MATERNAL SMOKING DURING PREGNANCY AND ITS ASSOCIATION WITH CHILDHOOD OVERWEIGHT AND OBESITY: SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

According to World Health Organization, abnormal or excessive deposition of fat, which becomes a risk factor for various health hazards later, is defined as obesity. BMI of 25 or more is termed as overweight and if the BMI is 30 or more, it is considered as obesity. Each year around 2.8 million adults die due to overweight or obesity. Overweight and obesity can contribute to development of various chronic diseases in later life. It is estimated that overweight or obesity are responsible for 44% of diabetes cases, 23% of ischemic heart disease and between 7 and 41% of cancer cases. Not only in the developed world, obesity now has become a major problem in the developing and least developed countries as well. The objective of this study was to perform a systematic review and a meta-analysis to see the association of maternal smoking during pregnancy with the childhood overweight or obesity.

Studies from PubMed and Ebsco Host Academic Search Premier databases published through March 2012 to September 2013 were searched. Included studies showed an association between prenatal maternal smoking and child overweight or obesity measured by adjusted odd's ratio with 95% confidence interval. The selected age of outcome (child age) was less than 19 years. We didn't include the systematic review and animal studies showing positive association.

Based on the selected 7 epidemiological studies, children of mother who smoked during pregnancy were at the greater risk of getting overweight (pooled adjusted odds ratio (OR) 1.51, 95% CI: 1.17, 1.97). The pooled aOR for younger children of less than 9 years was of 2.63 with 95% CI between 1.10 and 6.30 and for the older children, pooled adjusted odds ratio was 1.28 with 95% CI between 1.07 and 1.54. The risk of obesity was also greater among the children whose mother smoked during pregnancy (pooled adjusted OR1.37, 95% CI: 1.19, 1.57).

Maternal smoking during pregnancy is an independent risk factor for the childhood overweight and obesity. Maternal smoking being a modifiable risk factor can help to prevent the incidence of childhood overweight or obesity if preventive measures are considered.

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Thank you,
Anjali Shrestha

ABBREVIATIONS

aOR	Adjusted Odd's Ratio
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CPD	Cigarettes per day
CT	Computerized Tomography
CVD	Cardiovascular Disease
DEXA	Dual Energy X-ray Absorptiometry
DM	Diabetes Mellitus
GIV	Generic Inverse Variance
HDL	High Density Lipoprotein
HTN	Hypertension
IGF-1	Insulin like Growth Factor-1
IL-6	Interleukin-6
IOTF	International Obesity Task Force
Kg	Kilogram
LDL	Low Density Lipoprotein
m	Meter
MRI	Magnetic Resonance Imaging
MSH	Melanocortin Stimulating Hormone
NAFLD	Non-alcoholic fatty liver disease
NOO	National Obesity Observatory
OSA	Obstructive Sleep Apnea
OR	Odd's Ratio
PCOS	Polycystic Ovarian Syndrome
POMC	Proopiomelanocortin
RCT	Randomized Controlled Trial
RevMan	Review Manager
SFT	Skin Fold Thickness
TG	Triglycerides
TNF	Tumor Necrosis Factor

UK	United Kingdom
USA	United States of America
VLDL	Very Low Density Lipoprotein
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist to Hip Ratio

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1. INTRODUCTION

According to World Health Organization (WHO), abnormal or excessive deposition of fat, which becomes a risk factor for various health hazards later, is defined as obesity. Although not the definite one, BMI is most commonly used to measure obesity. BMI of 25 or more is termed as overweight and if the BMI is 30 or more, it is considered as obesity. Overweight and obesity are the fifth common cause of deaths worldwide. Each year around 2.8 million adults die due to overweight or obesity. Overweight and obesity can contribute to development of various chronic diseases in later life. It is estimated that overweight or obesity are responsible for 44% of diabetes cases, 23% of ischemic heart disease and between 7 and 41% of cancer cases (WHO 2013). Not only in the developed world, obesity now has become a major problem in the developing and least developed countries as well. As obesity is epidemic worldwide, it is also termed as Globesity (Delpeuch et al. 2009).

One of the major public health problems rising worldwide at the moment is childhood obesity. According to WHO 2011, greater than 40 million children under 5 years were overweight. It is estimated that out of these 40 million children, 30 million are residing in developing world and 10 million in developed world (WHO 2013). In adults, BMI is used to define the obesity. But, in children, their BMI is compared to the age and sex specific percentile cutoffs. Those children with BMI more than these specific cutoffs are categorized as overweight or obese (Anderson and Butcher 2006). As consequences of obesity, these children develop various non-communicable diseases in later life. Chronic diseases like cardiovascular diseases; diabetes, hypertension, cancers, etc. are the later consequences. There are also chances of having breathing difficulties along with increased risk of fractures in obese child. Study has also shown that childhood obesity is a risk factor for development of obesity in later life during adulthood (Serdula et al. 1993).

There are various factors that lead to childhood overweight and obesity. The factors may be prenatal or postnatal. One of the most important causes of childhood obesity is maternal smoking during pregnancy and cessation of maternal smoking leads to improved quality of offspring later life (Brisbois et al. 2013). Many studies have found the association between the development of childhood obesity and prenatal maternal smoking.

1.1. Risk factors of obesity

Whenever an individual takes excess amount of calories than required, the calories starts to accumulate in the body in terms of body fat and leads to excessive weight gain. Although

this is the basic and simple explanation for the development of overweight and obesity, there are many other factors, which play important role and accelerates this process. We can term these as risk factors for obesity development. The risk factors of obesity can be divided into preventable and non-preventable.

1.1.1. Preventable risk factors

A. Unhealthy diet

It is already known that unhealthy foods with high calories are responsible for development of obesity. The problem of consuming unhealthy diet is epidemic. In developed countries, people are mainly focused on their career and work. They lack the time for focusing on their health. They mainly live on fast foods rather than healthy foods like vegetables and fruits. There has been global shift in the diet intake i.e. people are more attracted towards high energy foods which are rich in fat and sugar and in other hand these foods lack vitamins, minerals and healthy micronutrients (WHO 2014) which ultimately is the leading cause of overweight and obesity. So, consumption of unhealthy foods is an important factor responsible for development of obesity worldwide.

a. Dietary Fat and Weight

There are two types of fats: saturated and unsaturated. The unsaturated fats are the healthy fats, which are mainly found in plant oils, fishes, nuts, etc. Many studies have also shown that consumption of these unsaturated fats can prevent an individual from diabetes and cardiovascular diseases (Kromhout et al. 2012; Gadgil et al. 2013). The unhealthy fat i.e. saturated fats are mainly found in meat and dairy products and are even responsible for raising the level of low density lipoproteins (LDL) in the blood (Harvard School of Public Health 2013). Processed foods mainly constitute of trans fats. These types of fat are also responsible for raising the blood LDL. LDL is very dangerous to human body because it deposits in the arterial wall leading to atherosclerosis, hypertension, diabetes and cardiovascular complications. Trans fat also has property of lowering high-density lipoprotein (HDL) (Hu and Willett 2002). So, one should be very careful while selecting the type of fat in the product they buy. Low fat diets are considered healthier but it is also evident that low fat diets are also responsible for increased weight. This is because the low fat diet can contain high carbohydrate (Harvard School of Public Health 2013).

