Influence of Menarche on Body Weight. A systematic review and meta-analysis

Does menarche transition influence or trigger an excess weight gain in young adolescent girls?

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ABSTRACT

It has been shown that post-menarcheal girls are more likely to have increased their body weight and body mass index (BMI) than pre-menarcheal girls of the same age. In addition to the metabolic changes which occur during this interval, behavioural risk factors synergize to promote weight gain, putting adolescents at a much higher risk for excess weight gain and its associated health complications. Moreover, obesity during adolescence increase the risk of becoming an obese adult. A systematic review of English and French articles using MEDLINE, EMBASE, Cochrane, and CINAHL was conducted. Studies underwent a three level screening assessment by two independent assessors. Only studies with post-menarcheal weight change information were selected for data extraction and quality assessment, which was conducted by two independent reviewers. A meta-analysis was conducted for weight change and included 389 girls. Five studies discussed the effects of menarche on body weight change. Pooled results for three studies indicated a 10.39 kg increase from pre to post-menarche (95% CI, 9.16-11.62). The other two studies showed significant increases in body fat mass ($p<0.05$) and higher skinfolds measurements for post-menarcheal girls compared to pre-menarcheal girls. It is important to further explore the bio-psychosocial and environmental factors influencing the weight, especially the total fat mass and body fat distributions in young adolescent girls during the menarche transition in order to develop and evaluate preventive intervention strategies to prevent adolescent and adult obesity.

PREFACE

The work presented to you today is three years in the making. Balancing school, a move to the East Coast, a wedding and part-time work has been quite challenging. However, I am happy to say I've learned tremendously these past three years and am grateful for the journey.

I am grateful to Heather MacDonald at the University of Ottawa Health Sciences Library who supported my systematic review by expertly sharing her knowledge in support of the creation of my search strategies.

I would also like to thank Sahar Razmjou, for having spent numerous hours as a second reviewer for this systematic review. This work could not have been done without you and I greatly appreciate it.

I'd like to thank my supervisor, Dr. Denis Prud'homme, for guiding me through the process of a master's degree, for answering my numerous questions, and for continuously challenging me. It is with great appreciation to have had you as a supervisor. Thank you.

Finally, I would like to thank my family who've been supportive during my studies and who've always believed in me, my friends who never understood the research world, but kept encouraging the journey. Last but not least, to my husband, for your patience, your support, your unconditional love. This could not have been possible without you.

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LIST OF ABBREVIATIONS

<	lower than
AAT	Abdominal adipose tissue
BF	Body fat
BMI	Body mass index
CI	Confidence intervals
cm	Centimeters
FFM	Fat free mass
FM	Fat mass
FSH	Follicule stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
IGF-1	Insulin-like growth factor-1
IR	Insulin resistance
kg	Kilograms
LH	Luteinizing hormone
m	Meters
MeSH	Medical subject headings
MetS	Metabolic syndrome
MIT	Massachusetts Institute of Technology
mm	Millimeters
MVPA	Moderate-to-vigorous physical activity
PCOS	Polycystic ovarian syndrome

PICO	Patient/Population, Intervention, Comparison, Outcome
PICOT	Patient/Population, Intervention, Comparison, Outcome, Type
PQDT	ProQuest Dissertations and thesis database
SAAT	Subcutaneous adipose tissue
SI	Insulin sensitivity
SHBG	Sex hormone-binding globulin
T2DM	Type 2 diabetes mellitus
VAT	Visceral fat
WHO	World Health Organization
WMD	Weighted mean difference

CHAPTER 1: INTRODUCTION

1.1 NORMAL GROWTH: BIRTH TO ADOLESCENCE

The development of the human body never ceases throughout its existence and is a crucial and natural process in order for it to function properly. It starts as early as conception, and continues until late adulthood until death. There are different developmental stages across the lifespan, 9 to be precise, and they start at the prenatal stage, followed by infancy, early childhood, middle childhood, late childhood, adolescence, early adulthood, middle adulthood, and late adulthood (Payne et al., 2012). Boys and girls develop differently as well as at various rate throughout its lifespan. The female body is unique in its development, growth, and maturity in order to procreate and carry a child. According to Payne et al., at birth, a girl's weight is an average of 3.18 kg and measures near 50cm. By their first birthday, girls triple in weight and grow an average of 25 cm. During their childhood stages, girls grow an average of 6.5 cm per year, and gain around 2.5 kg (Payne et al., 2012). Puberty is the last phase in the development of the young woman's reproductive capacity (Rees, 1993; Gupta, 1995). It begins with the appearance of the secondary sexual characteristics and ends with the arrival of menarche and the ovulation cycles (Marti-Henneberg, 1997). The definitions of various manifestations of puberty include adrenarche (activation of the adrenal medulla for production of adrenal androgens), pubarche (appearance of pubic hair), thelarche (appearance of breast tissue), and menarche (age of first menstrual period) (Biro, 2009). Girls tend to enter puberty two years earlier than boys and historically, studies have identified the typical age ranges for pubertal development as 9.5 years to 14.5 years for

girls (Marshall et al., 1969). However, current health literature suggests that there has been a decrease in the age of pubertal onset among both girls and boys (Fechner et al., 2003). Puberty commences in late childhood, however, it concludes during the adolescence stage of development. Adolescence is a time of dramatic changes including rapid physical growth, the onset of sexual maturation, the activation of new drives and motivations, and a wide array of social and affective changes and challenges (Forbes et al., 2010). During the first three years of adolescence, girls gain an average of 16 kg and attain 20% of adult stature, increasing their height by approximately 10 cm per year. Adolescence, as a physical development stage, ends when maximal height is reached. For girls, the average age is 17 years old (Payne et al., 2012).

Many countries use growth charts as guides for monitoring and assessing growth in infants and children. The Canadian Paediatric Society has adapted a version of the World Health Organization (WHO) growth charts (**Figure 1** and **Figure 2**). It demonstrates weight and height recommendations for age, as well as body mass index (BMI), which is calculated as the weight in kilograms divided by the square of the height in meters square (BMI= weight (kg)/height (m^2), (Guo et al., 2002)).

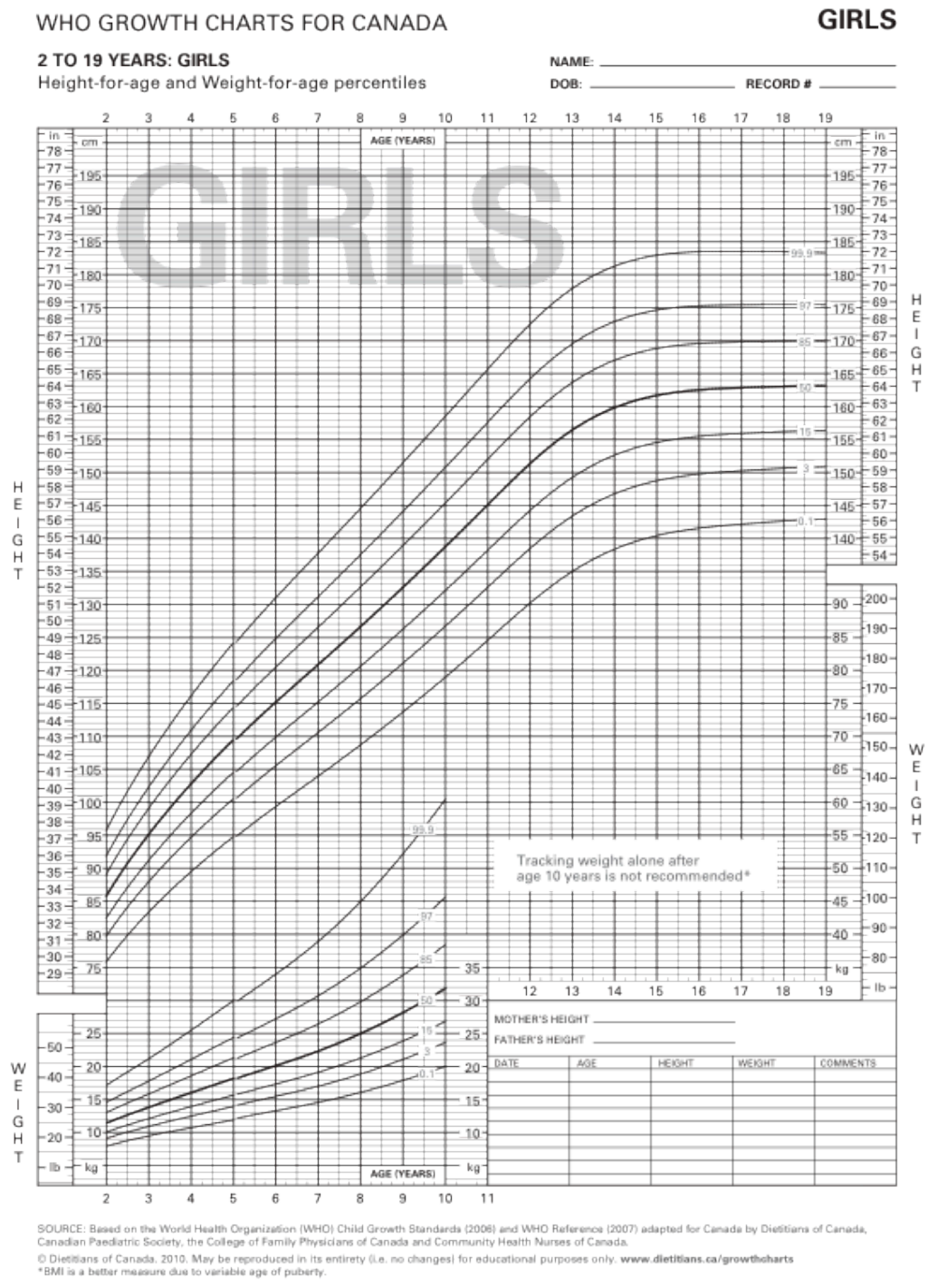

Figure 1: World Health Organization growth chart for Canadian girls; height for age and weight for age.

