



Revisión

Association of excessive GWG with adiposity indicators and metabolic diseases of their offspring: systematic review

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Abstract

Introduction: It has been reported that excessive gestational weight gain (GWG) during pregnancy is associated with an increase in adiposity indicators and metabolic disorders of the offspring.

Objective: The objective of this review, using the Institute of Medicine (IOM) criteria, was to analyze the association of excessive GWG in prospective studies with the adiposity indicators and metabolic diseases of the offspring, and the association of excessive GWG with adiposity indicators and metabolic disease of the ≥ 15 years offspring.

Methods: An electronic search was conducted in the MEDLINE/PubMed, EMBASE, and CINAHL databases of prospective cohort studies published from January 2004 to September 2014. Selection was restricted to prospective cohort studies where the definition of GWG was used according to the IOM-recommendations; and prospective cohort studies including offspring ≥ 15 years, independent of using the definition for excessive GWG.

Results: Nine prospective cohort studies meet the inclusion criteria. Five studies used the IOM-recommendations for assessing GWG, and six studies assessed adiposity or metabolic indicators of their offspring at ≥ 15 years. In seven of the nine studies, excessive GWG was associated with adiposity and metabolic diseases. Due to the limitations found, the evidence of the association was shown to be low.

Conclusions: The results of this review showed, that independently of the criteria used to diagnose excessive GWG, all the included studies, consistently showed an association of excessive GWG with adiposity indicators or other components of metabolic disease early in life, during adolescence or adulthood. However, due to the li-

ASOCIACIÓN DE GANANCIA DE PESO EXCESIVA DURANTE EL EMBARAZO CON INDICADORES DE ADIPOSIDAD Y ENFERMEDADES METABÓLICAS DE SUS DESCENDIENTES: REVISIÓN SISTEMÁTICA

Resumen

Introducción: Se ha reportado que el aumento excesivo de la ganancia de peso gestacional (GPG) durante el embarazo está asociada a un aumento en los indicadores de adiposidad y trastornos metabólicos de su descendencia.

Objetivo: El objetivo fue analizar la asociación del aumento excesivo de GPG en estudios prospectivos, utilizando los criterios del Instituto de medicina (IOM), con indicadores de adiposidad y enfermedades metabólicas de los descendientes y estudiar la asociación del aumento excesivo de GPG en estudios prospectivos con indicadores de adiposidad y enfermedad metabólica de los descendientes ≥ 15 años.

Métodos: Se realizó una búsqueda electrónica en las bases de datos MEDLINE/PubMed EMBASE y CINAHL, de estudios prospectivos de cohorte publicados de enero de 2004 a septiembre de 2014. La selección de artículos fue restringida a estudios en los que la definición de GPG siguiera las recomendaciones del IOM; y estudios prospectivos de cohorte incluyendo los descendientes ≥ 15 años de edad, con diferentes definiciones de GPG, independiente de la definición utilizada.

Resultados: Nueve estudios prospectivos cumplieron los criterios de inclusión. Cinco estudios utilizaron las recomendaciones del IOM para la evaluación de GPG, y seis estudios evaluaron indicadores de adiposidad o enfermedades metabólicas en los descendientes ≥ 15 años. En siete de los nueve estudios, se observó que a mayor GPG de la madre, de cualquier categoría de peso pre gestacional, mayor adiposidad y prevalencia de otros componentes del síndrome metabólico. Debido a las limitaciones explicadas en el estudio la evidencia de la asociación es baja.

Conclusiones: Los resultados de esta revisión muestran que independientemente de los criterios utilizados para diagnosticar el aumento de la GPG, todos los estudios muestran consistentemente una asociación entre la GPG y los indicadores de adiposidad u otros componentes del síndrome metabólico en la niñez, durante la adolescencia o la edad adulta. Sin embargo, debido a las limitaciones de los estudios, la fuerza de la evidencia es baja.

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mitations of the studies the strength of the evidence was low. Better designed studies are warranted to confirm a stronger evidence.