b. Protein and Weight

Consuming calories from protein diet can have some advantages for the weight control when compared to calories from carbohydrate or fat. Calories taken from protein make an individual full faster than the carbohydrate or fat (Harvard School of Public Health 2013). So, this will lead to less consumption of the calories. The energy required to metabolize the protein is much higher than the other nutrients. So, on taking protein diet, more energy will be burned out. High protein diet alone or when combined with exercises resulted in weight loss and reduced risk of metabolic syndrome in overweight and obese Canadian women (Meckling and Sherfey 2007).

c. Carbohydrate and Weight

As mentioned previously, high protein, lower carbohydrate diet play an important role in weight control. But it is also necessary to be selective regarding the quality of carbohydrate. There are some types of carbohydrate (found esp. in potatoes, sugary drinks, processed cereals, white bread and pasta), which are digested rapidly, making an individual hungry very fast and as a consequences result in overeating (Hu and Willett 2002). This overeating ultimately leads to weight gain. A randomized controlled trial has shown that the low carbohydrate diet resulted in significant amount of weight loss when compared to conventional diet (Foster et al. 2003).

B. Physical activity

Physical activity is another factor that determines or regulates the body weight of an individual. Low level of physical activity is associated with excessive weight gain. The increasing sedentary life style especially in the developed world is a major problem. About 60 minutes of moderate intensity physical activity daily can prevent the development of weight gain (Barbara 2013)

Television watching also adds an important role to overweight development (Hawkins 2006). Some important points for the television watching being the factor for overweight are:

- The advertisement of the junk food in the television is very much influencing especially for children.
- Also, the intake of food especially junk food is much common while watching television.

C. Sleep

Studies have also found that lack of proper sleep can lead to obesity (Moraleda-Cibrian and O'Brien 2013). It has been found that lack of sleep affects the hormones that regulate the appetite resulting in increases hunger. Lack of sleep also gives more time for an individual to eat as it increases the awakening time.

D. Prenatal and perinatal factors

Early life of an individual is very crucial. There are various factors that can affect the body weight of a child in later life. Prenatal factors like maternal smoking during pregnancy, maternal obesity (Baustista-Castano et al. 2013; Hawkins 2006) and gestational diabetes are mainly associated with obesity in later childhood. Few studies have also shown that breastfed children are less prone in developing obesity when compared to bottle fed children (Verstraete et al. 2013; Grummer-Strawn et al. 2004). There has also been strong relationship between the low socio economic conditions in early life of a child and development of obesity in later life (Parsons 1999).

1.1.2. Non preventable risk factors

Genetics

It has been now proved that genes alone are not responsible for the development of obesity. The obesity prone genes along with environmental factors contribute to the development of obesity. There are many types of genes that have been identified as obesity genes (Flier and Flier 2011). Some of the examples are following:

Lep (ob): leptin

LepR (db): leptin receptor

POMC: proopiomelanocortin

MC4R: type 4 receptor for MSH (Melanocortin Stimulating Hormone)

1.1.3. Others

a. Drug induced obesity: corticosteroids, anti-psychotic medications, calcium channel blockers, etc.

b. Obesity as a syndrome of disease

- Prader-Willi syndrome

- Laurence-Moon-Biedl Syndrome
- Ahlstrom's syndrome
- Cohen's syndrome
- Carpenter's syndrome
- Others
    - Cushing’s syndrome
    - Hypothyroidism
    - Insulinoma
    - Craniopharyngioma and other hypothalamic disorders

1.2. Health Consequences of Overweight and Obesity

Obesity can affect almost all the organs and systems of the human body. Following are the effects on various systems that may arise due to obesity.

1.2.1. Obesity and Diabetes

Many epidemiological studies have found that there is strong relationship between the obesity and diabetes especially Type II Diabetes Mellitus (DM) (Colditz et al. 1995; Koh-Banerjee et al. 2004). Increasing weight gain especially increases in the intra-abdominal fat is associated with insulin resistance. Following are the mechanisms involved for the development of insulin resistance (Flier and Flier 2011).

1. Insulin receptor down regulation by insulin itself.
2. Impairment of the functions of insulin by the increased free fatty acids.
3. Intracellular lipid accumulation.
4. Modifications of insulin action by the various peptides like cytokines, TNF, IL-6 that are released from the fat cells.

Obesity is one of the major risk factor for the development of diabetes and 80% of people with diabetes are found to be obese. There is evidence that losing weight by about 5% and daily physical activity can decrease the chance of developing diabetes by more than 50% (Flier and Flier 2011).

1.2.2. Obesity and Cardiovascular diseases

Increase in the body weight is linked with increased risk of hypertension (Akis et al. 2007; Sanchez-Zamorano et al. 2009). Along with the hypertension and insulin resistance, which

are itself risk factors for cardiovascular diseases, the possibility of development of heart diseases increases with obesity. The Framingham Study has described obesity as an independent risk factor for cardiovascular diseases including coronary artery disease, stroke and congestive heart failure. Obesity has been associated with increasing bad cholesterol i.e. LDL, very low-density lipoprotein (VLDL) and triglycerides leading the acceleration of atherosclerosis and obesity also decreases the protective lipoproteins like HDL (Public Health England 2013). Obesity induced hypertension leads to increase in the total peripheral resistance and cardiac output, increase sympathetic activity and salt retention, which eventually lead to cardiac failure (National Obesity Observatory 2009).

1.2.3. Obesity and Reproductive system

Obesity has been associated with various reproductive dysfunctions in both males and females. In males, increase in the body fat is associated with male hypogonadism (Flier and Flier 2011). Gynaecomastia may also be the result of obesity in males.

In females, because of the increase body fat, menstrual irregularities occur. Especially obesity is associated with polycystic ovarian syndrome (Public Health England 2013). It is a condition with features like oligomenorrhea, hirsuitism, acne, obesity and insulin resistance. There is increased androgen production and increased peripheral conversion of androgen to estrogen (Flier and Flier 2011).

In pregnant women, increases in the body weight more than the normal weight gain has 10-fold risk of developing hypertension and gestational diabetes (National Institute of Health 1998). Obesity during pregnancy has adverse effect on both mother and fetus (Bautista-Castano et al. 2013).

1.2.4. Obesity and Cancer

Cancer of esophagus, colon, rectum, pancreas, liver, and prostate are mainly associated with obesity in males and has shown to be higher causes of cancer mortality. In females, obesity associated cancer are cancer of the gall bladder, breasts, endometrium, cervix, and ovaries. Some of the mechanisms that may be responsible for development of these cancers are (Flier and Flier 2011):

1. Due to increase in the rate of conversion of androgen to estrogen in the adipose tissues of the obese people. (Esp. endometrial, breast and ovarian cancers)

2. Due to hormones that are linked with the increased fat cells like insulin, leptin, adiponectin and Insulin like Growth Factor-1 (IGF-1).