Source: Canadian Paediatric Society

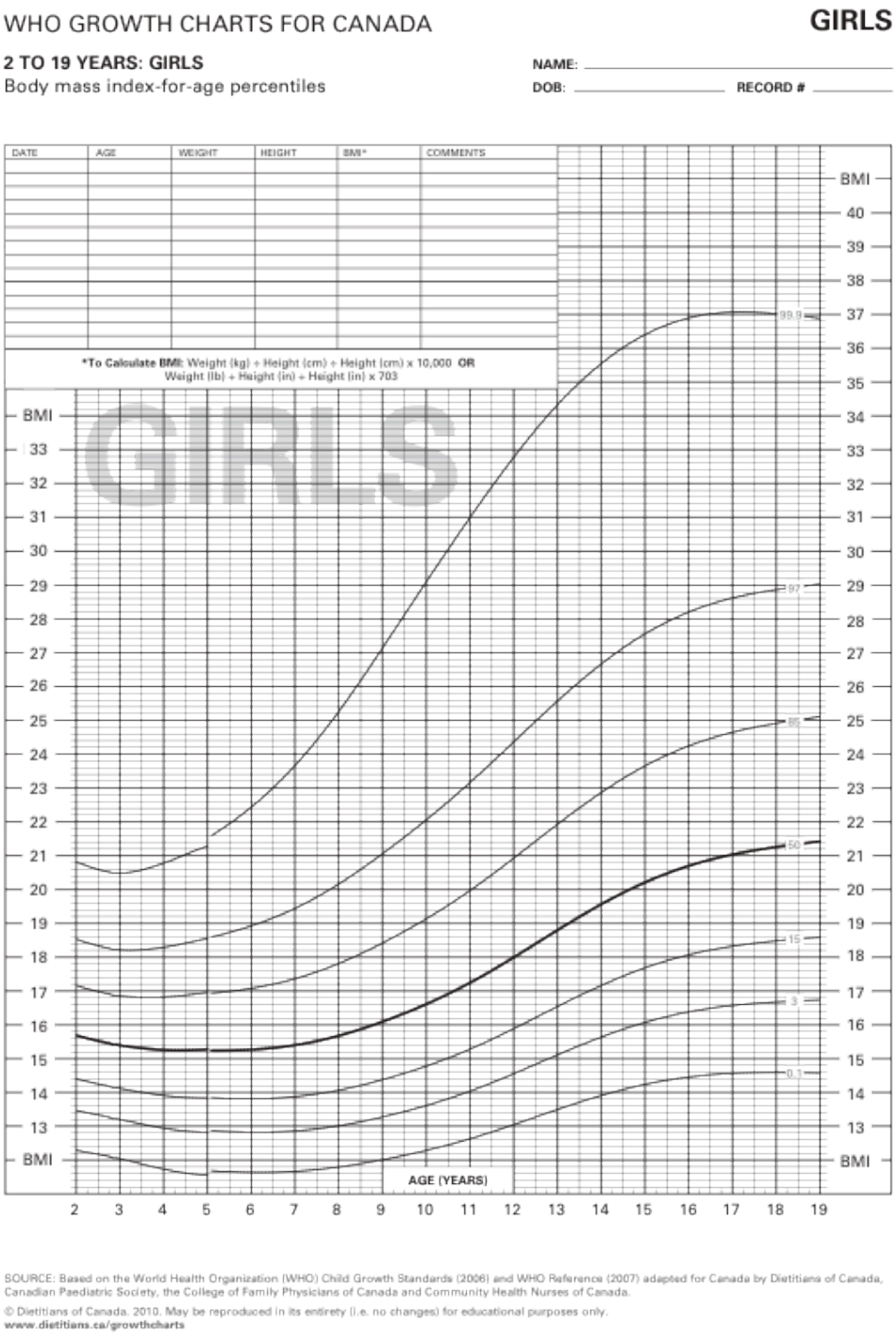

Figure 2: World Health Organization growth chart for Canadian girls; body mass index for age percentiles.

Source: Canadian Paediatric Society

1.2 ADOLESCENT OBESITY

Adolescence is the stage of physical, cognitive, and social maturation between childhood and adulthood (Lerner et al., 2004). The beginning of adolescence occurs around the onset of puberty and is therefore marked by dramatic changes in physical appearance (Blakemore et al., 2010). Though an increased amount of body fat develops during puberty, the way in which the fat is distributed, along with complex hormonal regulatory factors, all play an important role in this weight gain (de Ridder et al., 1992; Garn et al., 1983). In addition to the metabolic changes which occur during this interval, behavioural risk factors such as a sedentary lifestyle, poor eating habits and decision making, synergize to promote weight gain, putting adolescents at a much higher risk for excess weight gain and its associated health complications (Jasik et al., 2008; Sherar et al., 2007).

From the perspective of classification and terminology, prevalence, and recognized potential health consequences, obesity in childhood and youth has been in a state of flux (Biro et al., 2010). Consequently for the first time in history, epidemiologists predict that life expectancy could level off or decline within the next 50 years as a result of the obesity epidemic (Olshansky et al., 2005). Currently, "overweight" is defined by a BMI-for-age of $\geq 85^{th}$ percentile and "obesity" by a BMI-for-age of $\geq 95^{th}$ percentile in children and adolescents (Barlow et al., 2007). Adolescence is an unforgettable period of one's being, and a stage marked by many biological, psychological and social life experiences and changes. Dietz (1994) proposed the identification of critical periods for the development of obesity in order to focus on preventive efforts and promote characterization of the mechanisms that entrain body fat and distribution. A critical

period refers to a specific period of development when an insult has an enduring effect on the structure or function of organs, tissues, and body system (Daniels et al., 2005). According to Dietz, adolescence represents the final proposed stage of the critical periods for the development of obesity before adulthood. Both the risk of onset and persistence of obesity appear greater for females than males (Dietz, 1994). As reviewed by Jasik and colleagues (2008), studies suggest that early adolescence is a vulnerable stage for weight gain, and obesity during this stage predicts obesity in adulthood.

1.3 PREVALENCE OF ADOLESCENT OBESITY

Obesity has become a worldwide health issue, and children and adolescents are substantially affected (James et al., 2001). Despite recent increases in life expectancy, the rising global prevalence of obesity may reverse this trend (Olshansky et al., 2005). In the United States, the prevalence of overweight since 1970, among children aged 2 and 5 years old has doubled, and that of children and adolescents between the ages of 6 and 19 years old has tripled (Ogden et al., 2006). What are the concerns about child obesity? Immediate concerns include social and psychological stress, metabolic and physical disorders, and future health problems in adulthood. (Oken & Lightdale, 2000). Overweight in adolescence can result in immediate adverse effects on health before adulthood such as the metabolic syndrome, type 2 diabetes mellitus, cardiovascular abnormalities, inflammation, psychosocial abnormalities. (Mallory et al., 1989; Must et al., 2003; Rodriguez, 2002; Daniels et al., 2005). The Bogalusa Heart Study found that by age 10 years, 60% of overweight children have at least one biochemical or clinical cardiovascular risk factor and 25% have more than two (Freedman et al., 1999). Must et

al. (1992), showed that being an obese adolescent was associated with an increased risk of multiple comorbidities in adulthood even if the obesity did not persist. Additionally, studies have shown the likelihood of an obese child becoming an obese adult increases with the age of the child independent of the duration or developmental stage in which the child became obese. (Guo et al., 1999; Whitaker et al., 1997; Deshmukh-Taskar et al., 2006). There is a high likelihood of obese adolescents becoming obese adults. In fact, studies estimate that 80% of overweight adolescents become obese adults (Freedmand et al., 2005; Whitaker et al., 1997).

Adolescent obesity is associated with health problems such as, high blood pressure, adverse lipoprotein profiles, diabetes, heart diseases, etc. (Pietrobelli et al., 1998). Additionally, Renehan et al. (2008), showed an increased risk of several cancers with obesity, therefore calling attention to the link between childhood and adolescent obesity to adult diseases such as cardiovascular disease and cancer. The prevalence of metabolic syndrome in adolescents increases with higher BMIs; the odds of metabolic syndrome were 1.55 greater for every half-unit increase in BMI z score. (Weiss et al., 2004).

Long-term follow up studies of adolescents suggest that 30% of all obese adult women were obese in early adolescence. (Dietz, 1994). In support of these statistics, data from the 2009-2011 Canadian Health Measures Survey provide the most recent BMI data, based on measured height and weight, for children and adolescents in Canada. According to the WHO approach, in Canada, close to one-third (31.5%) of 5-to 17-year-olds, an estimated 1.6 million, were classified as overweight (19.8%) or obese (11.7%). This study also reported that 20.9% of adolescent girls aged 12-17 were overweight, and

9.6% of them were obese. (Roberts et al., 2012).

1.4 MENARCHE

The onset of menstruation is defined as menarche and it is an important physiological and psychological milestone in a woman's reproductive life (Barclay et al., 1982). Although research does not document conclusively the direct impact of physiological and psychological events during menarche on subsequent menstrual and reproductive events (Barclay, 1982; Golub & Catalano, 1983; Ruble & Brooks-Gunn, 1982), menarche is recognized as one of the most vivid and emotional events for the human female (Grief & Ulman, 1982; Koff, Rierdan, & Jacobson, 1981), regardless of the specific cultural practices of the society (Logan, 1980). Menarche is also a determinant factor of puberty, which is defined as the moment when reproduction is possible, and growth spurt has been reached (Swenson et al., 1987). The age at menarche varies widely between females; however, it is known that menarche occurs during their adolescent years. A Canadian study found the mean age of menarche for young Canadian females was 12.72 years (Al-Sahab et al., 2010). It seems to occur most frequently when a young woman reaches around 17% body fat. (Frisch, 1987)

1.5 MENSTRUAL CYCLE

The menstrual cycle is the result of precise co-ordination of events that occur in the ovaries, reproductive tract, hypothalamus, and anterior pituitary (Buffenstein et al., 1995). It continues until the onset of menopause around the age of 50, when the ovaries progressively reduce estrogen secretion; the reproductive system then gradually shuts

down. (van Noord et al., 1997; Gruber et al., 2002). In 95% of all menstrual cycles, the cycle length is between 15-45 days (Chiazze et al., 1968). In the majority of women, cycle length varies between 25-30 days, with a mean duration of 28 days. The day of onset of menstruation is generally referred to as day 1, and ovulation generally occurs on day 14. The cycle can be divided into four phases: menstruation or early follicular phase (days 1-4), late follicular phase (days 5-11), periovulation (days 12-15), and the luteal phase (days 16-28) (Buffenstein et al., 1995). Completion of the follicular phase usually occurs when ovulation takes place around day ~14. The luteal phase follows ovulation and lasts around 14 days until the onset of the next menstruation (Owen, 1975). The main hormones that regulate the menstrual cycle are the gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone and oestrogen (Davidsen et al., 2007). These hormones are secreted from different organs and physiological systems. The GnRH is secreted by the hypothalamus, the FSH and LH are stimulated by the anterior pituitary gland, and estrogens and progesterone are secreted from the ovaries. The GnRH stimulates the secretion of LH and FSH from the anterior pituitary gland. Both FSH and LH are gonadotropic hormones; FSH is primarily responsible for stimulating growth of the ovarian follicle and LH's main function is to cause ovulation. The secretion of FSH and LH in turn stimulate the release of estrogens and progesterone from the ovaries. (Mahesh, 1985). In the early follicular phase, follicular growth begins and is characterized by high circulating levels of FSH. Levels of plasma LH, progesterone and estradiol are low during this phase. Plasma FSH induces a rise in concentration of estradiol, which starts in the mid follicular phase and continues until the late follicular phase, where it peaks. This event triggers the mid cycle LH surge,

which lasts 40-48 hours and induces ovulation. Consequently, the level of estradiol decreases, though it remains slightly elevated throughout the luteal phase. Progesterone secretion follows ovulation, and its concentration increases until it reaches its peak during the luteal phase. Levels of LH and FSH have returned to their normal levels. If there is no conception, blood levels of estradiol and progesterone drop at the end of the luteal phase and eventually initiate menstruation followed by a new cycle (Davidsen et al.; 2007, Berstein et al., 1995; Kurzer, 1997). **Figure 3** demonstrates the hormonal changes and body temperature that take place during the menstrual cycle.

