Propst et al., 2015). A study in India proved that there is no significant correlation between FPG and BMI or waist to hip ratio (Taranikanti et al., 2014). Al Amiri and colleagues stated that high levels of triglycerides were independent risk factors for abnormal glycemic testing (P<0.05). Abnormal blood glucose testing was 2.28 times more common among students with high levels of triglycerides (Al Amiri et al., 2015). In another study in the US, BMI exhibited the strongest association with student reports of prediabetes diagnosis (OR:4.62-OR:4.67). BMI of students in 85% of cases was associated with more than four times the probability of prediabetes diagnosis (Duke, 2021).

Non-modifiable factors

Non-modifiable factors included in the reviewed studies were gender, race, and family history. Male gender, and a positive family history of diabetes were each independently predictive of prediabetes (Mamtani et al., 2014). The study in Indonesia found that gender and a history of DM affect the occurrence of prediabetes in students in all four public high schools. The obtained value was 0.130, which means that these variables can explain the incidence of prediabetes in high school students (Sylvia & Ardiyani, 2019). In Ecuador, gender and location were significant predictors of the six cardiometabolic risk factors such as HbA1c, TC, HDL, TG, LDL and VLDL (P=0.001) (Casapulla et al., 2017). In their analysis, Nagarajan and colleagues found that fully adjusted models for age, sex, and race had a significant and negative odds of adolescent prediabetes/diabetes (OR=0.74) (Nagarajan et al., 2017). Another study found no significant correlation between prediabetic status and family history of DM (Taranikanti et al., 2014). In the study of Liu and colleagues, the unadjusted prevalence of pre-diabetes was higher among boys than girls (P<0.001), lower among non-Hispanic blacks than non-Hispanic whites (P<0.05) and Mexican Americans (P<0.05) (Liu et al., 2012). In UEA study, family history of T2D in first-degree relatives (OR 1.87 P=0.028) was statistically correlated with abnormal glycemic testing based on fasting blood glucose and 2-h post-prandial blood glucose (OGTT) (Al Amiri et al., 2015).

4. Discussion

In this review, we found convergence of findings from retrospective and cross-sectional studies, demonstrating physical inactivity, poor diet, cardio-metabolic factors, and unhealthy lifestyles such as smoking habit as a modifiable risk factor. Meanwhile, gender, race, and family history of T2D presented as a non-modifiable risk factors. Between the two categories, modifiable risk factors have a strong relationship with the incidence of prediabetes reported by adolescents in various countries in the studies included in this review.

Modifiable risk factors of prediabetes in adolescents

Smoking was a significant risk factor of prediabetes in one study (Sylvia & Ardiyani, 2019). Previous studies show that smoking is a significant predictor of dyslipidemia, large waist circumference, and high insulin resistance (Awadalla et al., 2018; Yu et al., 2014). Pronounced frequency of smoking among men makes them more prone to its adverse metabolic effect as compared to women (Díaz-Redondo et al., 2015; Song et al., 2016). A prior experimental study have shown that cigarette smoking directly decreased insulin action and increased insulin resistance (Bergman et al., 2012). The higher scores on the Fagerström questionnaire-a well validated tool of nicotine dependence-were strongly associated with pre-diabetes, even after exclusion of cumulative smoking exposure from the score. These data suggest that the nicotinergic system and nicotine dependence may play a role in smoking related hyperglycemia, which is in line with a small experimental study showing that the long-term use of nicotine containing chewing gums was associated with insulin resistance and hyperinsulinemia (Haj Mouhamed et al., 2016; Yu et al., 2014). Furthermore, the majority of inhaled nicotine is catabolized into cotinine byanenzymatic activity, which is mediated by Cytochrome P450 2A6 (CYP2A6). Previous studies have shown that heavy smokers with a slow or poor metabolizer genotype were more susceptible to develop type 2 diabetes (T2D) compared to heavy smokers with a fast metabolizer genotype (Liu et al., 2012; Tanner et al., 2017; Wu et al., 2020).

In vitro studies have shown that nicotine in the presence of palmitate enhanced the production of reactive oxygen species and impaired glucose uptake in skeletal myocytes (Bhattacharjee et al., 2016; Wang et al., 2022; Yang et al., 2015). Fetal and neonatal nicotine exposure in rats resulted in dysglycaemia, pancreatic beta cell dysfunction, increased apoptosis, and loss of beta cell mass (Clair et al., 2015; Xia et al., 2019).