1.2.5. Obesity and Sleep Apnea

Obstructive sleep apnea is mainly associated with obesity. Obesity of the upper body part especially fat deposition around the neck leads to obstruction of airway leading to difficulty in breathing during sleep (Harvard School of Public health 2013). Snoring is one of the important features associated with sleep apnea. Sleep apnea results in following abnormalities (National Institute of Health 1998).

1. Arterial hypoxia
2. Recurrent awakening during sleep
3. Increase in the sympathetic tone
4. Pulmonary and systematic hypertension
5. Cardiac arrhythmias

It has been found that men with neck circumference of 17 inch or more and women with neck circumference of 16 inch or more develop higher risk of sleep apnea. Weight loss by 10-20 kg has shown effective responses in these cases (National Institute of Health 1998). Continuous positive pressure ventilation has also seen to have greater effect.

1.2.6. Obesity and pulmonary diseases

Obesity related pulmonary abnormalities might be following (Flier and Flier 2011; Harvard School of Public health 2013):

1. Decrease in compliance of the chest wall.
2. Increased work of breathing
3. Increase metabolic rate leading to Increase in minute ventilation
4. Decrease in functional residual capacity
5. Decrease expiratory reserve volume

1.2.7. Obesity and hepatobiliary system

Non-alcoholic fatty liver disease (NAFLD) is commonly associated with obesity. Steatosis improves with decrease in the weight. Rarely, NAFLD results to cirrhosis and hepatocellular carcinoma. With obesity, there is also greater risk of gallstones formation (esp. cholesterol gallstone) (National Institute of Health 1998).

1.2.8. Obesity and bone, joint and cutaneous disorder

Obesity has found to be associated with osteoarthritis, the mechanism being trauma due to additional weight bearing (Flier and Flier 2011). Along with obesity, the incidence of gout has also been increased. Skin condition like acanthosis nigricans is also related to obesity. Acanthosis nigricans is darkening and thickening of the skinfolds especially in neck, elbow and dorsal interphalangeal spaces (Bray 2004). Acanthosis nigricans also signifies underlying insulin resistance. Weight loss can diminish this condition.

Table 1. Summary of the health consequences of obesity (Flier and Flier 2011)

1. **Cardiovascular System**
   - Hypertension
   - Congestive heart failure
   - Cor pulmonale
   - Varicose veins
   - Pulmonary embolism
   - Coronary artery disease

2. **Respiratory**
   - Dyspnea
   - Obstructive sleep apnea
   - Hypoventilation syndrome
   - Pickwickian syndrome
   - Asthma

3. **Endocrine**
   - Metabolic syndrome
   - Type 2 diabetes
   - Dyslipidemia
   - Polycystic ovarian syndrome

4. **Gastrointestinal**
   - Gastroesophageal reflux disease
   - Nonalcoholic fatty liver disease
   - Cholelithiasis
   - Hernias

5. **Musculoskeletal**
   - Hyperuricemia and gout
   - Immobility
   - Osteoarthritis (knees and hips)
   - Low back pain
   - Carpal tunnel syndrome

6. **Genitourinary**
   - Urinary stress incontinence
   - Obesity-related glomerulopathy
   - Hypogonadism (male)
   - Breast and uterine cancer
   - Pregnancy complication

7. **Psychological**
   - Depression/low self-esteem
   - Body image disturbance
   - Social stigmatization

8. **Neurologic**
   - Stroke
   - Idiopathic intracranial hypertension
   - Meralgia paresthetica
   - Dementia

9. **Integument**
   - Striae distensae
   - Stasis pigmentation of legs
   - Lymphedema
   - Cellulitis
   - Carbuncles
   - Acanthosis nigricans
   - Acrochordon (skin tags)
   - Hidradenitis suppurativa

2. LITERATURE REVIEW

Tobacco smoking has been the major public health threats worldwide, responsible for six million deaths per year. Out of total 6 million deaths, more than five millions deaths are caused due to direct use of tobacco or active smoking and greater than 60,000 deaths occur due to second hand or passive smoking (WHO 2014). The prevalence of smoking is higher in low and middle income countries accounting for 80% of world's one billion smokers (WHO 2014). In order to prevent people from tobacco related illnesses and deaths, many countries have implemented strict legislation in order to regulate the supply of tobacco and also to restrict the advertisement of tobacco and its products.

2.1. Biological effect of smoking

More than 4000 chemicals constitute the tobacco, among which around 250 are known harmful and 50 has potential to cause cancer. Smoking not only has adverse effect on active smokers but also causes serious illness in passive smokers. Nearly every organ of the body can be affected by smoking. Some of the important ones are as follow:

- Smoking increases the incidence of various diseases when compared to non-smokers. Increase the risk of coronary heart disease and stroke by 2 to 4 times and lung cancer by 25 times (CDC 2014).
- Smoking is the risk factor for development of coronary heart disease and stroke.
- Respiratory system: Chronic obstructed pulmonary diseases, lung cancer.
- Cancer: smoking can cause cancer of almost every part of the body (CDC 2014).
- Smoking by pregnant mother leads to: preterm delivery, stillbirth, low birth weight, sudden infant death syndrome, ectopic pregnancy and child obesity.
- Increase risk for cataract and age-related macular degeneration.

2.2. Evaluation of overweight and obesity

There are different methods by which overweight or obesity can be measured or evaluated.

A. Body Mass Index

Although BMI is not a direct measure of body fat, it is the most common methods used. It is calculated with the formula:

$$\mathrm{BMI} = \frac{\mathrm{Weight(kg)}}{\mathrm{Height}^2(\mathrm{m}^2)}$$

Classification of BMI for adults (WHO 2006)

BMI range (kg/m^2)	**Classification**
<18.5	Underweight
18.5-24.9	Healthy weight
25-29.9	Overweight
30-34.9	Obesity I
35-39.9	Obesity II
≥40	Obesity III

Classification of BMI in children

Age and sex specific growth references are used in order to determine the weight status of a child (Public Health England 2013).

≤2nd centile	Underweight
>2 - <85th centile	Healthy weight
≥85th centile	Overweight
≥95th centile	Obese

Advantages

- Ease of measurement
- Has established cut-offs

Limitations

- BMI cannot differentiate body fat and body mass (National Obesity Observatory 2009).
- It does not differentiate between subcutaneous and visceral fat because of which it tends to be dangerous when abdominal fat remains undiagnosed.
- It is not accurate in measuring body fat especially in the elderly when compared to younger and middle aged.
- BMI lacks in reflecting the changes that occurs as the age increases and it is also an indirect measure of the body fat. Hence, BMI has poor sensitivity and specificity (Rothman 2008)

B. Waist Circumference

Waist circumference reflects the measurement of the abdominal obesity or central obesity (National Obesity Observatory 2009). It is the circumference that is measured in waist between lowest rib and top of the hipbone, umbilicus or at the narrowest mid-section point. The International Diabetes Federations of the metabolic syndrome for defining the abdominal obesity uses ethnic specific criteria.