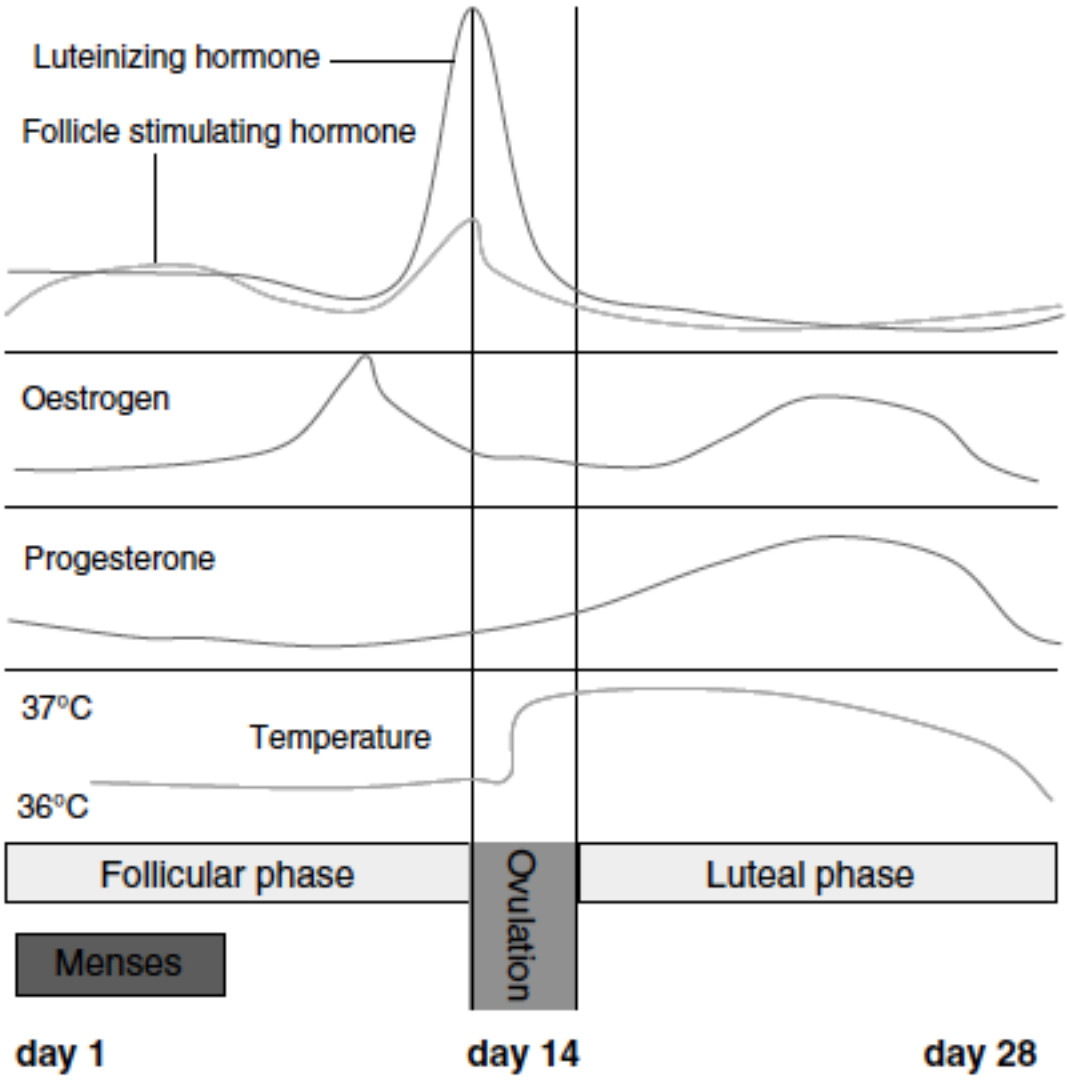

Figure 3: Changes in hormones and body temperature throughout the menstrual cycle.

Source: Davidsen, L., Vistisen, B., Astrup, A. (2007). Impact of the menstrual cycle on determinants of energy balance: a putative role in weight loss attempts. *International Journal of Obesity, 31***,** 1777-1185. See Appendix A.

1.6 INFLUENCE OF MENARCHE ON BODY WEIGHT AND BODY FAT DISTRIBUTION

Puberty consists of a series of biological changes, including maturation of the hypothalamic-pituitary-gland (HPG) axis, pubertal growth spurt, changes in body

composition, development of secondary sexual characteristics, and attainment of fertility status (Biro, 2009). It is also associated with increases in fat free mass as well as fat mass, with a greater increase in fat mass in girls compared with boys throughout childhood and puberty (Maynard et al., 2001; Biro et al., 2010; Demerath et al., 2006; Freedman et al., 2005; Huang et al., 2001). Studies have shown a rise in insulin resistance during puberty (Ball et al., 2006; Goran et al., 2001), as well as a worsening of various components of the metabolic syndrome, and concurrently, changes in leptin and adiponectin (Retnakaran et al., 2006; Weiss et al., 2005). As discussed above, menarche is an important milestone in every woman's life. The arrival of menarche signifies the potential of reproduction, however, menarche may also have a negative influence on body composition. Estrogen is a primary hormone involved in menarche and the menstrual cycle; furthermore, it has also been linked to excess adipose tissue (Jasik et al., 2008). According to Abraham et al. (2000), post-menarcheal girls are more likely to have increased their body weight and BMI than pre-menarcheal girls of the same age. Dietz et al. (1994) also believe that adolescence may be a critical stage for developing overweight due to the increase in body fat mass associated with the pubertal development. An additional study concluded that healthy girls increase their adiposity more from menarche to reproductive maturity at ages 16 to 18 years (Frisch et al., 1974).

1.7 LACK OF STUDIES

There have been many studies surrounding the effects of weight and the onset of menarche. The topic of early maturation versus late maturation has been of importance in the past years; however, there are very few studies that have explored the effects of

menarche on excess weight gain. After having searched through multiple studies and reviews, there were, to our knowledge, no systematic reviews addressing the effects of menarche on weight gain. As mentioned above, adolescent obesity is associated with an increased risk of developing health problems, and is a great predictor of adult obesity. Subsequently, a systematic review is strongly needed to evaluate the current scientific evidences in the literature discussing the influence of menarche transition (pre- to post-menarche) on body weight, especially on body fat mass and body fat distribution. A better understanding of the effect of menarche on excess weight gain is needed to educate the young adolescent girls' population and confirm whether preventive intervention such as healthy diet and physical activity should be developed and evaluated, thus justifying to pursue our research in this field.

1.8 OBJECTIVE

The objective of this review was to systematically identify, select, and evaluate the international literature examining the effects of menarche transition (pre- to post-menarche) on young adolescent girls' weight gain, especially on body fat gain and body fat distribution.

CHAPTER 2: METHODOLOGY

2.1 METHODS

A number of researchers often use a specialized tool called **P**atient/population, **I**ntervention, **C**omparison, and **O**utcome (PICO) (Miller et al., 2001) to form a question and to facilitate their literature search. . This PICO framework can be expanded to PICOTT adding information about the **T**ype of question being asked, and the **T**ype of study design for that particular question. Using the PICO tool can help the researcher articulate the important parts of the question and facilitate the search process by identifying the key concepts for an effective search strategy (Schardt et al., 2007). In this systematic review, the PICOT tool was used to identify the primary question and the key concepts to help find the most relevant studies. **Table 1** describes the PICOT design used to formulate the study question and highlight the key information to look for in studies.

Table 1: Patient/population, **I**ntervention, **C**omparison, and **O**utcome design used for this systematic review.

Population	Adolescent girls who have reached menarche and up to 4 years post-menarche (typically ages 10-19).
Intervention	Any type of intervention
Comparator	Any comparison
Outcome	Include body weight, overweight, obesity, % of body fat, fat distribution, body composition, fat mass, abdominal fat, visceral fat, body mass index , weight gain
Type of study	Non randomised control trials, randomised control trials, cross-sectional studies, retrospective studies, cohort studies, case series, longitudinal studies

The intervention and comparator categories were somewhat challenging due to risk of being over precise and possibly eliminating pertinent studies. The term "menarche" is a specific and defined term that is the core of this systematic review. Consequently, the intervention and comparator categories could not be too narrow in its specifications in order to gain the most credible information surrounding menarche and weight gain.

As mentioned in the introduction, numerous studies (Stark et al., 1989; Freedman et al., 2003; Ruder et al., 2010; Wang et al., 2006; Harris et al., 2008) have focused on the effect of body weight on the age of onset of menarche and thus, this question is not an objective of this systematic review. Therefore, studies focused on the age of onset of menarche and body weight were not included in this systematic review. Additionally,

studies that investigated young girls prior to menarche with no post menarche data were also excluded from this review.

The main outcomes examined/required for this review was body composition information, therefore, studies which did not have this information were excluded as well. Finally, because of language barriers and limited resources for translation, only evidence sources published in English and French were included in this review.

2.2 STUDY DESIGN

All experimental designs were accepted as well as some non-experimental design. These study designs included randomised control trials and non-randomised control trials, or other clinical trials evaluating the effects of menarche on body weight. Descriptive designs such as cross-sectional studies, retrospective studies, cohort studies, case series and longitudinal studies were also included in this review. Including randomised and non-randomised study designs was necessary in order to maximize our chances to identify all pertinent studies. While including all of these study designs expanded our search, this approach also implied that quality appraisal may be affected and heterogeneity between studies may increase.

2.3 SEARCH STRATEGY

The search strategy, found in **Appendix A**, has been developed with the help of the University of Ottawa liaison librarian, (H. D.) It has been divided in to three sections and focused on keywords related to menarche and body weight. This search strategy was used for all databases. The first section, lines 1 to 4, are Medical Subject Headings

(MeSH) and keywords used to locate studies addressing menarche. The second section, lines 6 to 16 identified studies addressing issues within the subject areas of weight change and body fat distribution.

The additional sections were designed to narrow the search by combining search terms and including parameters of language. Lines 5, and 17 combined MeSH and keywords for all the concepts which are shown in line 18. Line 19 describes language preferences.

Major databases were used to conduct our search : Medline, EMBASE, CINAHL and COCHRANE.