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Key words: *Gestational weight gain. Excessive gestational weight gain. Offspring obesity. Offspring BMI.*

Introduction

The worldwide prevalence of overweight in 2008 among women aged 20+ was 35% with 14% obese. The prevalence of overweight and obesity was highest in America, 62% for overweight and 26% for obesity. In Europe, the Eastern Mediterranean and America over 50% of women were overweight and 23% were obese¹. In the USA (2012), approximately 64% of women of reproductive age were overweight or obese with 35% of them obese². According to the National Health and Nutrition Examination Survey (2009-2010), 16.9% of children and adolescents, 2-19yo, were obese³.

In the UK, Drake and Reynolds (2010) mentioned that the rise in obesity among pregnant women parallels the upward trend of obesity in the general population. Besides, the short-term complications of obesity, there are long-term detrimental consequences of their offspring's health⁴.

According to Power et al. (2012), obesity during pregnancy is associated with an increase in metabolic disorders for the mother and their offspring. Type 2 diabetes, hypertension and cardiovascular diseases are more frequently found in offspring of mothers with obesity during pregnancy⁵. Some studies suggest that a child of an obese mother may suffer from exposure to a suboptimal *in utero* environment and that these early life adversities may extend into adulthood^{6-11,12-18}.

Given the obesity epidemic in the whole world, the relationship between gestational weight gain (GWG) and offspring adiposity has acquired great importance. GWG is a composite of the product conception, plasma volume expansion, extracellular fluid, and maternal fat deposition¹³. The Institute of Medicine (IOM) in the USA, has recently published revised guidelines for gestational weight gain (GWG), in which underweight (BMI <18.5) in women are recommended a weight gain during pregnancy from 12.5 to 18 kg, for normal weight women (BMI, 18.5-24.9) a GWG from 11.5 to 16 kg, for overweight women (BMI, 25.0-29.9) a GWG from 7 to 11.5 kg, and for obese women (BMI ≥30) GWG from 5 to 9 kg²⁰.

In a recent review conducted by O'Reilly et al. (2013), it is suggested that there is now evidence supporting a link between excessive GWG and offspring obesity as a neonate, child, adolescent and adulthood, as well as metabolic outcomes, including increased risk of insulin resistance, hypertension and dyslipi-

Son necesarios estudios mejor diseñados para confirmar esta asociación con una mayor fuerza de la evidencia.

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Palabras clave: *Aumento de peso durante la gestación. Aumento excesivo de peso durante la gestación. Obesidad en los descendientes. IMC de los descendientes.*

daemia²¹. Additionally, in a recent meta-analysis conducted by Tie et al. (2014), concluded that excessive GWG was associated with significant increased risk of childhood overweight/obesity. The combined adjusted OR was 1.33 (95% CI 1.18-1.50).

However, in this meta-analysis studies using different criteria of excessive GWG, were included having a combined large range observation periods²².

The objective of this review was to analyze, using the Institute of Medicine (IOM) criteria, the association of excessive GWG in prospective studies, with adiposity indicators and metabolic diseases of the offspring; the association of excessive GWG with adiposity indicators and metabolic disease of ≥ 15 years offspring were analyzed.

Methods

An electronic literature search was conducted in the MEDLINE/PubMed, EMBASE, and CINAHL databases of prospective studies published from January 2004 to September, 2014. We searched English and Spanish-language publications that examined the association between excessive GWG and offspring with adiposity indicators of metabolic diseases. The selection of articles was restricted to prospective studies where the definition of GWG was used according to the recommendations set by the Institute of Medicine (IOM); and prospective cohort studies included offspring ≥ 15 years, independent of the definition of excessive GWG. Keywords used in this electronic search were: "gestational weight gain", "excessive gestational weight gain" "offspring obesity", and "offspring BMI". In total 1312 potential related studies were identified (Fig. 1). After screening, 1186 articles were excluded according to the inclusion criteria. Of these, 126 articles were selected and full papers were reviewed. After the data was examined for eligibility, nine articles were identified; five of them used the IOM criteria to define GWG and six studies analyzed the association of GWG and offspring obesity at age ≥ 15 years.