According to the analysis of the reviewed studies, it seems that physical activity is one of the strongest predictors related to the occurrence of prediabetes among adolescents (Al Amiri et al., 2015; Duke, 2021; Mamtani et al., 2014; Nagarajan et al., 2017). Daily exercise, when compared with less than daily exercise, has a significant beneficial effect on several key anthropometric factors such as weight, BMI z–score, waist-to-height ratio, waist z-score and obesity which will directly affect metabolic conditions of glucose and insulin production (Kawasaki et al., 2018; Peirson et al., 2015). Individuals who lack activity tend to be obese. Obesity conditions will trigger an increase in insulin resistance in the muscles so that blood glucose cannot be used optimally by muscles as energy (Kahn & Jeffrey, 2000; Venkatasamy et al., 2013; Wondmkun, 2020).

In the studies included in this review, poor diet patterns were mainly related to low-calorie sweetened beverages, the sugar-sweetened drinks, and energy-dense snacks such as salty snacks (Duke, 2021; Nagarajan et al., 2017; Ratliff et al., 2019). Consumption of some carbohydrate-containing beverages is linked to increased caloric intake at the expense of providing nutritive value; thus, jeopardizing consumption of appropriate ratios of carbohydrate, protein, and fat, which raises concerns about risks to healthy growth and development (Khanferyan et al., 2018). Further, drinking fruit juice and juice drinks, sports and energy drinks has been linked to excess caloric intake and inappropriate weight gain (Larson et al., 2015). Sugar sweetened beverages disrupt metabolism via multiple mechanisms, including increasing caloric load devoid of nutrients with associated weight gain and increasing the risk for the development of obesity, increasing glycemic load resulting in insulin resistance and pancreatic beta cell dysfunction, contributing to a rise in inflammatory biomarkers signaling oxidative stress, and promoting accumulation of visceral fat tissue relating to liver lipogenesis (Malik & Hu, 2022; Schiano et al., 2021; Uloko et al., 2018).

Studies included in this review have pointed to cardio-metabolic factors including overweight and obesity as predictors of prediabetes (Casapulla et al., 2017; Propost et al., 2015; Taranikanti et al., 2014). The relationship between cardio-metabolic factors and the occurrence of pre-diabetes has been described in previous studies, and obesity has been mainly measured through BMI. Studies have also been conducted to analyze the relationship between BMI and prediabetes with the occurrence of diabetes (Pandey et al., 2017). Hyperglycemia has been associated with high levels of triglycerides. Improving glycemic control in individuals with moderate to severe hyperglycemia regardless of type of treatment is associated with improvement in lipid values (Arthur et al., 2016).

Non-modifiable risk factors of prediabetes in adolescents

The studies included in this review showed that there were different reports of prediabetes in various races. Nagarajan and colleagues in their study in the US tried to analyze the relationship between race and the incidence of prediabetes in adolescents, where African Americans had both lower healthy food availability and lower monthly super market spending levels, which corresponded to their higher mean HbA1C levels and prevalence of prediabetes and diabetes. However, non-Hispanic black adolescents are known to have higher HbA1C values than Mexican Americans and non-Hispanic whites; despite higher HbA1C levels in black and Hispanic adolescents compared to whites, there is no increased risk of hyperglycemia (Nagarajan et al., 2017).

A study in Qatar found that male gender is a major factor for the occurrence of prediabetes in adolescent (Mamtani et al., 2014). The same result was also obtained by Nagarajan and colleagues, where prediabetes was generally found in males compared to females (Nagarajan et al., 2017). This effect can be explained by differences in sex hormones among men and women (Kautzky-Willer et al., 2016). Estrogen generally reduces TG and LDL circulating levels, while increases HDL-C level thus, resulting in inherited cardioprotective effect in women as compared to men (Shahwan et al., 2019). The difference in body fat distribution may also explain the discrepancy in the association of dyslipidemia in prediabetic men and women. Women metabolically inclined to store fat in subcutaneous tissues rather than in abdominal region. Men, in contrast tend to store fat preferentially in visceral tissue in abdominal region. High proportion of fat as visceral adipose tissue is generally known as a significant predictor of dyslipidemia (Chang et al., 2018; Link & Reue, 2017) thus, portray male gender more prone to dyslipidemia as compared to women.