We also used extra resources to find essential articles. Grey Net (greynet.org) was used to search grey literature. Incomplete clinical trials were searched with the help of clinicaltrials.gov. A screening of conference papers as well as dissertations and thesis's was done using ProQuest Dissertations and Thesis Database (PQDT) through the University of Ottawa library. The Google and Google Scholar search engines were used to find any additional essential articles that could add any significant information to the review. Communications with experts in the field and any additional, published or unpublished research were sought throughout the process of finding and eliminating studies for the systematic review

All articles and references were stored in a Refworks account where all duplicates were excluded in order to minimize bias. Folders were created to help maintain organisation of the numerous studies and were divided by level of screening as well as the major database where they were found.

2.4 SCREENING OF STUDIES

The screening and selections of the included studies were conducted in three phases using standardized checklists and forms. Two independent reviewers (M.C. and S. R.) performed the screening of the studies. Studies show that the use of at least two investigators may reduce the possibility of rejecting relevant reports (Edwards et al., 2002).

Level 1: Title screen: The two independent reviewers screened titles of studies identified by our search strategies to find any studies concerning menarche and body weight. All titles of studies identified as "included" or "uncertain" were included in level 2 screening.

Level 2: Titles and abstract screen: The two independent reviewers evaluated the studies by looking at the titles and abstracts. The PICO inclusion/exclusion criteria's were used to evaluate the studies. All reasons for exclusions during this screening were tracked and recorded for further use with the help of a flow diagram. Any disagreement on whether the studies met the inclusion and exclusion criteria were reconciled by mutual agreement. Once again, all titles and abstracts identified as "uncertain" were included in level 3 screening.

Level 3: Full text review: All titles and abstracts selected during level 2 screening were reviewed by our two independent reviewers in this third level of screen. They screened the full text of each article with the help of the PICO criteria once again. All articles that were chosen at this level were subject to data extraction.

2.5 DATA EXTRACTION

All included studies had data collected by the two independent reviewers using a standardized data form formatted to our specific needs (**Appendix B**). The standardized form contains important information such as authors, objectives, characteristics of the study, as well as the results. After we extracted data, final inclusion and exclusion decisions were made regarding the articles. Exclusions made at this step were recorded, including the reason for exclusion for future reference. Differences between the two independent reviewers would have been reconciled by mutual agreement or by a third reviewer, however, there were no circumstances required for a third party to intervene.

2.6 QUALITY APPRAISAL

The quality of the remaining studies was examined independently by the two reviewers with the help of the Downs and Black risk of bias checklist (**Appendix C**). The reviewers evaluated the full text of studies selected at level 3 screening. The Downs and Black checklist helped export bias found in these remaining studies. Once again, any disagreement was resolved by a mutual discussion or by a third reviewer. While quality remains a difficult concept to define, all studies should include internal and external validity. The Downs and Black checklist contains 27 items distributed between five sub-scales: Reporting (9 items), External validity (3 items), Bias (7 items), Confounding (6 items), Power (1 item). Answers are scored 0 or 1, except for one item in the Reporting sub-scale, which scores 0 to 2 and the single item on power, which scores 0 to 5. The total maximum score is 32 points (Downs and Black, 1998). However, we removed the Power sub-scale because it only attempted to assess if the findings were due to chance

and was not a user-friendly question. For this reason, we decided to eliminate this last question and had 26 items evaluated on a total of 27 points. We deemed this was appropriate for our research objective.

2.7 DATA ANALYSIS AND RESULTS

After having included and excluded studies based on the study quality, data analysis and results were conducted. The information extracted in tabular format includes population type, anthropometric measures, and the main outcomes for each study. A meta-analysis is not always indicated nor feasible because of clinical heterogeneity between studies with regards to populations, interventions, or form of outcome assessment (Egger et al., 1998), which was certainly the case for this review. However, following our quality appraisal, we determined a meta-analysis was possible for 3 of the 5 studies (similar participants, settings, outcomes) which complements this systematic review. Review Manager 5.2 was used to manage the data. All outcomes could not be compared for the meta-analysis. Only the change in weight from pre-menarche to post-menarche could be compared and analyzed. Given that weight (kg) is a continuous measure, the weighted mean difference (WMD) was estimated using a random-effects meta-analysis with 95% confidence intervals for both pre-menarche and post-menarche measures. We also took into account both the study sample size and the estimate heterogeneity in the selected studies using the I^2 test for heterogeneity. This test describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins et al., 2003).

CHAPTER 3: ARTICLE

Influence of Menarche on Body Weight. A systematic review and meta-analysis.

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3.1 ABSTRACT

Background: Adolescence is a critical period for excess weight gain, and one of many factors that can lead to adult obesity. It has been shown that post-menarcheal girls are more likely to have increased their body weight and body mass index than pre-menarcheal girls of the same age. Adolescent obesity is associated with an increased risk of developing health problems such as dyslipidemia, type 2 diabetes and cardiovascular diseases.

Objective: To evaluate the scientific evidence on the influence of menarche on body weight in adolescent girls.

Methods: A systematic review of English and French articles using MEDLINE, EMBASE, Cochrane, and CINAHL. Studies underwent a three level screening assessment by two independent assessors. Only studies with post-menarcheal weight change information were included in the present review. Data extraction was conducted by two reviewers using a standardized extraction form and a quality assessment was also performed. A meta-analysis was conducted for weight change for those papers of similar comparable methods.

Results: Five observational studies discussed the effects of menarche on body weight change. Pooled results for three studies indicated a 10.39 kg increase from pre to post-menarche (95% CI, 9.16-11.62) based on results of 389 girls. One study showed a significant increase in body fat mass ($p<0.05$) for post-menarcheal girls and additional studies determined that menarche had a significant effect on subcutaneous adipose tissue accumulation, as measured by skinfolds thickness and magnetic resonance imaging, showing greater measurement values for post-menarche versus pre-menarche girls.

Conclusion: The meta-analysis revealed a significant increase in body weight of approximately 10 kg during puberty transition as well as documenting a change in body fat distribution. Future studies are needed to identify the bio-psycho-social and environmental factors and the underlying mechanisms of the weight change, especially of the excess weight gain, during this critical period to prevent adolescent and adult obesity in women.

Keywords: menarche - weight gain – adipose tissue – obesity – body fat distribution

3.2 INTRODUCTION

Adolescent obesity remains prevalent across the developed world, and prevalence continues to increase in most developing countries [1,2]. Adolescence occurs around the onset of puberty and is therefore marked by dramatic changes in physical appearance [3]. For boys and girls, puberty is a critical physiological, psychological and social development stage of life. For adolescent girls, the onset of menstruation is defined as menarche and is an important milestone in a woman's reproductive life [4]. The age at menarche varies widely between females; however it is known that menarche occurs during their adolescent years with a Canadian mean age of 12.72 years [5]. Estrogen is a primary hormone involved in menarche and the menstrual cycle; furthermore, it has also been linked to excess adipose tissue and change in body fat distribution [6,7]. Post-menarcheal girls are more likely to have increased their body weight and body mass index (BMI) than pre-menarcheal girls of the same age [8]. Furthermore, adolescence may be a critical period for developing overweight due to the increase in body fat mass associated with the pubertal development [9]. A study concluded that healthy girls increase more their adiposity more from menarche to reproductive maturity between ages 16 to 18 years [10].

Obesity in adolescence can result in adverse effects on health even before adulthood [11,12,13]. There is a high likelihood of obese adolescents becoming obese adults. In fact, studies estimate that 80% of overweight adolescents become obese adults [14,15]. In Canada, 29% of women are considered overweight (≥25 kg/m^2), and 25% are obese (class I, II, III) (≥30 kg/m^2) [16]. Fecundity of overweight or obese women is lower than normal weight women [17]. However, if they become pregnant, they have a higher risk of

pregnancy complications such as miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes and fetal morbidity and mortality [18,19] Associated with obstetric complications in obese women, fetal overgrowth is a major concern with recent studies showing an increase in mean birth weights (large for gestational age) subsequently leading to an increase risk of childhood and adolescent obesity [20,21,22,23].

There are, to our knowledge, no systematic reviews addressing the effects of menarche on body weight. Menarche is defined as the beginning of the menstrual function, especially the first menstrual period [24]. A recent American longitudinal study collected urine samples from 10 girls for two years and concluded that regular menses with ovulation occurred between 6-12 months post-menarche in all of the girls [25]. The overall purpose of this systematic review was to evaluate the current scientific evidence concerning the influence of menarche on body weight, especially on excess body fat and body fat distribution. Additionally, to determine whether existing literature demonstrated a weight change significantly higher than usual in adolescent post-menarcheal girls.

3.3 METHODS

A systematic review protocol was established *a priori* and the results were reported by using the PRISMA reporting guidelines and the AMSTAR tool was used to assess the review [26,27].

Eligibility criteria

All types of studies that focused on menarche and weight changes were eligible to be included in the review. Participants had to be adolescent girls who have had menarche

and up to four years post menarche (typically ages 10 -18 years old). There were no limits to interventions or comparators in order to decrease the risk of losing pertinent studies. The selected outcomes included all the following anthropometric measures: body weight, BMI (weight (kg) / height (m^2)), body composition (fat mass (FM) and fat free mass (FFM)), percentage of fat, body fat distribution indices and abdominal fat (subcutaneous and visceral fat). Although we included studies focused on menarche, we excluded studies that focused solely on the age of onset of menarche since this has been a popular topic in the past. Additionally, studies that did not report post-menarche data, or body weight information were excluded. Only studies published in English and French were evaluated. See **Table 1** for patient/intervention/comparator/outcomes/type of study (PICOT).

Information sources

An expert reference librarian (H.M.) designed and conducted the electronic search strategy with input from our main investigator (M.C.) at the University of Ottawa. To identify eligible studies, our systematic search included electronic databases MEDLINE, EMBASE, CINAHL, and Cochrane from their inception to February 7th, 2012. Other sources that were searched were clinical trials in progress using greyliterature.net, a screening of conference papers, dissertations and theses, as well as communication with experts in the field. We also hand searched the references of selected studies in order to maximize our pool of studies. All duplicates were excluded before the study selection began. See **Table 2** for details.

Study selection

To minimize risk of bias two assessors (M.C, and S.R.) independently screened all eligible studies [28]. There were three screening levels: level 1, which the assessors screened titles only, level 2 which title and abstract were screened, and level 3 where the full article was screened. Assessors screened each level independently. All disagreements were reconciled by mutual agreement and any ratings of included or unsure by one assessor stayed included to the next level.

Data extraction

Independently and in duplicate, the two assessors extracted data from included studies. A data extraction sheet was developed to consistently capture the important information. We extracted the following data from each eligible study: journal information, year, authors, country, study design, study objectives and outcomes, participant information, the study's inclusion and exclusion criteria, methods, and results. No major disagreements were recorded, however inconclusive decisions were discussed and confirmed.