Results

In this systematic review we reviewed nine prospective cohort studies with the purpose to assess the as-

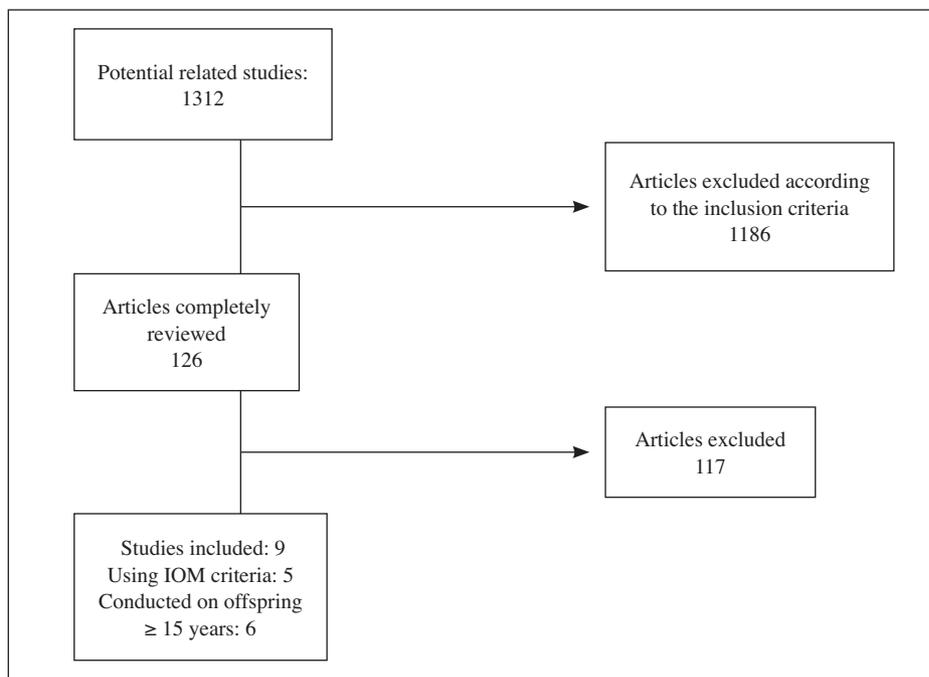


Fig. 1.—Flow diagram of the study selection.

sociation of excessive GWG with adiposity indicators and metabolic diseases of their offspring.

Five of the nine prospective studies included in the review used the USA Institute of Medicine (IOM) guidelines for assessing GWG. Two studies were conducted in the USA, one in the UK, one in Australia and one in Germany. Overall, more than 20,000 mother-child dyads were analyzed in those studies. Detailed characteristics of the included studies are shown in table I. The study population ranged from 2 432 to 6 254, mother offspring pairs. Offspring ranged from 5 to 21 years.

Mamun et al. (2009)²³ carried out a prospective study in Australia. The study included 2432 mother-offspring pairs with maternal self-reported GWG and the offspring's measured BMI and blood pressure (BP) at 21 years of age. The mean weight gain of each mother was 14.8 ± 5.1 kg (average=0.4 kg/wk). At 21 years of age, offspring mean BMI was 24.2 ± 4.9 kg/m², Systolic Blood Pressure (SBP)= 116.4 ± 14.5 mm Hg and Diastolic Blood Pressure (DBP)= 67.7 ± 8.5 mm Hg. According to the IOM-recommendations, 34% of the women gained excessive weight, 41% gained adequate weight, and 25% gained inadequate weight. At 21 years of age, 21.17% of the young adults were OW, and 11.98% were obese. Men had higher hypertension levels than women (12% and 1.55%, respectively). The authors' findings showed that greater maternal GWG was associated with greater BMI in offspring and that association extended into early adulthood. The limitations of this study were the self-reported GWG from the mothers, the loss to follow-up (66%) and the lack of statistical power estimation.