Family history of T2D also has major contribution in the risk of prediabetes in adolescent as presented in the results of the included studies (Al amiri et al., 2015; Mamtani et al., 2014; Taranikanti et al., 2014). A previous study found that family history was more associated with a perception of risk for type 2 diabetes than was genetic risk testing (Wu et al., 2017). Other cases may show no association between family history and risk of prediabetes. What can be explained is the possibility of the age of the parents who are still under 40 years old, where the manifestations of DM may not be clearly appears (Taranikanti et al., 2014).

Considering the prominent role of modifiable risk factors in the occurrence of prediabetes in adolescents, it seems necessary to include lifestyle modification programs for this age group. It is also important to pay attention to gender as a non-modifiable factor in the development of prediabetes in adolescents.

5. Conclusion

Based on a total of 10 studies reviewed, the association between risk factors and adolescents' prediabetes appeared to be strongest among modifiable factors such as physical activity, poor diet, smoking, and cardiometabolic factors. Several non-modifiable risk factors also support the severity of prediabetes among adolescents. The most significant modifiable factor was BMI. For non-modifiable factors, the most significant was gender. This review provides a definite picture of the importance of controlling weight as a major factor in the incidence of prediabetes in adolescents, especially by gender. Conducting systematic reviews focusing on the impact of interventional studies on the control of prediabetes in adolescents as well as studies on genetic modification of the incidence of prediabetes and diabetes are suggested.

Limitations

Although a comprehensive literature search was conducted, some articles relevant to this review might have missed out. The focus of this review is limited and only grouped relevant data for adolescent in both modifiable and non-modifiable risk factors. Data was not pooled for meta-analysis owing to the heterogeneity in study design, exposure evaluated, and study outcome that limits the possibility to fully compare review findings. No attempts were made to contact the author to obtain full papers of eligible abstracts that could not be found as free full text on the web search. Finally, the search was limited to English language.

Ethical Considerations

Compliance with ethical guidelines

The authors of this article have all provided valuable help in conducting this study and have approved the final version. "Guest authorship" and "ghost authorship" were avoided. All duplicate evidence was removed. Data were extracted independently by two of the authors and discrepancies were resolved. Decisions on which data to include are also agreed upon by all authors.

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Authors' contributions

Structured review questions, compiling the manuscript, literature search, screening: Arvida Bar; Literature search, extracting, screening: Agusriani; Literature search, extracting, screening: Halimahtussa' diyah.

Conflict of interest

The authors declare no conflict of interests.

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References

Al Amiri, E., et al., 2015. The prevalence, risk factors, and screening measure for prediabetes and diabetes among Emirati overweight/obese children and adolescents. *BMC Public Health*, 15, pp. 1298. [DOI:10.1186/s12889-015-2649-6] [PMID] [PMCID]

Arthur, R., et al., 2016. Association between baseline serum glucose, triglycerides and total cholesterol, and prostate cancer risk categories. *Cancer Medicine*, 5(6), pp. 1307-18. [DOI:10.1002/cam4.665] [PMID] [PMCID]

Awadalla, H., Almobarak, A. O. & Ahmed, M. H., 2018. Prevalence of smoking in Sudanese individuals with diabetes and associated complications: Population-based study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 12(5), pp. 749-51. [DOI:10.1016/j.dsx.2018.04.038] [PMID]

Bayfield, N. G. R., Pannekoek, A. & Tian, D. H., 2018. Pre-operative cigarette smoking and short-term morbidity and mortality after cardiac surgery: A meta-analysis. *Heart Asia*, 10(2), pp. e011069. [DOI:10.1136/heartasia-2018-011069] [PMID] [PMCID]

Bergman, B. C., et al., 2012. Novel and reversible mechanisms of smoking-induced insulin resistance in humans. *Diabetes*, 61(12), pp. 3156-66. [DOI:10.2337/db12-0418] [PMID] [PMCID]

Bhattacharjee, A., et al., 2016. Possible involvement of iNOS and TNF-α in nutritional intervention against nicotine-induced pancreatic islet cell damage. *Biomedicine & Pharmacotherapy*, 84, pp. 1727-38. [DOI:10.1016/j.biopha.2016.10.079] [PMID]

Brufani, C., et al., 2010. Glucose tolerance status in 510 children and adolescents attending an obesity clinic in Central Italy. Pediatric Diabetes, 11(1), pp. 47-54. [DOI:10.1111/j.1399-5448.2009.00527.x] [PMID]