Country/Ethnic Group	**Waist Circumference Cut Points**
Europids **Sub-Saharan Africans** **Eastern Mediterranean** **Middle East (Arab) populations**	Male: ≥ 94 cm Female: ≥ 80 cm
South Asians **Ethnic South** **Central Americans**	Male: ≥ 90 cm Female: ≥ 80 cm
Chinese	Male: ≥ 90 cm Female: ≥ 80 cm
Japanese	Male: ≥ 90 cm Female: ≥ 80 cm

C. Waist to Hip Ratio (WHR)

Measurement of WHR provides a good correlation with the body fat. But the fact that it requires two different measurements that is waist circumference and hip circumference may lead to measurement error (WHO 2008).

D. Other methods

Skinfold Thickness
Bioelectric Impedance
Underwater Weighing (Densitometry)
Air Displacement Plethysmography
Dilution Method (Hydrometry)
Dual Energy X-ray Absorptiometry (DEXA)
Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI)

2.3. Previous reviews showing association between maternal smoking during pregnancy and childhood overweight and obesity

Huang et al. (2007) conducted a systematic review of eight observational studies to provide evidence regarding the advantage of prenatal programming of childhood overweight and obesity. The study found that the odds of obesity for children aged 5 to 21 born to mother who smoked during pregnancy was higher i.e. with OR around 1.5 to 2. The obesity was measured according to BMI. Other risk factors, which were significantly associated with childhood overweight or obesity, were gestational diabetes and maternal malnutrition.

A systematic review (Monasta et al. 2010) was conducted to review all the published systematic reviews in order to find out early determinants of obesity. This review found out that along with other various factors like maternal diabetes, rapid infant growth, no or short breastfeeding, obesity in infancy, short sleep duration, less than 30 min of daily physical activity, consumption of sugar-sweetened beverages, maternal smoking has strong co-relation with the childhood obesity.

Oken et al. (2008) performed a systematic review of 14 observational studies that found obesity in children at least 2 years of age who were born to mothers who smoke during pregnancy. The risk of overweight is higher in children (3-33 years) of mothers who had smoked prenatally with pooled adjusted OR 1.50 (95% CI: 1.36, 1.65) when compared to children born to mothers who didn't smoke during pregnancy. This study has limitations like publication bias; recall bias as the smoking information collected at the time of clinical assessment of the child obesity. Self-reported smoking status also was a major confounder, as there seems to be a possibility of under reporting.

Based on seventeen studies, Ino (2010) found that the odds for obesity in children who was born to mothers who smoked prenatally was 1.64 (95%CI: 1.42–1.90) when compared to the children whose mothers didn't smoke prenatally. The pooled odds ratio after adjustment was found to be 1.52 (95% CI: 1.36-1.70) in children from 3-22 years of mothers who smoked during pregnancy. This study also has several limitations like using only one database i.e. PubMed in order to search the articles. Ino (2010) also failed to gather the information regarding the important confounding factors, how obesity or overweight were defined and the dose response relationship between the exposure and the outcome. However, the study showed consistency in relationship between the maternal smoking during pregnancy and childhood overweight and obesity. There was also evidence that the fetal exposure to smoking cab lead to metabolic syndrome in later life.

The systematic review and meta-analysis conducted by (Weng et al. 2012) found seven studies that show an association between prenatal smoking and later childhood obesity. The result showed that the children born to mothers who smoked during pregnancy were 47% (95% CI 1.26 to 1.73) more likely to be overweight as compared to children born to mothers who did not smoke during pregnancy. There was evidence of strong association between the childhood overweight and maternal pre- pregnancy overweight, high infant birth weight and rapid weight gain during the first year of life.

In 2013, Behl et al. conducted a review of total 101 studies, 83 in human and 18 experimental animal studies to assess the association of maternal smoking or nicotine exposure during pregnancy with childhood obesity at any age. All epidemiological studies conducted till March 2012 was reviewed. All the prospective studies included in this review showed positive association of maternal smoking during pregnancy and childhood overweight and obesity in both human and in animals. Animal studies also showed that the nicotine exposure in fetus leads to destruction of β-cells of the pancreas, which further results in Type 2 Diabetes Mellitus. Although meta-analysis has not been performed in this review, our review will be an update of this review along with the meta-analysis and hence is also the reason for including the studies from March 2012.

3. OBJECTIVE

The main objective of this study is to review epidemiological studies published between March 2012 and September 2013 that show association between maternal smoking during pregnancy and childhood obesity according to estimates like adjusted odd's ratio.