Fraser et al. (2010)²⁴ conducted "The Avon Longitudinal Study of Parents and Children (ALSPAC)". They used data from 5154 mother-offspring pairs for adiposity and blood pressure. Offspring of mothers who gained more than IOM-recommended levels of GWG were more likely to have been overweight/obese and with central obesity, OR: 1.73 (1.45, 2.05) and 1.36 (1.19, 1.57) respectively, compared with those whose mother gained the IOM recommendations. The risk of overweight for the offspring was greater from mothers who gained more than 500 g/wk. GWG between 14 and 36 weeks was positively associated with adverse lipid and inflammatory profiles of the offspring, as well as greater adiposity and adverse cardiovascular risk factors. The main limitation of this study was the high level of attrition (57% at offspring age 9 y).

Margerison Zilko et al. (2010)²⁵ examined the association between GWG and small- and large-for-gestational-age (SGA and LGA), infant overweight, and maternal postpartum weight retention taken from a diverse sample of the National Longitudinal Survey of Youth 1979 (NLSY79) (aged 2-20y). The study sample consisted of 4496 cases. Mean total maternal GWG was 14.2 ± 6.9 kg. According to the IOM-recommendations 30% of the women gained below or within the recommended GWG, and 40% of the women gained excessive GWG. Eleven percent of the infants were SGA and 12% were LGA. Underweight women were more likely to have an SGA birth, and overweight and obese women were more likely to have an LGA birth, cesarean delivery, or overweight child. Excessive GWG was associated with increased odds of LGA (OR, 2.15; 95% CI, 1.57-2.95), postpartum weight retention (OR, 1.58; 95% CI, 1.19-2.09) and child overweight (OR,

Table I
Prospective cohort studies analyzing excessive GWG and their offspring, according to IOM criteria

Reference	Population N	Cohort (year of enrollment)	Offspring age (years)	Definition of excessive GWG	Outcome measure	Adjusted OR (95%CI)	Findings
Mamun et al. 2009	Australia 2432	1981-1983	21	GWG above IOM	BMI, SBP and DBP.	1.7 (1.2 to 2.4)	Greater GWG is associated with greater offspring BMI into early adulthood, and greater mean blood pressure.
Fraser et al. 2010	UK 5154	1991-1992	9	GWG above IOM	BMI, waist, fat mass, leptin, systolic blood pressure, C-reactive protein, and interleukin-6 levels and lower high-density lipoprotein cholesterol and apolipoprotein A1 levels.	1.73 (1.45, 2.05)	Greater GWG up to 36 weeks of gestation are associated with greater offspring adiposity and adverse cardiovascular risk factors.
Margerison Zilko et al. 2010	US 4496	1979	14-22	GWG above IOM	BMI Overweight $\geq 85^{\text{th}}$ percentile	1.27 (1.10-1.48)	GWG was associated with increased risk of LGA and child overweight.
Hinkle et al. 2012	US 3600	2001	5	GWG above IOM	BMI Z-score	NA	Excess GWG was associated with an increase in child BMI Z-score among normal and overweight mothers. No significant association was observed between GWG and child BMI Z-score among underweight or obese mothers.
Beyerlein et al. 2012	Germany 6254	1996-2001	5-6	GWG above IOM	BMI SDS	1.28 (1.02-1.61)	Positive associations of total and excessive GWG with mean BMI and overweight were observed only in children of non-overweight mothers.

GWG: Gestational weight gain, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LGA: Large for gestational age, NA: Not available.

1.27; 95% CI, 1.10-1.48) between 2 and 20 years old. The main limitation of this study was that most data in the NLSY79 was self-reported, which reduces the accuracy of the data.