Casapulla, S. L., et al., 2017. Cardiometabolic risk factors, metabolic syndrome and pre-diabetes in adolescents in the Sierra region of Ecuador. *Diabetology & Metabolic Syndrome*, 9, pp. 24. [DOI:10.1186/s13098-017-0224-2] [PMID] [PMCID]

Chang, E., Varghese, M. & Singer, K., 2018. Gender and sex differences in adipose tissue. *Current Diabetes Reports*, 18(9), pp. 69. [DOI:10.1007/s11892-018-1031-3] [PMID] [PMCID]

Chen, C. M., Lou, M. F. & Gau, B. S., 2014. Prevalence of impaired fasting glucose and analysis of related factors in Taiwanese adolescents. *Pediatric Diabetes*, 15(3), pp. 220-8. [DOI:10.1111/pedi.12081] [PMID]

Clair, C., et al., 2015. The effect of cigarette smoking on diabetic peripheral neuropathy: A systematic review and meta-analysis. *Journal of General Internal Medicine*, 30(8), pp. 1193-203. [DOI:10.1007/s11606-015-3354-y] [PMID]

Consortium, R., 2014. Restoring Insulin Secretion (RISE): Design of studies of β-cell preservation in prediabetes and early type 2 diabetes across the life span. *Diabetes Care*, 37(3), pp. 780-8. [DOI:10.2337/dc13-1879] [PMID] [PMCID]

Di Bonito, P., et al., 2017. Impaired fasting glucose and impaired glucose tolerance in children and adolescents with overweight/obesity. *Journal of Endocrinological Investigation*, 40(4), pp. 409-16. [DOI:10.1007/s40618-016-0576-8] [PMID]

Díaz-Redondo, A., et al., 2015. Modifiable risk factors associated with prediabetes in men and women: A cross-sectional analysis of the cohort study in primary health care on the evolution of patients with prediabetes (PREDAPS-Study). *BMC Family Practice*, 16, pp. 5. [PMID] [PMCID]

Duke, N. N., 2021. Youth beverage intake and reported prediabetes: Choice and frequency matter. *Journal of Pediatric Health Care*, 35(2), pp. 216-25. [DOI:10.1016/j.pedhc.2020.10.005] [PMID]

Ehrhart, M. D., et al., 2017. Predictors of physical fitness among southwestern native American adolescents at risk for diabetes. *Journal of Pediatric Endocrinology (Jersey City, NJ)*, 2(1), pp. 1013. [PMID]

Geva, M., et al. The association between fasting plasma glucose and glycated hemoglobin in the prediabetes range and future development of hypertension. *Cardiovascular Diabetology*, 18(1), pp. 53. [PMID] [PMCID]

Hadaegh, F., et al., 2017. Pre-diabetes tsunami: Incidence rates and risk factors of pre-diabetes and its different phenotypes over 9 years of follow-up. *Diabetic Medicine*, 34(1), pp. 69-78. [PMID]

Hagman, E., et al., 2014. Impaired fasting glucose prevalence in two nationwide cohorts of obese children and adolescents. *International Journal of Obesity*, 38(1), pp. 40-5. [DOI:10.1038/ijo.2013.124] [PMID] [PMCID]

Kahn, B. B. & Jeffrey, S., 2000. Flier obesity and insulin resistance. *The Journal of Clinical Investigation*, 106(4), pp. 473-81. [DOI:10.1172/JCI10842] [PMID] [PMCID]

Kautzky-Willer, A., Harreiter, J. & Pacini, G., 2016. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocrine Reviews*, 37(3), pp. 278-316. [PMID] [PMCID]

Kawasaki, M., et al., 2018. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PloS One*, 13(1), pp. e0190676. [DOI:10.1371/journal.pone.0190676] [PMID] [PMCID]

Khanferyan, R. A., et al., 2018. [Consumption of carbohydratecontaining beverages and their contribution to the total calorie content of the diet (Russian)]. *Voprosy Pitaniia*, 87(2), pp. 39-43. [PMID]

Larson, N., et al., 2015. Sports and energy drink consumption among a population-based sample of young adults. *Public Health Nutrition*, 18(15), pp. 2794–803. [DOI:10.1017/S1368980015000191] [PMID] [PMCID]