Quality assessment

To ascertain validity and assessment of risk of bias for eligible studies, the pair of assessors used the Downs and Black checklist [29]. The Downs and Blacks checklist has been validated and found reliable for critically evaluating experimental and non-experimental studies. This checklist was deemed appropriate due to the heterogeneity of

the study designs, mainly being non-randomized and observational studies. Four important aspects were measured at the outcome level such as: Reporting (9 items), External validity (3 items), Bias (7 items), Confounding (6 items) for a total of 26 items and a total of 27 points. The two assessors determined a three level scoring system: 0-8 - high risk of bias, 9-17 - moderate risk of bias, 18-27 - low risk of bias (weak). The reviewers independently assessed the quality for each eligible study and shared the information afterwards. If there were any disagreements, which there was none recorded, they were to be discussed and reported.

Analysis

Meta-analysis was used for outcomes with comparable measures. Review Manager (version 5.2. Copenhagen) was used to estimate a weighted treatment effect with 95% confidence intervals defined as standardized mean differences for continuous measures [30]. All data were analyzed with a random effects model because of the diverse nature of the studies.

3.4 RESULTS

Search results

Figure 1 describes the flow of citations and eligible studies. After searching the electronic databases, we identified 3697 publications. After removing duplicates, 1981 publications remained. Of these screened at level 2, 225 publications were deemed as relevant by title and abstract screening. The full text of the remaining 68 publications, collected from level 3, was explored entirely. There were nine publications that met the

criteria, however five of these publications came from the same cohort study, therefore five studies were included in the systematic review. No unpublished relevant studies were obtained and no additional studies were added.

The five studies (9 publications) included in this systematic review focused on the effects of menarche on weight change (see **Table 3**). All five studies selected for this review were non-randomized observational cohort studies published in English. The included studies involved 3412 participants. The main inclusion criteria entailed young adolescent girls aged 10-18 years old who've had menarche and up to four years post menarche. There were no interventions involved in these studies. Studies were strictly observational with anthropometric measurements and took part in the United States (3 studies (n= 2628)), Brazil (1 study (n= 550)) and India (1 study (n= 479)). In all studies, the primary outcome assessed was weight change from baseline (pre-menarche), up to four years post-menarche. All of the studies focused on weight gain, fat mass, and % of body fat (BF). One study shared additional results on body fat distribution such as abdominal adipose tissue (AAT), visceral fat (VAT), subcutaneous adipose tissue (SAAT). Another study discussed waist circumference measurements as well.

Methodological quality

Table 4 shows the reported methodological quality of the eligible trials based on the Downs and Black risk of bias checklist [29]. Almost all trials lacked confounding and external validity. The overall average score was 7 out of 11 for reporting, 0.5 out of 3 for external validity, 4.5 out of 7 for internal validity and 1.75 out of 6 for confounding for a total of 9.75 out of 27, which gives a rating of moderate risk of bias.

Weight change

Of five studies, three measured change in weight from pre- to post-menarche for a total of 389 girls [11,31,32,33,34,35,36]. The remaining two studies did not report direct body composition measurements for post menarcheal girls. Compared to pre-menarche, post-menarcheal girls have an increase mean weight of 10.39 kilograms (95% CI of 9.16 - 11.62) (**Figure 2**). The funnel plot of our meta-analysis shows little evidence of bias and the level of heterogeneity was fairly low ($I^2 = 35\%$). **Table 5** shows the characteristics of the included studies.

Body fat mass

Of five studies, two compared body FM from pre-menarche to post-menarche. A first study documented FM changes in Japanese and Caucasian girl cohorts [37]. They observed a significant increase ($p< 0.05$) in body FM, from 7.9 ± 3.4 to 16.4 ± 4.8 kg and from 9.3 ± 4.5 to 17.1 ± 5.1 kg in the Japanese and Caucasian group respectively. Analysis also confirmed that, based on the menarche status, all body-composition-related variables (such as weight, BMI, FFM) were statistically higher in the post-menarcheal girls in both cohorts. The MIT Growth and Development Study reported significant increases of % BF (4.4 ± 3.8 %; $p < 0.001$) from baseline to study exit (4 years post-menarche) [31]. Magnetic resonance imagery scans performed in a subgroup of 24 girls at menarche and 4 years post-menarche showed significant increases ($p<0.01$) in %BF as well as an increase of approximately 1kg/year for FM and FFM. Also, they reported significant increases ($p <0.01$) in AAT and SAAT [33]. Finally, an article published by

Spadano et al., using data from the MIT Growth and Development Study, show significant increases in FM and FFM taken from pre-menarche, menarche, and post menarcheal girls. According to this study, FM increased from 8.4 to 13.1 to 16.4 kg and FFM increased from 25.3 to 32.3 to 42.0 kg, respectively ($p < 0.001$ for FM and $p < 0.0001$ for FFM for the differences between visits) [35].

Skinfolds

Two of the five studies measured skinfolds using a Harpenden skinfold caliper [37,38]. Both studies determined that menarche had a significant effect on adiposity by showing greater skinfolds thickness measurement (mm) in post-menarche versus pre-menarche girls independently of race or culture.

Body fat distribution

The MIT Growth and Development Study found a significant increase ($p<0.01$) in AAT (1.56±0.81 to 1.85±0.75 (L)) and SAAT (1.45±0.77 to 1.69±0.66 (L)) in post-menarcheal girls [33]. The VAT was of borderline significance between baseline measures and study exit, 4 years post-menarche (0.104±0.05 to 0.160±0.139; $p=0.066$ (L)). The study from Bhadra et al., showed a significant increase ($p<0.0001$) in waist (53.4±4.5 to 61.5±6.3 cm), hip (69.6±6.3 to 80.7±6.6 cm), abdomen (58.4±5.5 to 69.1±8.1 cm), chest (63.5±5.3 to 75.0±6.1 cm), thigh (31.3±4.7 to 40.0±5.8 cm), medial calf (23.6±3.1 to 29.7±3.7), and upper arm (16.7±2.2 to 20.5±2.3 cm) circumference in post-menarcheal girls versus pre-menarcheal girls.

3.5 DISCUSSION

In the present systematic review and meta-analysis on the effects of menarche on weight change, we found three main outcomes: 1) a statistically significant increase in body weight of 10.39 kg in post-menarcheal girls across studies; 2) a significant increase in skinfolds thickness measurements post-menarche 3) a significant increase in body FM in post-menarcheal girls, regardless of ethnicity and; 4) a significant increase in AAT and SAAT in post-menarcheal girls.

The high prevalence of obesity is affecting adolescents' health more than ever. Young females have their puberty earlier, and show an increase weight at a younger age [39,40]. It is normal to observe changes in body weight and fat distribution in post-menarcheal girls. However, according to Frisch and McArthur [41], the changes in weight observed tend to be over and above what the body needs. These researchers have theorized the existent of an association between menstrual regularity and the level of BF, suggesting that a level of at least 17% BF is critical for the onset of menstruation and the maintenance of a regular cycle. There is some controversy surrounding this theoretical number, however, no new hypothesis have surfaced. The majority of the published studies concerning menarche, weight changes, and regular menses, date as early as 1952 [42]. There has been a limited amount of new published information regarding adolescent females, menarche, and weight changes. The results from our meta-analysis show a statistically significant mean weight increase of 10.39 kg in post-menarcheal girls. The challenge in interpreting these results is to determine how to define what should be considered an excess weight gain (or FM gain) during the menarche transition. This review contributes to improve our knowledge concerning the effects of menarche on

weight and adiposity in young girls, yet, the question remains whether the mean weight change documented in the present study is considered normal or an excess weight gain? The significant weight changes found in post-menarcheal girls are important and can play a large role in the development of adult obesity. Further studies are needed to determine at which levels of weight gain, fat gain and/or abdominal fat gain affect the bio-psychosocial health of adolescent girls.

Limitations and strengths

Our systematic review has some limitations. Firstly, a classical meta-analysis often include randomized controlled trials, however, since our systematic review focused on weight change after menarche, an observational measure over time, it was not appropriate to only search for randomized controlled trials [43]. Observational studies that focused on pre- and post-menarcheal girls were important to be considered base on the objective of this review. Additionally, observational studies have a record of making successful contributions to medicine and improve our knowledge about potential causes and pathogenesis [44]. Nonetheless, we understood that our decision to include non-randomized controlled trials and observational studies could potentially affect the quality of our review and increase the risk of bias [44]. Secondly, although our team scanned numerous databases and had a thorough screening system, we may have missed eligible studies. However, to decrease this publication bias, we had searched references, and spoke with professionals in the research community as well as searched through thesis, dissertations. Also, to avoid selection bias, we had two reviewers screen each level independently and use a common data extraction form [28]. The language criteria of French

and English only articles may have decreased the number of pertinent articles we found. We know that the main objective of a meta-analysis is to summarize and integrate results from a number of individual studies and increase precision in estimating effects [45]. Our meta-analysis could only be done with three studies; still, these three studies had similar participant characteristics, and similar outcomes.

3.6 CONCLUSION

Based on the five studies that have measured body weight changes from pre- to post-menarche we observed a 10.39 kg increase in body weight. The objective of this systematic review was ultimately to capture and analyze the existing literature surrounding weight changes during menarche (pre and post-menarche). To our knowledge, this review was the first of its kind to address the weight change during menarche transition. We hope this review can be a baseline reference for future studies and inspire new research in this domain. We believe it is important to further explore the bio-psychosocial and environmental factors influencing the change in weight, especially total body fat mass and body fat distributions (including ectopic fat depots) as well as documenting the associated health problem(s), in young adolescent girls during the menarche transition in order to develop and evaluate preventive intervention strategies including physical activity and healthy diet to prevent adolescent and adult obesity. This review raises the importance of determining the healthy levels of weight change, or which levels of weight gain (or FM or ectopic fat gain) exceeds the physiological needs, consequently increasing the risk of obesity and its associated health problem(s) in young adolescent girls and during women lifespan. Additionally, knowledge translation

strategies and weight control decision aids for girls at a young age could help them better understand the expected outcomes of puberty and its effect on the body weight, body composition and body fat distribution in order for them to integrate healthy lifestyle practice to decrease the risk of excess weight gain following menarche and during adolescent period.

Conflict of interest

The authors declare no conflict of interest.

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3.8 FIGURES LEGEND

Figure 1. A flow diagram showing the details of the search strategy, screening process, and selection of studies for this systematic review. Reasons for exclusion are presented as well.

Figure 2. A forest plot showing the results of a meta-analysis of three studies regarding weight changes in post-menarcheal girls. There was a mean difference of 10.39 kg between pre-menarcheal and post-menarcheal girls (95% CI, 9.16-11.62).

Table 1. Description of the PICOT strategy.