4. METHODS

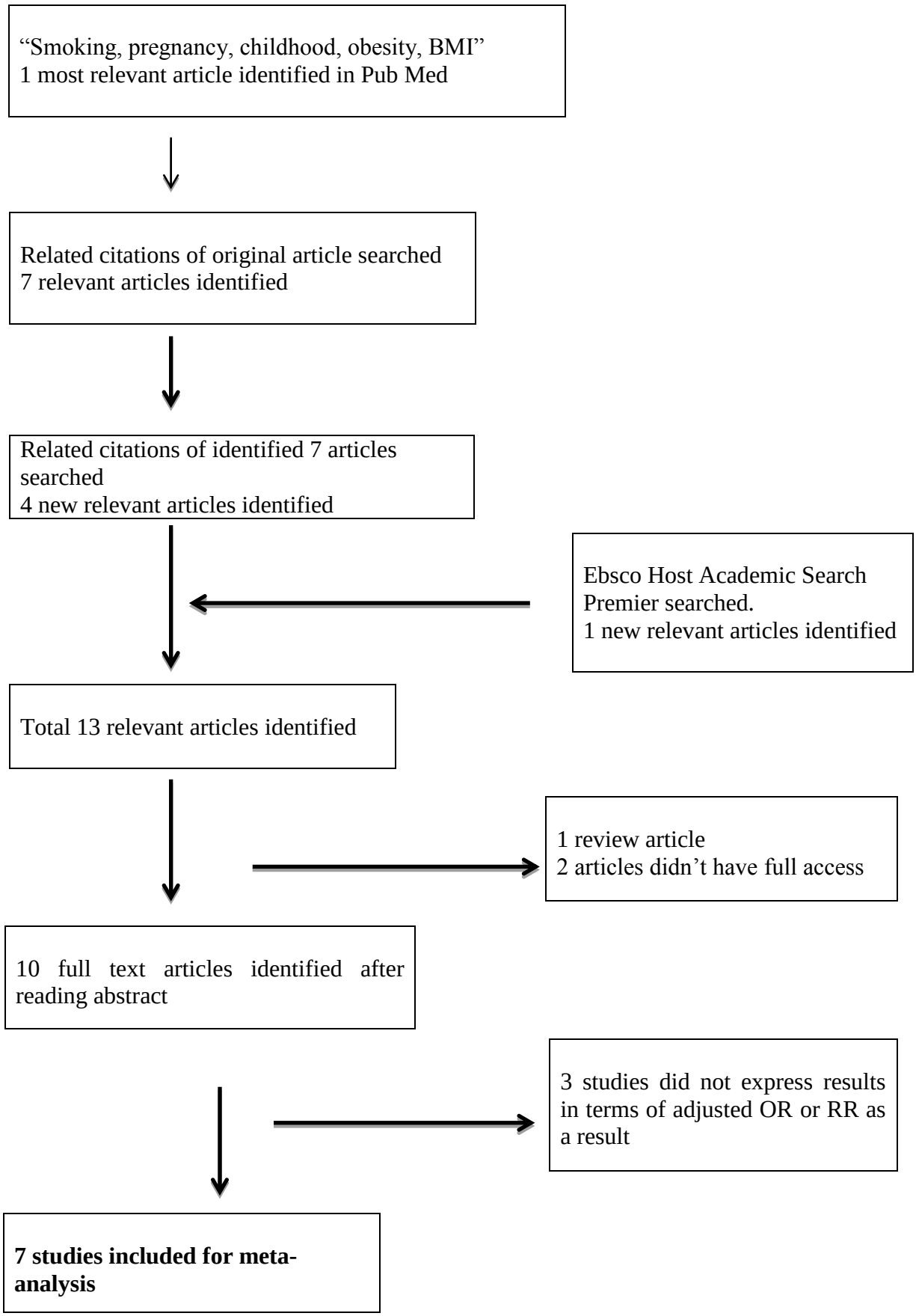
4.1. Data Source

We used databases like PubMed and Ebsco Host Academic Search Premier in order to perform the literature search. The literature search was conducted from March 2012 to September 2013. Only English language was included for the search of the relevant literatures. Combinations of following keywords were used in order to retrieve the articles:

"Maternal smoking, pregnancy, obesity, overweight, BMI"

After entering the combination of above keywords in PubMed, we selected one most relevant article. Following it, we searched for the related citation of the original article, which yielded 7 new relevant articles. To avoid the possibility of missing any relevant articles, we again searched through related citation of 7 new articles retrieved by related citation search of the original article. As a result, we were able to retrieve 4 new relevant articles. We also entered the same key words in Ebsco Host Academic Search Premier and it retrieved 1 more new article. In total we were able to retrieve 13 relevant articles according to the title. We went through the abstract of all these articles and excluded three articles. Among the 10 full text articles, we finalized to include 8 articles, as two of them were not fulfilling the inclusion criteria. The summary of the whole search process is shown in Figure 1. We also searched for the reference list of all the articles we selected. The overview of previous systematic reviews and meta- analysis is also summarized in Table 3.

Fig.1 Flow chart showing data sourcing and selection



4.2. Criteria for selection of the literatures

Inclusion criteria

- ✓ Studies published from March 2012 to September 2013.
- ✓ All types of epidemiological studies i.e. prospective, retrospective, controlled trials.
- ✓ Studies done in humans.
- ✓ Studies included should show maternal smoking during pregnancy as an independent factor that causes childhood obesity.
- ✓ The outcome BMI has been measured under 19 years age.

Exclusion criteria

- ✓ A study that also shows association of childhood obesity with other factors other than prenatal maternal smoking.
- ✓ Studies whose result show obesity in > 18 years of age.
- ✓ Systematic reviews.
- ✓ Studies done in animals.

4.3. Data Extraction

We gathered following data from the selected articles: type of studies, first author, year, country, number of subjects, expression of the independent variable i.e. maternal smoking (yes/no, heavy smoking/no smoking), expression of obesity or overweight, age of children when weight has been measured, adjustment and OR with confidence intervals. Table 2 summarizes the selected studies and data gathered. Two independent researchers were involved in assessing the whole process, which involves the assessment of the fulfillment of selection criteria and methodological quality of the studies included.

4.4. Data Analysis

We used Generic Inverse Variance (GIV) mode of RevMan for the meta-analysis. The GIV gives the random effect pooled analysis of adjusted odd's ratio. The pooled odds ratio along with 95% confidence interval was calculated using RevMan version 5.2.

Table 2: Summary of selected studies

First author/ year/ country	Type of study	Population	Child age	Expression of maternal smoking	Expression of outcome	Adjustment	Adjusted OR	95% CI Lower	95% CI Upper
Suzuki 2013, Japan	Cohort	1644	5	Smoking/No smoking (have quit smoking & have never smoked)	BMI (**Overweight**) (Acc. To WHO cut off points)	Maternal age, maternal body mass index, smoking status and breakfast consumption.	4.5	2.0	10.2
Chen 2012, Taiwan	Cross-sectional	7930	9-14	Yes/No	**Overweight** BMI ≥ 85 percentile	Sex, age, parental education, sibling number, exercise habit, perinatal and behavioral factors.	1.1	0.8	1.5
					Obesity BMI ≥ 95 percentile		1.3	1	1.7
Birbilis 2013, Greek	Cross-sectional	2294	9-13	Yes/No	**Overweight**	Socio-demographic, socioeconomic, perinatal and parental factors, dietary energy intake and physical activity levels.	1.42	1.07	1.88
					Obesity (Acc. To IOTF)		1.37	1.05	1.98
Timmermans 2012, the Netherlands	Cohort	2698	6-7	Yes/No	**BMI** ≥ 85 percentile	Recruitment group, gender of child, maternal age at pregnancy, maternal BMI before pregnancy, maternal educational level, maternal alcohol use during pregnancy.	3.72	1.33	10.4
					SFT		4.45	1.63	12.2
					WC		2.65	1.06	6.59

Table 2 continued

First/author/year/ country	Type of study	Population	Child age	Expression of maternal smoking	Expression of outcome	Adjustment	Adjusted OR	95% CI Lower	Upper
Wang 2012, the USA	Cross-sectional	1041	School aged	Never smoking and ever smoking within 1 year before the birth of child.	BMI ≥85th percentile or over- weight	Maternal: age, education, living status, poverty and breast- feeding status Child: sex, ethnicity and birth weight.	1.39	1.01	1.94
Risvas 2012, Greece	Cross-sectional	2093	10-12	**Smoking habits at conception** 1–9 cigarettes/day 10–20 cigarettes/day >20 cigarettes/day **Smoking habits at gestation** 1–9 cigarettes/day >10 cigarettes/day	BMI (Acc. To IOTF cut off points)	Children: age, gender, physical activity status quality of diet. Maternal: age at pregnancy, body mass index before conception, % body mass index change.	1.32 0.97 2.02 1.31 2.24	0.99 0.70 1.23 0.87 0.88	1.77 1.36 3.33 1.97 5.67
Harris 2013, the USA	Cohort	35794	18	Yes/No If Yes (cigarette/day) 1-4 15-24 > 25	**Overweight** BMI 25-30 **Obesity** >30	Socioeconomic and behavioral variables	1.33 1.4 1.15 1.41 1.69 2.36	1.18 1.2 0.79 1.14 1.31 1.44	1.5 1.64 1.69 1.75 2.18 3.86

Table 3: Summary of previous systematic reviews

Authors	Year	Types of studies reviewed	Number of included studies	Results
Huang et al.	2007	Observational studies	8	Odds ratios for childhood obesity ranged from 1.1 to 2.9, with most of the OR's clustering around 1.5 to 2.0
Oken et al.	2008	Observational studies	14	Pooled adjusted odds ratio (OR) 1.50 (95% CI 1.36-1.65) at ages 3–33 years
Monasta et al.	2010	Systematic reviews	8	OR 1.52–2.22
Ino T	2010	Observational studies	17	Pooled adjusted odds ratio: 1.52 (95%CI: 1.36–1.70)
Weng et al.	2012	Prospective observational studies	7	Adjusted odds ratio (AOR): 1.47 (95% CI 1.26 to 1.73)
Behl et al.	2013	Epidemiological and experimental animal studies	83: human 18: animals	Meta-analysis was not performed but all prospective studies showed positive association between maternal smoking and child obesity, also majority of articles showed positive association considering overweight.