Hinkle et al. (2012)²⁶ analyzed data from the “Early Childhood Longitudinal Study-Birth Cohort (ECLS-B)”, 3600 children born in 2001 were assessed. The assessment of BMI Z-score was conducted at 5 years of age. At the 5-y interview, 1.7% of children were underweight, 63.9% were normal weight, 18.6% were overweight, and 15.8% were obese. Excess GWG was associated with an increase in child BMI Z-score among normal ($P < 0.001$) and overweight mothers only ($P = 0.013$). The main study limitation was the high level of attrition (46%).

Beyerlein et al. (2012)²⁷ assessed the association of total end excess GWG with offspring’s BMI, among three German cohorts: the Kiel Obesity Prevention Study (KOPS, $n=3678$ children), the LISA Study ($n=1937$ children), and Ulm Birth Control Cohort Study ($n=639$). The mean age of the children at the age of assessment was 5.9 ± 0.6 y. The mean GWG was 14.3 kg, and 37.0% of the mothers had excessive GWG according to the IOM criteria. In this study the increased risk of overweight in offspring was significant only among normal-weight mothers (28% increased risk). The attrition rate was 31%.

In the five studies, it was observed that excess GWG was associated to adiposity and other components of metabolic diseases. However, in the study of Hinkle et al. (2012) the association was only observed among normal and overweight mothers, and in the study of Beyerlein et al. (2012) the association of total and excessive GWG with BMI and overweight was only observed in children of non-overweight mothers. All the studies showed an end attrition rate greater than 30%. Thus, while the association of excessive GWG with adiposity indicators in normal weight women was consistent, the association among overweight and obese was inconsistent, and due to the high attrition rate the strength of evidence shown was low.

Six prospective cohort studies with offspring age ≥ 15 years were analyzed. One study was conducted in Denmark, one in each of the USA, Australia, Israel, Sweden and Finland. Detailed characteristics of the included studies are shown in table II. The study population ranged from 1400 to 146,894. With offspring age at assessing time ranging from 16 to 42 years.

The study conducted from Mamun et al. (2009)²³ showed that greater maternal GWG was associated with greater BMI in offspring and that association was extended into early adulthood (OR, 1.7; 95% CI, 1.2-2.4) at 21 yo.

Schack-Nielsen et al. (2010)²⁸ examined the “The Copenhagen Perinatal Cohort”, which included individuals born from 1959 to 1961. Adult BMI at 42 years was assessed. Gestational weight gain was reported as those with <6 kg, ranging from 6-8, 9-10, 11-12, 13-15kg or >16 kg. The prevalence of overweight in adul-

thood was 33% for women and 53% for men. GWG was positively associated with obesity [OR, 1.08; 95% CI, (1.03-1.14), $P=0.003$ per kg of GWG, $n=1540$] and with overweight [OR, 1.03; 95% CI (1.00-1.06), $P=0.095$, $n=1540$]. The increase risk of obesity [OR, 2.36; 95% CI (1.08-5.15)] and overweight [OR, 1.28 (0.89-1.85)] was shown in the highest (≥ 16 kg) compared to the lowest (<6 kg) GWG category. At the age of 42 years, there was a significant effect on the mean BMI (0.10 kg/m^2 per kg GWG), and a significantly increased risk of obesity with increasing GWG (8% per kg GWG). The main study limitation was the high level of attrition (41%).

The study conducted by Margerison Zilko et al. (2010)²⁵ showed that excessive GWG was associated with offspring overweight (OR, 1.27; 95% CI, 1.10-1.48) between 2-20 years old.

Lawlor et al. (2011)²⁹ conducted a study with all men born in Sweden between 1973 and 1988 ($n=146,894$ individuals from 136,050 families). In this study the mean maternal gestation weight (MGW) was assessed by subtracting the weight at the first antenatal clinic assessment (at 10 wk gestation) from the weight measured after delivery (within the first 12 h of delivery). In normal-weight women, the mean MWG was 14.2 ± 4.2 kg, similar to the MWG in overweight/obese women (13.4 ± 4.8 kg). In normal-weight women, a positive overall association was found between greater MWG and greater offspring BMI at age 18 years, but only between unrelated men (non-siblings) 0.07 (95% CI: 0.06, 0.07) per 1-kg greater MWG. The main strengths of this study were its large sample size and the ability to examine associations among siblings. The main limitation of the study was that GWG was not assessed according to the IOM guidelines, and the attrition at the end of the study was very high (64%).