Acronym	Definition	Description
P	Patient or problem	Adolescent girls who have reached menarche and up to 5 years post-menarche (typically ages 10-18).
I	Intervention	Any type of intervention
C	Control of comparison	Any comparison
O	Outcome	Include body weight, overweight, obesity, % of body fat, fat distribution, body composition, fat mass, abdominal fat, visceral fat, body mass index , weight gain
T	Type of study	Non randomised control trials, randomised control trials, cross-sectional studies, retrospective studies, cohort studies, case series, longitudinal studies

Table 2. Literature search strategy

1	exp Menarche/ (3714)
2	menarche.tw. (5291)
3	(first adj period$).tw. (2329)
4	(first adj menstra$).tw. (0)
5	1 or 2 or 3 or 4 (9074)
6	body weight/ or body weight changes/ or weight gain/ or exp overweight/ (259014)
7	(body adj weight).tw. (123675)
8	obes$.tw. (129055)
9	overweight.tw. (26116)
10	(weight adj2 gain$).tw. (38631)
11	bmi.tw. (51971)
12	(percent$ adj2 fat).tw. (7272)
13	((body adj fat) or (body adj2 distribution) or (body adj2 composition)).tw. (31717)
14	(abdominal adj fat).tw. (3349)
15	excess weight gain.tw. (229)
16	((fat adj mass) or (visceral adj fat)).tw. (11594)
17	or/6-16 (442008)
18	5 and 17 (1889)
19	limit 18 to (english or french) (1644)

Table 3. Characteristics of the included studies.

Authors, year, country	Design	Purpose	Participants	Interventions	Outcomes
MIT Growth and Development Study, Bandini et al. 2008, USA	Cohort	To present a visual representation of changes in body composition, pattern of change in RMR, leptin, insulin, estradiol, and FSH levels in relation to menarche in girls	196 pre-menarche girls	Observational with anthropometric measures	Body composition, weight, leptin, estradiol, FSH, insulin, fat mass, fat free mass, % fat
Bhadra et al., 2001, India	Case-control	Study differences in BMI, regional adiposity, and central body fat distribution between PMG, and MG Bengal Hindu girls, of similar age. Furthermore this study has investigated the influence of menarche on regional adiposity and central body fat distribution.	245 girls aged 11-14; 111 pre-menarcheal and 123 post-menarcheal	Observational with anthropometric measures and questionnaire	Weight, waist conference, BMI, skinfolds
Frisch, 1976, USA	Non-experimental	To determine the normal pattern of changes in fatness of girls at each adolescent event from initiation of the adolescent growth spurt to maturity.	181 menarcheal girls aged 14-18	Observational with anthropometric measures	Weight, height, % of fat
Garn et al., 1983, USA	Non experimental	To compare the fatness distributions of pre-menarcheal and post-menarcheal girls at successive ages during adolescence.	2251 pre-menarche and post-menarcheal girls aged 11-15	Observational with anthropometric measures	Weight, skinfolds,
Sampei et al., 2003, Brazil	Cross-sectional	Compare the various anthropometric and body composition parameters based	550 girls 122 Japanese and 179 Caucasian (10-11 years old pre-	Observational with anthropometric measures	Height, weight, fat mass, fat free mass, % of fat

	on the ethnicity and the absence or presence of menarche.	menarcheal) 72 Japanese and 177 Caucasian (16-17 years old post-menarcheal	

Table 4. Methodological quality of included studies using Downs and Black checklist.

Study	Reporting (10 items)	External validity (3 items)	Bias (7 items)	Confounding (6 items)	Overall (27 points)
Bhadra, 2001	6/11	1/3	5/7	3/6	15[b]
Frisch, 1976	4/11	0/3	3/7	0/6	7[a]
Garn, 1983	7/11	0/3	3/7	1/6	11[b]
Sampei, 2003	7/11	2/3	4/7	0/6	13[b]
MIT – Spadano, 2005	8/11	1/3	5/7	2/6	16[b]

[a] High risk of bias = 0-8
[b] Moderate risk of bias = 9-17
[c] Low risk of bias = 18-27

Table 5: Characteristics of selected studies for the meta-analysis.

Study	Age of participants	Ethnicity	Longevity of observation	Levels of physical activity measured
Bandini et al., 2008	8-12	Multi-ethnic	5 years	no
Bhadra et al., 2001	11-14	Indian	1 year	no
Frisch, 1976	14-18	Caucasian	4 years	no

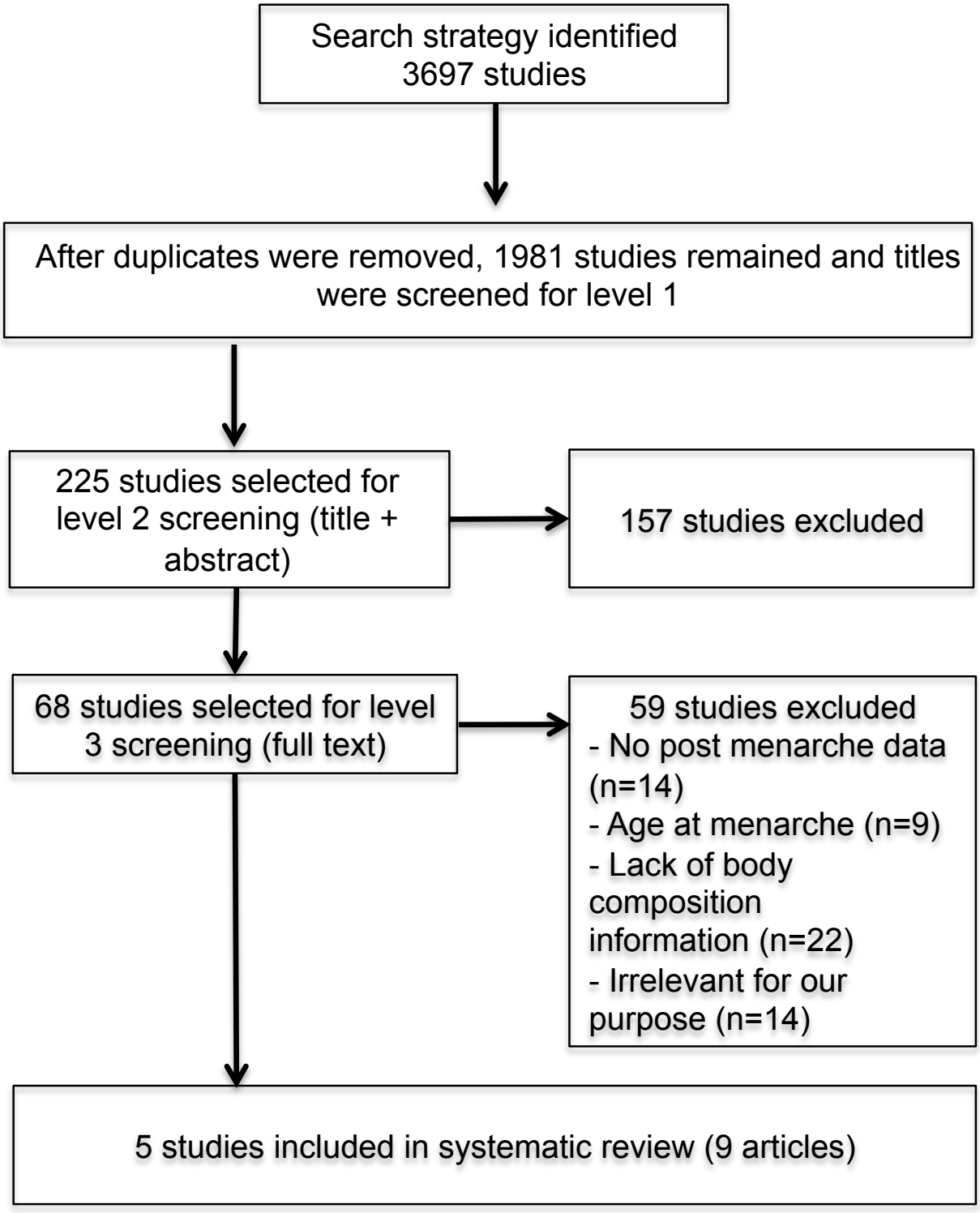

Figure 1. Flow diagram describing screening process.

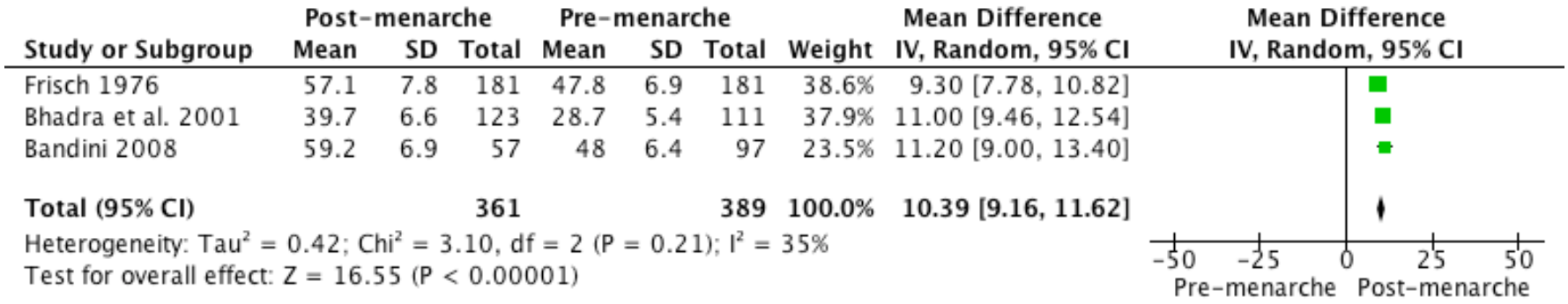

Figure 2. Results of meta-analysis conducted for three studies regarding weight changes from pre-menarcheal to post-menarcheal girls.

CHAPTER 4: DISCUSSION

4.1 HOW MENARCHE MAY INFLUENCE WEIGHT GAIN IN YOUNG ADOLESCENT GIRLS.

As mentioned before, menarche influences several physiological, psychological and behavioural changes that could be accentuated or attenuated by social and environmental factors. It is important to understand the factors that may have an impact on weight, in particularly on body fat gain, during puberty and adolescence in order to diminish the risk of obesity.

4.2 PHYSIOLOGICAL FACTORS

Changes in hormonal regulation of appetite, satiety, and body fat distribution that occur during puberty may put adolescents at increased risk for excess weight gain as reviewed by Jasik et al., (2008). For girls, these physiological hormonal changes during puberty lead to increased adiposity, which is chronologically age-appropriate. Weight gain during puberty is, for females, likely a requirement to develop the physiologic capacity for reproduction (Jasik et al., 2008). Though an increased amount of body fat is observed during puberty, the way in which the fat is distributed, along with complex hormonal regulatory factors, also play an important role in the development of menarche and its effect on body weight (DeRidder et al., 1992; Garn et al., 1983)

Insulin has numerous metabolic effects, but in terms of body weight control, its effects on adipocytes and hypothalamus are relevant. Its main role is to facilitate glucose transport into the cell after a meal, however, this can lead to increased energy storage in a

positive energy balance condition (Ramsay et al., 1996). At the hypothalamic level, insulin may interfere with leptin signaling, which plays a role in body energy balance, leading to leptin resistance and allowing for a greater energy intake favoring a positive energy balance and thus increasing the risk of weight gain, consequently, favouring further fat mass gain (Lustig et al., 2006).