5. STUDY DESIGN

Systematic review and meta-analysis of epidemiological studies.

6. REVIEW OF INCLUDED STUDIES

Suzuki et al. (2013) performed a cohort study in Japan with a sample population of 1644. The study considered body mass index as the measure of overweight and obesity. The smoking status of mother during pregnancy was obtained by the self-report questionnaire filled by the pregnant ladies during registration of the pregnancy (compulsory in Japan). The smoking status was assessed using "smoking mother" and "non-smoking mother". The adjustments were made with many important variables like maternal age, maternal body mass index, breakfast consumption and smoking status of mother. The result showed that smoking during pregnancy by mother is highly associated with child obesity before the age of 5 years especially in boys (adjusted odds ratio, 4.5; 95% confidence interval, 2.0–10.2).

Chen et al. (2012) conducted a cross sectional analysis in Taiwan and found that various factors are associated with childhood overweight and obesity like male gender, high birth-weight, exposure to in utero maternal smoking and current exposure to household environmental tobacco smoke. The age group included in this study was 9-14 years children. The outcome overweight and obesity was measured by BMI. Sex-age specific BMI $\geq$ 85 percentile were considered overweight and Sex-age specific BMI $\geq$ 95 percentile were considered obese. Sex, age, parental education, sibling number, exercise habit, perinatal and behavioral factors were used as the covariates. The aOR for child overweight was 1.1 with 95% CI between 0.8 and 1.5 and aOR for child obesity was 1.3 with 95% CI between 1 and 1.7.

A cross sectional study conducted in four countries of Greek also showed that the odds of being overweight is 1.42 with 95% CI between 1.07 and 1.88 in a child born to mother who smoked during pregnancy. The study also showed that the odds of being obese is 1.37 with 95% CI between 1.05 and 1.98 in a child born to mother who smoked during pregnancy when compared to child born to mother who didn't smoke during pregnancy (Birbilis et al. 2013). The adjustment was made with variables like Socio-demographic, socioeconomic, perinatal and parental factors, dietary energy intake and physical activity levels.

A cohort of 2698 mother-child pair showed that smoking during pregnancy is significantly associated with child overweight at 6-7 years of age (aOR 3.72; 95% CI 1.33–10.4) after adjusted with gender of child, maternal age at pregnancy, maternal BMI before pregnancy, maternal educational level and maternal alcohol use during pregnancy (Timmermans et al. 2013). This study also concluded that maternal smoking during pregnancy is associated

with lower weight at birth followed by weight catch-up and overweight development in the childhood. There was a positive association between the maternal smoking during pregnancy (ever smoking within 1 year before the birth of child) and child overweight (OR = 1.39, 95% CI: 1.01, 1.94) even after adjustment of maternal factors like age, education, living status, poverty and breast- feeding status and child factors like sex, ethnicity and birth weight (Wang et al. 2012).

Two studies explained the dose-response association between the maternal smoking during pregnancy and childhood overweight and obesity. Study conducted by Risvas et al. 2012 and Harris et al. 2013 showed that the odds of having overweight and obesity increases along with the higher number of cigarettes smoked by mother during pregnancy. But both studies also support that even with lower number of cigarettes smoked per day by the mother during pregnancy, there is higher chances of developing childhood overweight or obesity.

Table 4. Quality Assessment of the included studies

First Author	Epidemiological method	Subject selection	Method of data collection	Data information	Comments
Suzuki 2013	Prospective	Babies of mother who answered questionnaire during early pregnancy	Questionnaire at pregnancy registration	Target: 1644 Measured: 1269	This study can be considered as good quality as it is prospective and the missing data is also not so high.
Chen 2012	Retrospective	Randomly selected Taiwanese community children aged 9-14.	Questionnaire	Target: 7930 Measured: 7930	Although with possibility of recall bias, this study can be considered as of good quality with no missing data.
Timmermans 2012	Prospective	Babies of mother who answered questionnaire	Questionnaire	Target: 2698 Measured: 2698	Top quality
Birbilis 2013	Retrospective	Randomly chosen children from schools in Greece	Questionnaire	Target: 4145 Measured: 2294	Poor quality due to retrospective study design and large number of missing data.
Harris 2013	Retrospective	Children of Nurse Health study II participants	Questionnaire	Target: 35794 Measured: 35794	Good quality
Risvas 2012	Retrospective	10-12 years school children	Questionnaire	Target: 4786 Measured: 2093	Poor quality due to retrospective study design and large number of missing data.
Wang 2012	Retrospective	Sample from National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development (SECCYD).	Questionnaire	Target: 1041 Measured: 1041	Good quality

7. RESULTS

In this study, we have used only those studies, which have expressed the adjusted odds ratio for the outcome i.e. childhood overweight, or obesity associated with maternal smoking during any point of time during the pregnancy. Even though the covariates used were not exactly similar in all the included studies, we used fully adjusted final model if different models were used. We used the lowest smoking dose if the author has reported multiple smoking doses in the study and smoking during early pregnancy or throughout the pregnancy rather than smoking in later pregnancy. In case of multiple outcomes, we took BMI as a primary measure of overweight or obesity. For the calculation of pooled odds ratio, we used random effect model in RevMan 5.2.

7.1. Maternal smoking during pregnancy and child overweight

Our search in various databases yielded 7 studies that showed positive association between maternal smoking during pregnancy and childhood overweight (Table 2). Out of these studies, three were cohort and remaining four were cross sectional studies. We excluded the study conducted by Seipel and Shafer et al. although it showed the significant association between the maternal smoking during pregnancy and child obesity. The main reason for not involving this study in the meta-analysis was the lack of data on confidence interval and standard error, which resulted in difficulty to pool the odds ratio.

Based on the meta-analysis we performed with the seven studies, we found that the risk of being overweight is higher in the child less than 19 years, whose mother smoked during pregnancy when compared to child whose mother did not smoke during pregnancy. The pooled adjusted odds ratio was found to be 1.51 with 95% confidence interval between 1.17 and 1.97. The P for heterogeneity was found to be 0.03 and I^2 = 56% (Figure 2). The study performed by Birbilis et al. had the maximum effect on the pooled estimated with the weight of 23.9% but when this study was excluded, the result was not so much affected with the pooled adjusted odds ratio (aOR1.60, 95% CI: 1.13, 2.26, P for heterogeneity = 0.02, I^2 = 64%).