Hochner et al. (2012)³⁰ analyzed data of 1400 young adults of The Jerusalem Perinatal Study (JPS) at age 32. They examined the associations in maternal pre-pregnancy BMI (mppBMI) and GWG with offspring adiposity and related cardio-metabolic outcomes. In this study GWG was examined as a categorical variable grouped by quartiles of distribution (Q1: <9 kg, Q2: 9-11kg, Q3: 12-14kg, Q4: >14 kg). Results showed that one unit increase in mppBMI was associated with offspring BMI ($p<0.0001$), WC ($p<0.0001$), SBP ($p=0.003$), DBP ($p=0.017$), insulin ($p=0.007$) and triglycerides ($p=0.02$). GWG adjusted for mppBMI and all confounders was also associated with offspring adiposity traits, including BMI ($p=0.0001$), WC ($p=0.024$), and TG ($p=0.04$). The differences in BMI and WC among offspring of mothers in the upper (GWG >14 kg) and lower (GWG <9 kg) quartiles of GWG were 1.6 kg/m^2 in BMI and 2.4 cm in WC. The main limitation of this study, was that GWG was self-reported.

Laitinen et al. (2012)³¹ examined the association between maternal GWG during the first 20 weeks of gestation and overweight/obesity and abdominal obe-

Table II
Prospective cohort studies on the association of excessive GWG and offspring obesity at age ≥ 15 years

Reference	Population N	Cohort (year of enrollment)	Offspring age (years)	Definition of excessive GWG	Outcome measure	Adjusted OR (95%CI)	Findings
Mamun et al. 2009	Australia 2432	1981-1983	21	GWG above IOM	BMI, SBP and DBP	1.7 (1.2 to 2.4)	Greater GWG is associated with greater offspring BMI into early adulthood, and greater mean blood pressure.
Schack-Nielsen et al. 2010	DK 2485	1959-1961	42	GWG >16 kg	Overweight (BMI ≥ 25 kg/m ²) and obesity (BMI ≥ 30 kg/m ²)	1.08 (1.03-1.14)	Greater GWG is associated with an increased BMI in childhood through adulthood and with an increased risk of obesity in adults.
Margerison Zilko et al. 2010	US 3162	1979-1994	14-22	GWG above IOM	BMI Overweight $\geq 85^{\text{th}}$ percentile	1.27(1.10-1.48)	GWG (kg) was associated with increased risk of LGA and child overweight
Lawlor et al. 2011	Sweden 146894	1973-1988	18	MWG=weight (10 wk gestation)-weight after delivery (12 h delivery)	BMI	NA	GWG was positively associated with BMI at a mean age of 18 y in the offspring of normal-weight women.
Hochner et al. 2012	Israel 1400	1974-1976	32	GWGQ1: <9kgQ2: 9-11kg Q3: 12-14kgQ4: >14kg	BMI, WC, SBP, DBP; insulin and triglycerides.	NA	GWG was positively associated with offspring adiposity, including BMI (p=0.0001) and WC (p=0.024), and with TG (p=0.04)
Laitinen et al. 2012	Finland 6642	1985-1986	16	GWG Q1 ≤ 3.0 kg Q2 < 5.0 kg Q3 ≤ 7.0 kg Q4 > 7.0 kg	BMI and abdominal obesity	1.46(1.16-1.83)	Maternal overnutrition during the first half of gestation predicted offspring overweight/obesity and abdominal obesity in adolescence.