Insulin resistance can be a consequence of obesity, but also may be associated with additional weight gain once present (Odeleye et al., 1997; Sims et al., 1996; Moran et al., 1995; Boran et al., 2006). A physiological increase in insulin secretion and insulin resistance occurs at the onset of puberty in girls, and is thought to facilitate the physiologic increase in adiposity (Welt et al., 2004; Moran et al., 1999; Travers et al., 1995). Increased insulin secretion compensates for the transient decrease in insulin secretion (SI) during adolescence (Caprio et al., 1989; Ball et al., 2005). Physiological insulin resistance may also be involved in the initiation of adrenarche (Saenger & Dimartino-Nardi 2001). Furthermore, hyperinsulinemia can reduce hepatic sex hormone-binding globulin (SHBG) production, increasing sex steroid bioavailability; and in adult women, insulin can augment LH-stimulated ovarian steroidogenesis (Poretsky *et al.* 1999). Notably, the insulin resistance of puberty may be exaggerated in the setting of obesity, especially in girls (Roemmich *et al.* 2002, Brufani *et al.* 2009, Pilia *et al.* 2009). Therefore, the development of insulin resistance during the process of puberty may drive further weight gain, in order for girls to achieve reproductive competency.

Estrogen also has an essential role in the initiation and progression of puberty. The physiologic functions of estrogen in women include the promotion of secondary sexual characteristics development, regulation of gonadotropin secretion for ovulation, preparation of tissues for progesterone response, maintenance and increase of bone mass, regulation of

lipoprotein synthesis, regulation of insulin responsiveness, and maintenance of cognitive function (Cagnacci et al., 1992).

Thelarche, the initial appearance of breast tissue in girls (beginning as a "breast bud" underneath the areola), normally indicates gonadotropin-driven ovarian estrogen production. Increasing estrogen secretion in girls promotes continued breast development; it also contributes to the pubertal changes of body fat composition and distribution. Menarche, the onset of menstruation, denotes increasing maturity of the GnRH pulse generator and follicular development, but does not necessarily imply ovulatory cycles. Regular, ovulatory cycles typically develop within two years of menarche. (Solozarno et al., 2010)

Ovarian aromatase activity is regulated by follicle-stimulating hormone (FSH) secretion, whereas peripheral aromatase activity is dependent on total fat mass. Increases in estrogen are essential for normal progression of puberty, beginning with thelarche (Nelson et al., 2001). As the GnRH pulse generator promotes early ovarian function, estrogen secretion leads to increases in growth hormone (GH) and insulin-like growth factor- 1 (IGF-1) secretion (Leung et al., 2004). These three all conspire to increase the degree of insulin resistance, promoting hyperinsulinemia, and energy deposition into adipose tissue (Bjorntorp et al., 1996). With excess fat stores, there is increased estrogen production.

4.3 PSYCHOLOGICAL AND BEHAVIORAL FACTORS

Metabolic changes during puberty only tell part of the story. Changes in diet, physical activity, family dynamics, and developmental factors are also important factors that could influence body weight regulation during early adolescence. The adolescence period is a time of risk-taking behavior as children test their autonomy and assert independence.

Healthy eating habits and levels of physical activity has been found to decrease, as academic and social pressures become more demanding (Sherar al., 2007). More time spent in sedentary activities, such as TV, video games, cell phone and computer use, along with higher caloric intake and less daily physical activity, especially of moderate and vigorous intensity, are associated with an increase risk of weight gain during that period (Berkey et al., 2000; Cresco et al., 2001). It has been of great concern that physical activity decreases drastically during adolescence, with females becoming significantly more sedentary than males (Department of Health and Human Services, 1996). In support of this, a study conducted by Sherar et al. (2007), compared the level of moderate-to-vigorous physical activity (MVPA) in Canadian boys and girls aged 8-13. When aligned on chronological age, boys had a higher MVPA at all ages then girls. In agreeance, Colley and colleagues (2011) analyzed data collected from the 2007-2009 Canadian Health Measures Survey and found that only 4% of girls accumulate 60 minutes of MVPA. Regardless of age group, boys are more active than girls. As they get older, they are less active. Girls aged 11-14 had an average of 47 minutes of MVPA per day, and girls aged 15-19 averaged 39 minutes of MVPA per day (Colley et al., 2011).

Common weight-related problems among adolescent girls include obesity, body dissatisfaction, and the use of disordered eating behaviors, such as unhealthy weight control behaviors and binge eating (Neumark-Sztainer et al., 2010). Research shows that these weight-related problems are inter-related. For example, 76% of obese adolescent girls engage in unhealthy weight control behaviors (e.g., skipping meals, fasting, taking diet pills, or smoking cigarettes for weight control) as compared to 51% of normal-weight girls. Similarly, 66% of obese girls have low levels of body satisfaction, compared to 38% of normal-weight girls. Unhealthy weight control behaviors and body dissatisfaction have been

found to longitudinally predict excessive weight gain in adolescent girls (Haines et al., 2007; van den Berg et al., 2007). These weight-related problems are of concern, given their high prevalence and harmful consequences for physical health and emotional well-being (Kimm et al., 2002; Neumark-Sztainer et al., 2002).

It has also been reported that during adolescence there is a rapid increase in the number of calories consumed, a reduction in the quality of nutritional intake, and an increase in "obesogenic" eating behaviors such as eating more outside the home, skipping meals, and a decrease in participating in family meals (Jasik et al., 2008). In fact, adolescents seem to develop a "calorie-rich, nutrient poor" diet, which is widely considered to be one of the main causes of rapid weight gain during this time period (Field et al., 2003).

Consequently, young girls often turn to dieting and disordered eating. A 10-year longitudinal study conducted by Neumark-Stzainer et al., reported that about half of the girls reported dieting and the number remained fairly constant from adolescence to young adulthood. As for extreme weight control behaviors, significant increases from adolescence to young adulthood were found in girls (8.4% to 20.4%). They also observed an increase in prevalence of binge eating from 9.9% during middle adolescence to 14.1% in middle young adulthood. Use of extreme weight control behaviors during middle adolescence predicted greater risk for these behaviors 10 years later during young middle adulthood. Research has shown that adolescent dieters, particularly those practicing unhealthy weight-control behaviors, may be less likely to consume fruits and vegetables and adequate amounts of calcium rich foods, compared to non-dieters (Neumark-Sztainer et al., 1997). Although weight control is viewed to be a positive management of obesity, extreme weight control such as the ones observed in these adolescent girls do not encourage a healthy and balanced lifestyle. Additionally, the consequences resulting from extreme weight control behaviors

such as being underweight and overweight (Frisch et al., 1986) can influence the menstrual cycle and its hormonal regulation tremendously and could negatively influence the physiological cycle of a woman. Consequently, adolescent dieters may actually experience excess weight gain or the onset of obesity and also increase their risks of developing depression; a risk factor often overlooked in adolescence (Stice et al., 1999; Stice et al., 2000). The potential impact of mental health problems and medication side effects on body weight as well as the impact of obesity on treatment outcomes is important. Children with a history of depression, anxiety, or more severe mental health disorders are at increased risk for weight gain (Richardson et al., 2010; Goodman et al., 2002). The mechanism is likely a combination of poor lifestyle along with the increased appetite and weight gain accompanying many medications. A reoccurring trend is body dissatisfaction. Adolescent girls are sensitive to body dissatisfaction, which can lead to immediate distress, low self-esteem, and depressive mood (Cash et al., 2002). A theoretical rationale for body dissatisfaction in predicting an increase in depression in girls has been articulated by Stice and Bearman (2001). They proposed that puberty moves away girls from the current thin beauty ideal and this change precipitates body dissatisfaction. As appearance is a critical evaluative dimension for girls in Western culture, body dissatisfaction directly contributes to increase in depressive mood. It is important to consider these factors when trying to understand the increase in weight during puberty.

4.4 SOCIAL AND ENVIRONMENTAL FACTORS

In addition to the changes in diet and physical activity, family dynamics, and developmental factors, the “built environment” plays an important role in increasing the risk

for weight gain among young teens (Jasik et al., 2008). The built environment refers to the neighborhoods, schools, food sources, and communities in which children live.

This environment has an effect on what adolescent eat. The final area unique to adolescents is their cognitive and social development. Adolescent development includes increasing independence, autonomy, greater peer affiliation, sexual awareness, formation of identity, and increasing cognitive ability to process complex information.

In early adolescence, the peer group takes on a primary role and this is important, as peer pressure is one of the major factors in the onset of risk-taking behaviour (Irwin et al., 1992). Research indicates that adolescent friends tend to resemble one another on a wide range of dimensions, including physical and social attributes and attractiveness, attitudes and behaviors, especially health-risk behaviours such as smoking, sexual behavior, alcohol consumption, and drug use (Tolson et al., 1993; Berscheid et al., 1971; Moore et al., 1994). Peer pressure has been described as the primary mechanism for transmitting group norms. It has been suggested that peers exert influence by offering desirable rewards to those who conform to group norms and/or undesirable consequences to those who resist them (Brown et al., 1989; Lieberman et al., 2001).

Peers may also influence eating behaviours and attitudes through weight-related teasing. Studies have shown that high levels of perceived teasing are associated with negative effects in both obese and nonobese individuals, particularly body image disturbance (Stormer et al., 1996). Few studies have focused on teasing in adolescent populations. Fabian and Thompson (1989) examined if retrospective accounts of having been teased about one's weight predicted current levels of body esteem and eating disturbance in a small sample of pre- and postmenarcheal females. Results showed that in premenarcheal girls, low body esteem was associated with greater frequency and reported negative emotional

consequences of weight-related teasing, while in postmenarcheal girls, body esteem was correlated with teasing frequency. Social and environmental factors are very present during adolescence and can have positive and negative influences on a young girl's psychological and physiological development.

4.5 SHORT TERM AND LONG-TERM EFFECTS OF ADOLESCENT OBESITY

Adolescence is a time when many future health behaviors begin (Spear & Kulbok, 2001) and provides an opportunity for interventions that encourage positive health behaviors, including participation in physical activities.

The physiological and behavioral factors that predispose to weight gain during early adolescence also make prevention and treatment in this population challenging (Mietus-snyder et al., 2007; ACOG, 2006**;** Resnicow et al., 2006). Programs with the most success are those that incorporate simple messages, have long-term follow-up, and include an approach that takes the developmental stage into account. In addition, if an adolescent has already developed significant self-esteem problems, eating disorder, and depression related to obesity, these can serve as huge barriers to lifestyle changes (Mietus-Snyder et al., 2007).