7.2. Maternal smoking during pregnancy and overweight in younger child of age <9 years

Three studies showed that the odds of being overweight in younger children of less than 9 years is higher in those who were born to mothers who smoked during the pregnancy. Our

meta-analysis showed the pooled adjusted odds ratio of 2.63 with 95% CI between 1.10 and 6.30 and P for heterogeneity 0.010 and I^2 = 78% (Figure 3). The study done by Wang et al. showed the highest effect on the analysis.

7.3. Maternal smoking during pregnancy and overweight in older child of age 9-18 years

Four studies among the extracted articles reported the higher adjusted odds of being overweight in older children whose mother smoked during prenatal period when compared to older children of non-smoking mothers (Figure 4). On the basis of our meta-analysis the risk of being overweight were higher in older children of mothers who smoked during pregnancy (pooled adjusted odds ratio 1.28, 95% CI 1.07, 1.54; P for heterogeneity= 0.70; I^2= 0%).

7.4. Maternal smoking during pregnancy and child obesity

We found three studies that reported that there was significant association and higher adjusted odds ratio for being obese in the child born to mothers smoking during pregnancy when compared to child born to mothers who did not smoke during pregnancy. The pooled adjusted odds ratio of our meta-analysis was found to be 1.37 with 95% CI between 1.19 and 1.57, P for heterogeneity 0.89 and I^2 0% (Figure 5). The highest weight was given by the study conducted by Harris et al.

First Author, Year	OR (95% CI)
Birbilis, 2013	1.42 (1.07, 1.88)
Chen, 2012	1.10 (0.80, 1.51)
Harris, 2012	1.33 (0.60, 2.94)
Risvas, 2012	1.31 (0.87, 1.97)
Suzuki, 2013	4.50 (2.00, 10.12)
Timmermans, 2012	3.72 (1.33, 10.41)
Wang, 2013	1.39 (1.01, 1.91)
Combined	1.51 (1.17, 1.97)

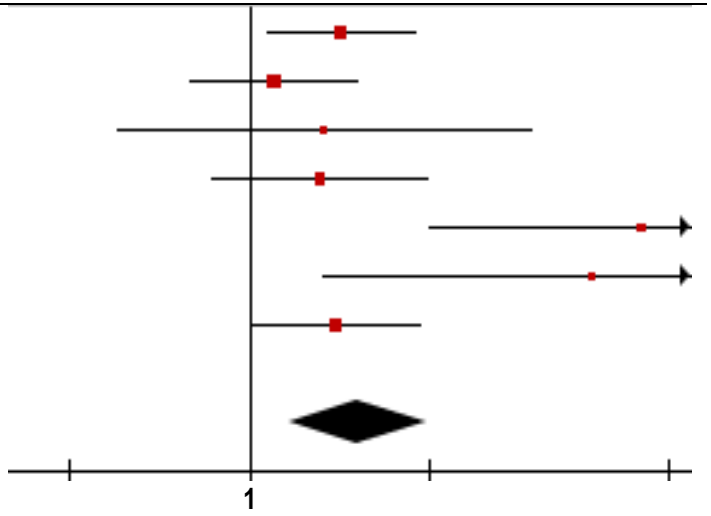


Figure 2: Results of meta-analysis of maternal smoking during pregnancy and child overweight.

First Author, Year	OR (95% CI)
Suzuki, 2013	4.50 (2.00, 10.12)
Timmermans, 2012	3.72 (1.33, 10.41)
Wang, 2013	1.39 (1.01, 1.91)
Combined	2.63 (1.10, 6.30)

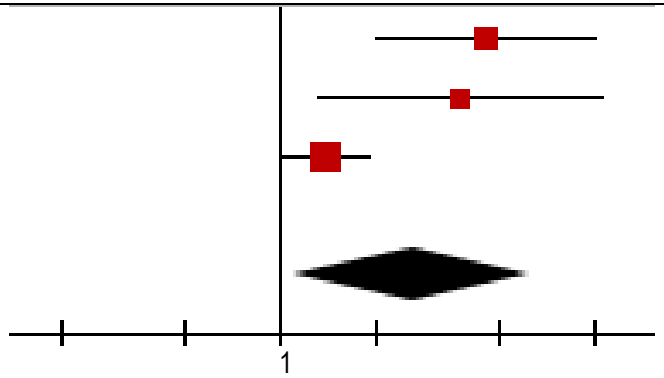


Figure 3: Results of meta-analysis of maternal smoking during pregnancy and overweight in younger child of less than 9 years.

First Author, Year	OR (95% CI)
Birbilis, 2013	1.42 (1.07, 1.88)
Chen, 2012	1.10 (0.80, 1.51)
Harris, 2012	1.33 (0.60, 2.94)
Risvas, 2012	1.31 (0.87, 1.97)
Combined	1.28 (1.07, 1.54)

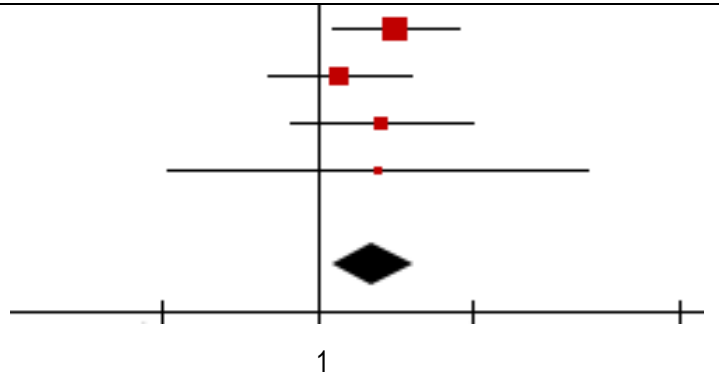


Figure 4: Results of meta-analysis of prenatal smoking and overweight in older child.

First Author, Year	OR (95% CI)
Birbilis, 2013	1.37 (1.05, 1.79)
Chen, 2012	1.30 (1.00, 1.69)
Harris, 2012	1.41 (1.14, 1.74)
Combined	1.37 (1.19, 1.57)

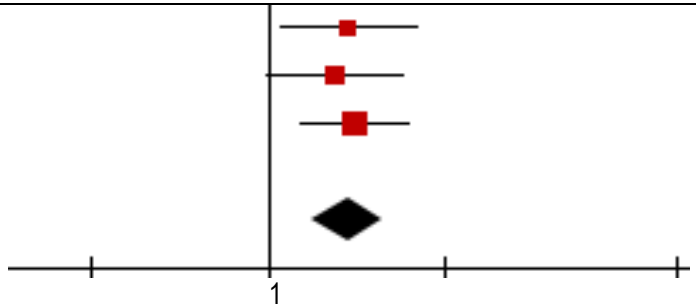


Figure 5: Results of meta-analysis of maternal smoking during pregnancy and child obesity.