Lee C. J., et al., 2015. Impaired fasting glucose and impaired glucose tolerance do not predict Hypertension: A community cohort study. *American Journal of Hypertension*, 28(4), pp. 493–500. [PMID]

Libman, I. M., et al., 2008. Reproducibility of the oral glucose tolerance test in overweight children. *The Journal of Clinical Endocrinology & Metabolism*, 93(11), pp. 4231-7. [DOI:10.1210/jc.2008-0801] [PMID] [PMCID]

Link, J. C. & Reue, K., 2017. Genetic basis for sex differences in obesity and lipid metabolism. *Annual Review of Nutrition*, 37, pp. 225–45. [DOI:10.1146/annurev-nutr-071816-064827] [PMID] [PMCID]

Liu, T., et al., 2012. Relationship between amounts of daily cigarette consumption and abdominal obesity moderated by CYP2A6 genotypes in Chinese male current smokers. *Annals of Behavioral Medicine*, 43(2), pp. 253-61. [PMID] [PMCID]

Luo, K., et al., 2020. Urinary organophosphate esters metabolites, glucose homeostasis and prediabetes in adolescents. *Environmental Pollution*, 267, pp. 115607. [DOI:10.1016/j.envpol.2020.115607] [PMID]

Malik, V. S. & Hu, F. B., 2022. The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. *Nature Reviews Endocrinology*, 18(4), pp. 205-18. [PMID] [PMCID]

Mamtani, R., et al., 2014. Adolescent prediabetes in a high-risk Middle East country: A cross-sectional study. *JRSM Open*, 5(8), pp. 2054270414536550. [DOI:10.1177/2054270414536550] [PMID] [PMCID]

Haj Mouhamed, D., et al., 2016. Effect of cigarette smoking on insulin resistance risk. *Annales de Cardiologie et d'Angéiologie*, 65(1), pp. 21-5. [DOI:10.1016/j.ancard.2014.12.001] [PMID]

Nagarajan, S., et al., 2017. Family consumer behaviors, adolescent prediabetes and diabetes in the National Health and Nutrition Examination Survey (2007-2010). *Journal of the American College of Nutrition*, 36(7), pp. 520-7. [DOI:10.1080/07315724.2017.1327828] [PMID]

Narayanappa, D., et al., 2011. Prevalence of prediabetes in school-going children. *Indian Pediatrics*, 48(4), pp. 295–9. [DOI:10.1007/s13312-011-0061-6] [PMID]

National Heart, Lung and Blood Institute (NHLBI)., 2021. Study Quality Assessment Tools. Retrieved from: [Link]

Page, M. J., et al., 2021. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery*, 88, pp. 105906. [DOI:10.1016/j.ijsu.2021.105906] [PMID]

Pandey, U., et al., 2017. Anthropometric indicators as predictor of pre-diabetes in Indian adolescents. *Indian Heart Journal*, 69(4), pp. 474-9. [PMID]

Peirson, L., et al., 2015. Treatment of overweight and obesity in children and youth: A systematic review and meta-analysis. *CMAJ Open*, 3(1), pp. E35-46. [DOI:10.9778/cmajo.20140047] [PMID] [PMCID]

Propst, M., et al., 2015. Diabetes and prediabetes are significantly higher in morbidly obese children compared with obese children. *Endocrine Practice*, 21(9), pp. 1046-53. [DOI:10.4158/EP14414.OR] [PMID]

Ratliff, J. C., Riedt, C. S. & Fulgoni III, V. L., 2019. Consumption of low-calorie sweetened beverages and water is associated with lower intake of carbohydrates and sugars and not associated with glycemic response in US non-diabetic adolescents: Results from the 2001-2014 National Health and Nutrition Examina. *Nutrition (Burbank, Los Angeles County, Calif.)*, 67-68S, pp. 100003. [PMID]

Schiano, C., et al., 2021. Soft drinks and sweeteners intake: Possible contribution to the development of metabolic syndrome and cardiovascular diseases. Beneficial or detrimental action of alternative sweeteners? *Food Research International*, 142, pp. 110220. [DOI:10.1016/j.foodres.2021.110220] [PMID]

Shahwan, M. J., et al., 2019. Prevalence of dyslipidemia and factors affecting lipid profile in patients with type 2 diabetes. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 13(4), pp. 2387-92. [DOI:10.1016/j.dsx.2019.06.009] [PMID]