Childhood and adolescent obesity is associated with a number of medical complications, among the most worrisome being metabolic risk factors for future cardiometabolic diseases (e.g., insulin resistance, hyperglycemia, hypertension, and dyslipidemia) (Cali & Caprio 2008). Metabolic syndrome (MetS) is a constellation of cardiometabolic risk factors associated with insulin resistance (IR), glucose intolerance, dyslipidemia, hypertension, and central obesity (Ford et al., 2002). There is a growing

appreciation that adolescents are at increasing risk for type 2 diabetes mellitus (T2DM). In fact, the prevalence of T2DM increased in paralleled to the increase of obesity in this population (Cook et al., 2003; de Ferranti et al., 2004; Weiss et al., 2004)).

Pediatricians are increasingly concerned about the long-term health effects of childhood and adolescent MetS and believe that it may be associated with early cardiovascular diseases in adult-hood (Cook et al., 2004). Progress in defining the nature of the long-term cardiovascular risk is hampered by the lack of consensus on criteria for the diagnosis of the MetS in adolescents (Goodman et al., 2004) as well as the lack of longitudinal studies with cardiovascular endpoints as opposed to surrogate markers. Cardiovascular event endpoints are difficult to target because of the long latency period between the onset of atherosclerosis and the first cardiovascular event (Coviello et al., 2006).

Excess adiposity may also influence various aspects of pubertal development, such as the timing of pubertal initiation and hormonal parameters during puberty. These alterations may not be innocuous. For example, earlier puberty in girls appears to be associated with a higher risk of psychological problems, risk-taking behavior, hyperandrogenemia and even future breast cancer (Golub *et al.* 2008).

Exaggerated weight gain, and obesity in the postpubertal female has specific detrimental effects on menstruation. The most common cause of ovulatory infertily, polycystic ovarian syndrome (PCOS), affects 1-5% of women and is a condition characterized by hyperandrogenism and chronic oligo-anovulation (Gambineri et al., 2002). Obesity characterizes about 50% of women with classic PCOS, and it is even more common among adolescents (Lewy et al., 2001). PCOS has been found to result in amenorrhea and/or dysfunctional uterine bleeding in obese adolescents (Blank et al., 2006). It mainly increases the chance of abnormal menstruation, anovulation, subfertility and pregnancy loss in women

(Metwally et al., 2008). PCOS is particularly interesting as it is intimately intertwined with insulin resistance and the metabolic syndrome. The two major biochemical substances that are associated with anovulation during obesity leading to infertility are insulin and leptin (Pantasri et al., 2013; Sam et al., 2003). Ninety percent of anovulatory infertility in women is caused by PCOS and both PCOS and obesity decrease the chances of conception and the success rate of assisted reproductive techniques (Balen et al., 2007;Brewer et al., 2010). Infertility also impacts the psyche and quality of life, especially in women (Chachamovich et al., 2010; Klemetti et al., 2010).

4.6 POTENTIAL RISKS FOR THE MOTHER AND CHILD

The increasing prevalence of severe obesity in girls reaching reproductive capacity at younger ages is particularly disturbing because untreated obesity contributes to the perpetuation and spread of the disease through maternal-fetal nongenomic transmission. Although obesity causes early menarche and late menopause, severe obesity is associated with subfertility and irregular menses resulting from the PCOS with gonadal steroid imbalance (Salehi et al., 2004). Obesity also, has numerous potential detrimental effects in women who do become pregnant, including gestational diabetes, pre-eclampsia and eclampsia, pseudotumor cerebri, preterm fetal loss and stillbirth, and complicated delivery, often-requiring caesarian section. The increased caesarian rate, in itself, predisposes to increased risk of stillbirth in subsequent pregnancies (Smith et al., 2003). The relative risk of gestational diabetes is 5.2 in obese and 2.4 in overweight women compared with their lean counterparts (Sebire et al., 2001). Furthermore, the risk increases in subsequent pregnancies (MacNeil et al., 2001) and is a precursor of T2DM later in the mother's life. The relative risk

of preeclampsia is 3.3 in obese and 2.0 in overweight women, with a 12-fold relative risk in subsequent pregnancies (Lie et al., 1998). Women who have had preeclampsia die from cardiovascular disease and stroke at an alarmingly increased rate (Irgens et al., 2001). New findings have revealed that low levels of sex hormone-binding globulin, a marker of insulin resistance in obese women, are an early predictor of preeclampsia, allowing preventive treatment (Wolf et al., 2002).

In conclusion, obesity in adolescent girls has many detrimental effects on health, cardiometabolic diseases and reproduction. It is alarming and very important to develop and implement interventions at a young age in order to prevent childhood and adolescent obesity. Interventions or programs should include knowledge translation tools concerning physical activity, dietary information, how to access to psychological aid, and fitness assessment. Further longitudinal studies are needed to investigate and document the bio-psycho-social and environmental factors and there interaction, that affect the excess weight gain during the puberty period in adolescent to develop and validate new interventions and tools to promote a healthy weight in girls.

CHAPTER 5: CONCLUSION

The main objective of this systematic review and meta-analysis was to underline the existing literature surrounding body weight changes during menarche transition. Of the five studies included in this review, three showed a significant increase in body weight of approximately 10kg in post-menarcheal girls compared to pre-menarcheal girls. . Furthermore, this systematic review highlights the importance of performing more longitudinal studies on larger cohorts of pre-menarcheal girls using gold standard methods to measure key phenotypes such as: weight, body composition, body fat distribution (including ectopic fat depots) caloric intake, and energy expenditure and cardiometabolic indices. We also believe that it is important to identify the bio-psychosocial, behavioral and environmental factors influencing the excess weight gain associated with menarche, as well as documenting the associated health problems. This new knowledge could be useful to develop and evaluate preventive and innovative intervention strategies to prevent obesity in young adolescent girls and women obesity. It is suggested that physical activity and nutritional guidance be considered in all type of interventions (Brown et al., 2009). Going forward, it is important to determine the healthy levels of weight gain and body fat gain during this stage of a woman's life; hence, determining which levels of weight gain exceeds the physiological needs of the body, consequently increasing the risk of obesity and associated health problems. Knowledge translation is an instrumental tool in order to help young adolescent girls to better understand the expected outcomes of puberty (menarche) and its effect on their body weight, body composition and body fat distribution. An appropriate action for the near future is to develop and evaluate strategies to educate young adolescent girls on how to integrate healthy lifestyle practice to decrease their risk of obesity

and associated health problem during the menarche transition, and to improve their quality of life.

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APPENDIX A:

JOURNAL PERMISSION

Dear Martine,

Thank you for your email. You are welcome to reference the figure in your thesis.

Best wishes
Chantal

Chantal Botha
IJO Editorial Office

From: Martine Belliveau [mailto:martine_bellivo@hotmail.com] **Sent:** 27 June 2013 18:35 **To:** International Journal of Obesity **Subject:** Requesting permission to reference figure

Hello,

I am a master's student at the University of Ottawa and I'm in the process of completing my thesis. I would like to reference a figure from an article published in your journal.

Davidsen, L., Vistisen, B., Astrup, A. (2007). Impact of menstrual cycle on determinants of energy balance: a putative role in weight loss attempts. ***International Journal of Obesity, 31,*** 1777-1785.

Could this be possible?

Thank you kindly,
Martine Belliveau

APPENDIX B:

SEARCH STRATEGY

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

---

1 exp Menarche/ (3714)
2 menarche.tw. (5291)
3 (first adj period$).tw. (2329)
4 (first adj menstra$).tw. (0)
5 1 or 2 or 3 or 4 (9074)
6 body weight/ or body weight changes/ or weight gain/ or exp overweight/ (259014)
7 (body adj weight).tw. (123675)
8 obes$.tw. (129055)
9 overweight.tw. (26116)
10 (weight adj2 gain$).tw. (38631)
11 bmi.tw. (51971)
12 (percent$ adj2 fat).tw. (7272)
13 ((body adj fat) or (body adj2 distribution) or (body adj2 composition)).tw. (31717)
14 (abdominal adj fat).tw. (3349)
15 excess weight gain.tw. (229)
16 ((fat adj mass) or (visceral adj fat)).tw. (11594)
17 or/6-16 (442008)
18 5 and 17 (1889)
19 limit 18 to (english or french) (1644)

APPENDIX C:

DATA EXTRACTION FORM

Abbreviations:

REF	References
ID	Identification
NR	Not reported
IN	Included
EX	Excluded
DB	Database

Study information:

Reviewer ID	
Reviewer, Date	
Study ID	
Study full reference	
Country of origin	
Publication type	

Study intervention basics:

Objectives	
Experimental intervention	
Outcomes measured	
Outcomes unit of measurement	

Participants:

Total #	
Sample size	
Age	
Sex	
Diagnostics criteria	
Ethnicity	
Inclusion criteria	
Exclusion criteria	
# of participants in intervention groups	
# of dropouts	

Methods:

Study design	
Study duration	
Setting	
Sample size	
Duration of treatment	
Frequency of treatment	
Length of follow-up	
# of intervention groups	
Type of intervention	
Intervention details (replicable)	

Results:

# of participants in analysis	
Statistical methods used	

Outcome:

Outcome	
Outcome definition	
Unit of measurement	
Statistics	
# of patients evaluated for this outcome	
Outcome results	
Means, SD's etc.	

Main conclusion

REVIEWER COMMENTS OR CONCERNS

Accepted or not for systematic review	

Reasons for exclusions:

Methods	
Participants	
Outcomes	
Other	

APPENDIX D:
DOWNS AND BLACK CHECKLIST

STUDY ID:
REVIEWER ID:

Downs and Black quality assessment checklist

Reporting

1. Is the hypothesis/aim/objective of the study clearly described?

Yes	1
No	0

2. Are the main outcomes to be measured clearly described in the Introduction or methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes	1
No	0

3. Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

Yes	1
No	0

4. Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1
No	0

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.

Yes	2
Partially	1
No	0

6. Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical

tests which are considered below).

Yes	1
No	0

7. Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0

8. Have all-important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

Yes	1
No	0

9. Have the characteristics of patients lost to follow-up been described?
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

Yes	1
No	0

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

Yes	1
No	0

External validity
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1
No	0
Unable to determine	0

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1
No	0
Unable to determine	0

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1
No	0
Unable to determine	0

Internal validity – bias

14. Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1
No	0
Unable to determine	0

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	1
No	0
Unable to determine	0

16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	1
No	0
Unable to determine	0

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ? Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	1
No	0
Unable to determine	0

18. Were the statistical tests used to assess the main outcomes appropriate?
The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0
Unable to determine	0

19. Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	1
No	0
Unable to determine	0

20. Were the main outcome measures used accurate (valid and reliable)?
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

Yes	1
No	0
Unable to determine	0

Internal validity - confounding (selection bias)

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and casecontrol studies where there is no information concerning the source of patients included in the study.

Yes	1
No	0
Unable to determine	0

22. Were study subjects in different intervention groups (trials and cohort studies) or were

the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	1
No	0
Unable to determine	0

23. Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1
No	0
Unable to determine	0

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	1
No	0
Unable to determine	0

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1
No	0
Unable to	0

determine	

26. Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	1
No	0
Unable to determine	0

TOTAL: /27