Note:

Figure 2-5: Individual study estimates are indicated by red boxes with 95% CIs indicated by lines. The size of the box is inversely proportional to the variance. The pooled estimate is represented by the diamond, with the width of the diamond representing the pooled CI. The right hand side from the mid-point 1 in the x-axis indicate odds ratio >1 and the left hand side indicate odds ratio of <1.

8. DISCUSSION

From the systematic review and meta-analysis we performed, we found that the maternal smoking during pregnancy is significantly associated with childhood overweight. Even after the adjustment of the risk factors for overweight like maternal age at pregnancy, maternal BMI before pregnancy, maternal educational level, maternal alcohol use during pregnancy, child's age, gender, physical activity status, quality of diet, socioeconomic and behavioral variables, the result remained the unchanged or showed positive association between the maternal smoking the pregnancy and child overweight. In all of the studies included in our research, smoking at any point of pregnancy was associated with childhood overweight. Few studies also showed that smoking during pregnancy also is associated with childhood obesity. The association of maternal smoking during pregnancy with overweight was higher among the younger children. This may be due to other factors like high level of physical activity seen especially in school going older children prevents from getting overweight.

Biological mechanism showing association between maternal smoking and child obesity

Although many studies have been conducted till date in regard to show maternal smoking during pregnancy being a major risk factor for childhood overweight or obesity, the mechanism by which it occurs is still unclear. Few researchers have tried to explore the mechanism in animals and human as well. Nicotine is the most addictive substance and is the main component of the tobacco. It has capacity to suppress the appetite, decrease the food intake and eventually leading to weight loss (Jo et al. 2002). Many studies have found that quitting of smoking results in subsequent weight gain (Cropsey et al. 2010; Kasteridis et al. 2012; Williamson et al. 1991). Nicotine has a special property of crossing the placenta like many other drugs and remains concentrated in amniotic fluid and fetal blood (Bruin et al. 2010). It was also found that the concentration of nicotine was much higher in the fetus of smoking mothers when compared to the serum nicotine concentration in the smoking mother herself (Luck et al. 1985).

This clearly explains the mechanism by which smoking during pregnancy by a mother can result in child overweight or obesity in later life. That is the nicotine level, which was higher in the fetus because of the smoking mother before birth starts decreasing after the separation of placenta and this cessation of smoking or decreasing nicotine leads to

overweight, or obesity as the child grows. Also, many other risk factors mentioned earlier for obesity plays role in the development of obesity as the child grows. Nicotine also acts as a vasoconstrictor leading to fetal hypoxia. This explains results of some studies showing lower weight in the child of smoking mother at birth (Timmermans et al. 2013).

Animal studies have shown that prenatal nicotine exposure damages the β- cells of pancreas of the infant rats, which leads to metabolic changes and followed by obesity and impaired glucose homeostasis (Bruin et al. 2008; Holloway et al. 2005; Somm et al. 2008). Exposure of nicotine in pregnant rats has also shown that there is increase in the body weight of their infant rats postnatal (Gao et al. 2005; Somm et al. 2008) and during adulthood (Oliviera et al. 2009; Somm et al. 2008). Wideroe et al. (2003) has suggested that the regulatory center for food intake and energy expenditure is located in the hypothalamus and nicotine has property of affecting the various neurotransmitters and hormones that regulates these centers in the hypothalamus which may result in increased appetite and hence obesity.

All the systematic reviews till date have provided strong evidence of maternal smoking during pregnancy being one of the most important risk factor for the development of overweight or obesity in child. A recent review done on National Toxicology Program has shown strong relationship between childhood obesity and maternal prenatal smoking (Behl et al. 2013). They have meticulously reviewed all the epidemiological studies published till 8 March 2012. The authors have also reviewed the animal studies separately. The result of this review has shown that the prenatal smoking is associated with overweight or obesity in child later life and development of metabolic disorders as well. The study has shown the effect estimates of all included studies separately but they have not calculated the combined effect size of the comparable studies. In our study, we have included the articles published March 2012 onwards and also calculated the pooled odds ratios of the various studies in combine.

Methodological quality of the included studies

We also assessed the methodological quality of the included studies. We considered the information on the type of epidemiological method used, selection methods for study subjects, method on collecting data for smoking status and information regarding data as the important points in order to assess the quality. Among the studies included, we found that Birbilis et al (2013) and Risvas et al. (2012) were of poor quality because of the study

design being retrospective and also consisting of large numbers of missing data. Other studies even though being retrospective with possibility of recall bias had no missing data and can be considered as good quality. Timmermans et al. (2012) and Suzuki et al. (2013) were the prospective studies with no and small number of missing data respectively making it top quality studies (Table 4).

Limitations

The limitation of our study was the difficulty in selecting the results of the studies when there were multiple outcomes. For example, some studies estimated the adjusted odds ratio according to the numbers of the cigarettes smoked by the mother during the pregnancy (Harris et al. 2013; Risvas et al. 2012). We tried to overcome this limitation by using the lowermost numbers of cigarettes smoked by a mother so that any dose of cigarette exposure to the child has not been missed.

Another limitation is the narrow range of time period (March 2012 to September 2013) has been used for selecting the studies. But the good numbers of subjects in all the study groups and the snowball selection method used to avoid missing of any studies during this period have solved this problem to some extent. The maternal smoking status was mostly self-reported. This may have led to bias in the study because of the under reporting or manipulation of the status by the mother. In some studies, the smoking status of the mother was assessed at the same time when the child weight and height were examined. This may also have led to recall bias to some extent.

Although the maternal smoking status during pregnancy were self-reported, child obesity and overweight were assessed by the calculation of BMI i.e. BMI= Weight (kg)/ (Height) ^{2} (m). Clinical assessment of the child was done by the anthropometric measurement (weight, height, skin fold thickness, weight circumference, etc.), which was followed by calculation of BMI in most of the studies. All the included studies have adjusted the likely confounding factors. Although many epidemiological studies like cross-sectional and cohort studies have provided evidence on the positive association between prenatal smoking and child overweight or obesity, there is no evidence that cessation of smoking during pregnancy results in fewer incidences of childhood obesity or overweight. Future Randomized Controlled Trials (RCT) of smoking cessation during pregnancy and following of their child may provide evidences and help in this matter.

9. CONCLUSION

This review has gathered information from all kind of epidemiological studies that have been conducted recently and provide evidence that there is strong association of maternal smoking during pregnancy as an independent factor for childhood overweight and obesity. This study will help health professionals to understand the adverse effect of maternal smoking during pregnancy on later child health and hence, help to implement various public health interventions. Most importantly, recognizing maternal smoking being a risk factor, which is a modifiable, can help to prevent the incidence of childhood obesity if preventive measures are considered.

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APPENDICES

Appendix 1: Characteristics of excluded studies.

Study	Study design	Reasons for exclusion
Liem 2013	Cohort study	Result is not expressed in terms of adjusted OR or relative risk
Florath 2012	Cohort study	Result is not expressed in terms of adjusted OR or relative risk
Suzuki 2012	Survival analysis	Full text not found
Shi 2013	Cross-sectional	Full text not found
Seipel 2013	Cross-sectional	Result is not expressed in terms of adjusted OR or relative risk