Siddiqui, S., et al., 2020. Gender differences in the modifiable risk factors associated with the presence of prediabetes: A systematic review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 14(5), pp. 1243-52. [DOI:10.1016/j.dsx.2020.06.069] [PMID]

Song, X., et al., 2016. Gender-related affecting factors of prediabetes on its 10-year outcome. *BMJ Open Diabetes Research and Care*, 4(1), pp. e000169. [DOI:10.1136/bmjdrc-2015-000169] [PMID] [PMCID]

Sylvia, E. I. & Ardiyani, V. D., 2019. Determinants of pre-diabetes on teenagers in Palangka Raya City. *GHMJ (Global Health Management Journal)*, 3(3), pp. 117-23. [Link]

Tabák, A. G., et al., 2012. Prediabetes: A high-risk state for diabetes development. *Lancet (London, England)*, pp. 379(9833), 2279–90. [PMID]

Tanner, J. A., et al., 2017. Variation in CYP2A6 and nicotine metabolism among two American Indian tribal groups differing in smoking patterns and risk for tobacco-related cancer. *Pharmacogenetics and Genomics*, 27(5), pp. 169-78. [DOI:10.1097/FPC.0000000000000271] [PMID] [PMCID]

Taranikanti, M., et al., 2014. Prediabetes in South Indian rural adolescent school students. *Indian Journal of Physiology and Pharmacology*, 58(1), pp. 77-80. [Link]

Tuomilehto, J., et al., 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England Journal of Medicine*, 344(18), pp. 1343-50. [DOI:10.1056/NEJM200105033441801] [PMID]

Tuso, P., 2014. Prediabetes and lifestyle modification: Time to prevent a preventable disease. *The Permanente Journal*, 18(3), pp. 88-93. [DOI:10.7812/TPP/14-002] [PMID] [PMCID]

Uloko, A. E., et al., 2018. Prevalence and risk factors for diabetes mellitus in Nigeria: A systematic review and meta-analysis. Diabetes Therapy, 9(3), pp. 1307-16. [PMID] [PMCID]

Venkatasamy, V. V., et al., 2013. Effect of physical activity on insulin resistance, inflammation and oxidative stress in diabetes mellitus. *Journal of Clinical and Diagnostic Research: JCDR*, 7(8), pp. 1764-6. [PMID]

Wang, D., et al., 2022. Berberine ameliorates glucose metabolism in diabetic rats through the alpha7 nicotinic acetylcholine receptor-related cholinergic anti-inflammatory pathway. *Planta Medica*, 88(1), pp. 33-42. [DOI:10.1055/a-1385-8015] [PMID]

Wondmkun, Y. T., 2020. Obesity, insulin resistance, and type 2 diabetes: Associations and therapeutic implications. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 13, pp. 3611-6. [DOI:10.2147/DMSO.S275898] [PMID] [PMCID]

Wu, P., et al., 2020. Smoking-by-genotype interaction in type 2 diabetes risk and fasting glucose. *PloS One*, 15(5), pp. e0230815. [PMID] [PMCID]

Wu, R. R., et al., 2017. Impact of genetic testing and family health history based risk counseling on behavior change and cognitive precursors for type 2 diabetes. *Journal of Genetic Counseling*, 26(1), pp. 133-40. [PMID]

Xia, N., et al., 2019. Review of the role of cigarette smoking in diabetic foot. *Journal of Diabetes Investigation*, 10(2), pp. 202-15. [PMID] [PMCID]

Yamamoto-Kimura, L., et al., 2006. Prevalence and interrelations of cardiovascular risk factors in urban and rural Mexican adolescents. *The Journal of Adolescent Health*, 38(5), pp. 591-8. [PMID]

Yang, S., et al., 2015. GPR109A expression in the murine min6 pancreatic beta cell line, and its relation with glucose metabolism and inflammation. *Annals of Clinical & Laboratory Science*, 45(3), pp. 315-22. [PMID]

Young J. M.& Solomon, M. J., 2009. How to critically appraise an article. *Nature Clinical Practice Gastroenterology & Hepatology*, 6, pp. 82-91. [DOI:10.1038/ncpgasthep1331]

Yu, M., et al., 2014. Associations of cigarette smoking and alcohol consumption with metabolic syndrome in a male Chinese population: A cross-sectional study. *Journal of Epidemiology*, 24(5), pp. 361–9. [PMID]