MGW=Maternal weight gain; GWG=Gestational weight gain; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

sity of offspring at age of 16 years. The population was composed of the mothers and their adolescent offspring (3265 boys and 3372 girls) from the Northern Finland Birth Cohort (1985-1986). The mothers' weight gain during the first 20 weeks of gestation was based on the difference between weight at 20 weeks of gestation and self-reported pre-pregnancy weight, and was classified into quartiles. The quartile cutoff values for GWG were as follows: Q1: ≤ 3.0 kg; Q2: $3.0-5.0$ kg; Q3 $5.0-7.0$ kg; Q4: >7.0 kg. The prevalence of adolescents who were overweight or obese was 16.2% in boys and 13.8% in girls, whereas 15.1% of the boys and 16.1% of the girls had abdominal obesity. The highest quartile of maternal GWG was significantly associated with overweight and obesity at 16-year-old offspring (adjusted OR, 1.46; 95% CI, 1.16-1.83). The odds ratio for overweight or obese offspring associated with maternal pregravid obesity was 4.57 (95% CI 3.18- 6.57). Maternal weight gain >7.0 kg during the first half of pregnancy was associated with a nearly 1.5-fold increased likelihood for the offspring at 16yo to become overweight, obese or having abdominal obesity. A limitation of the study was the use of self-reported maternal pregravid weight data and having an attrition rate of 28%.

In the six studies reviewed, it was observed that excess GWG was associated to adiposity and other components of the metabolic syndrome, one with additional greater mean blood pressure, one with additional large for gestational age child and child overweight, one with additional higher waist circumference and triglycerides, and one with additional abdominal obesity during adolescence. However, Lawlor et al., (2011) did not find those associations among offspring of overweight and obese mothers. In addition, only one study reported an attrition rate lower than 30%.

Discussion

In this review, it was found that, using the IOM criteria, only one study conducted in adults showed an association between excessive GWG with obesity and metabolic diseases of their offsprings²³, while four studies showed an association of GWG with greater adiposity at nine years of age²⁴, large for gestational age and childhood obesity among 14 to 22 year olds having childhood obesity²⁵, increase of child BMI z-score at age of 5years among children of normal and overweight mothers²⁶, and increased overweight among children 5 to 6 years of age of non-overweight mothers²⁷. Although the results are consistent with other findings¹³⁻¹⁶, there is a lack of consistency shown among overweight and obese mothers, only one study has been conducted among adults' offspring, and most studies analyzed showed a high attrition rate.

In the studies conducted among offspring at age ≥ 15 years, only two of them used IOM criteria^{23,25}. In these studies we found a positive association be-

tween greater GWG and offspring BMI into late adolescence (16-18 years of age)^{29,31} the early adulthood (20-21 years of age)^{23,25} and adulthood (32-42 years of age)^{28,30}. However, these studies used different criteria to evaluate excessive GWG^{23,25}, one used the excessive weight gain higher than 16kg²⁸, independently of initial weight; one used the excessive weight gain higher than the mean weight gain (14.0kg)³⁰, which was similar between normal weight and obese women; one used units of maternal pregnancy gain in BMI, and one used quartiles³¹, with the highest quartile reflecting an increase of GWG equal or higher than 7kg. Only studies that used the IOM criteria considered the initial weight status to assess the excessive GWG. Additionally, two studies used self-reported initial weight or GWG.

Although these findings are consistent with the O'Reilly et al., (2013)²¹ review and with the Tie et al. (2014)²² meta-analysis, there are relevant limitations that should be considered.

In addition to the difference in the criteria of excessive weight gain used, the inconsistency of some results showing an association only in non-overweight women, and the attrition at the end of most studies was high.

In conclusion the results of this review showed, that independently of the criteria used to diagnose excessive GWG, all studies analyzed among normal weight mothers, showed a consistent association of excessive weight gain with obesity or other metabolic diseases early in life, during adolescence or adulthood; seven out of nine studies show an association between GWG with obesity of their offspring and other components of the metabolic syndrome for mothers of any weight status. However, due to the limitations mentioned the strength of the evidence found was low. More studies using homogenous criteria for GWG including strategies to reduce the attrition rate are needed.

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