

**Title:** Early menarche and blood pressure in adulthood: systematic review and meta-analysis

**Authors:** Bubach S. **\*\*Professor of Public Health\*\***<sup>1,2</sup>, Loret De Mola C. **\*\*Professor of Epidemiology\*\***<sup>3</sup>, Hardy R. **\*\*Professor of Epidemiology\*\***<sup>4</sup>, Dreyfus J. **\*\*Research\*\***<sup>5</sup>, Santos A.C. **\*\*Professor of Public Health\*\***<sup>6,7</sup>, Horta B.L. **\*\*Professor of Epidemiology\*\***<sup>2</sup>

<sup>1</sup> Department of Health Sciences, Federal University of Espírito Santo, São Mateus, 29932-540, Brazil

<sup>2</sup> Postgraduate Programme in Epidemiology, Federal University of Pelotas, Pelotas, 96020-220, Brazil

<sup>3</sup> Department of Nursing, Federal University of Pelotas, Pelotas, 96010-610, Brazil

<sup>4</sup> MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, WC1B 5JU, United Kingdom

<sup>5</sup> School of Public Health, University of Minnesota, Minneapolis, MN 55455, United States

<sup>6</sup> EPI-Unit, Institute of Public Health, University of Porto, Porto, 4050-600, Portugal

<sup>7</sup> Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, 4200-319, Portugal

Address correspondence to Susana Bubach, E-mail: sbubach@gmail.com

## **Abstract**

**Background:** It has been reported that early menarche is associated with high blood pressure and hypertension. However, some studies have failed to observe such association. We carried out a systematic review and meta-analysis on the association of early menarche with hypertension and high blood pressure in adulthood. **Methods:** PUBMED, SciELO, Scopus and LILACS databases were searched. Studies that evaluated the association of early menarche with hypertension or high blood pressure, among women aged 20 years or more were included. Random effects models were used to pool the estimates. Meta-regression was used to evaluate the contribution of different co-variables to heterogeneity. **Results:** We identified 17 studies with 18 estimates on the association of early menarche with hypertension and high blood pressure. The odds of hypertension/high blood pressure was higher among women with early menarche [pooled (OR):1.25; 95% Confidence Interval (CI): 1.17-1.34;  $p < 0.001$ ]. In the meta-regression analysis, studies evaluating 1500 subjects or more had a higher pooled OR [1.27; 95%CI (1.19;1.36)] than those with less participants. Although funnel plots showed some asymmetry, Egger tests were not statistically significant. Therefore, it is unlikely that the observed association was to publication bias. **Conclusions:** Early menarche is associated with hypertension among adult woman.

**Keywords:** menarche; puberty; hypertension; blood pressure; review; meta-analysis

## **Introduction**

Worldwide, the prevalence of early menarche ( $\leq 11$  years) has increased<sup>1-7</sup>. It has been suggested that early menarche could be associated with a higher risk of obesity<sup>8</sup> and the development of metabolic cardiovascular risk factors<sup>9-12</sup>.

For example, Lakshman *et al.* (ref. 9) reported that early menarche was associated with high systolic and diastolic blood pressure and risk of hypertension. Heys *et al.* (ref. 13), evaluated Chinese women aged 50 or more, and also reported that the odds of high blood pressure was higher among women who had early menarche ( $\leq 12.5$  years) [Odds ratio (OR): 1.34 (95% Confidence Interval (CI): 1.09; 1.65)] in comparison to those whose age at menarche was  $\geq 14.5$  years. Another study, in the United Kingdom<sup>14</sup>, also observed among woman aged between 40 and 69 years that early menarche ( $\leq 11$  years) was associated with higher odds of hypertension [OR:1.13 (95% CI: 1.10; 1.16)], in relation to those whose menarche was at 13 years.

However, other studies have failed to observe such association<sup>12-15</sup>. Previous systematic review on the association between age at sexual maturation and cardiometabolic risk factors (Prentice; Viner, 2013) reported that there was an increased risk of high blood pressure among those who mature early, but the studies were heterogeneous and some of them assessed men and women. Besides that given the heterogeneity among the studies examining the association of early age at menarche with hypertension and high blood pressure among adult woman, we decided to carry out a systematic review and meta-analysis. Furthermore, we evaluated whether design related characteristics were associated with the heterogeneity among the studies.

## **Materials and methods**

Following the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis)<sup>16</sup>, two researchers (SB, CLM) carried out independent electronic searches on the PUBMED, SciELO, Scopus, and LILACS databases covering the entire period of each database (last access on March 16, 2016), with no language restrictions, following the study protocol.

We included studies that assessed the association of early menarche with systolic and/or diastolic blood pressure or hypertension/high blood pressure among women aged 20 years and older. If the study compared more than two groups of age at menarche, the

extremes were compared, i.e., the lowest (early) with the highest menarche age category (late), which was the reference category. Studies that analyzed the association in specific groups, such as women with polycystic ovary syndrome, hirsutism, hyperandrogenia<sup>17-19</sup>, lupus<sup>20</sup>, anorexia<sup>21</sup>, type-1 diabetes<sup>22</sup>, Turner's syndrome<sup>23</sup>, pregnant<sup>24</sup>, or athletes<sup>25</sup> were excluded.

In the literature search, each of the menarche terms (menarche; menstrual; maturation; puberty; menstruation) were combined with the blood pressure terms 'blood pressure', hypertension, hypotension, systolic, diastolic, arterial. In the LILACS database, we used the term "pressure" instead of "blood pressure", because the later was not accepted. The databases do not provide universal coverage of the published studies. For this reason, we searched different databases, decreasing the likelihood of missing eligible manuscripts.

After excluding the duplicates, titles and abstracts were perused in order to exclude the clearly irrelevant studies. This process was done by two researchers independently. The remaining full texts were assessed and only those meeting the inclusion criteria were included in the meta-analysis. The selection of studies was carried out, independently, by two researchers. Disagreements were solved by consensus. In addition, we perused the reference lists of the included studies and searched for studies citing the included manuscripts.

Figure 1 shows the study selection flow diagram based on PRISMA<sup>16</sup> recommendations. If the study explored the association between early menarche and blood pressure, but did not report the corresponding measures of association or did not provide the appropriate estimate, we requested the information from the authors. We contacted authors of 13 manuscripts that appeared to have the data required to be included in the meta-analysis: three<sup>26-28</sup> provided the requested information, one<sup>29</sup> did not have access to data for further analysis, one evaluated the same studied population as another study<sup>30</sup> included in the review, and others did not return the mail or did not provide data. Therefore, six<sup>26-29,31-32</sup> were included in this meta-analysis.

Two researchers independently extracted the data from the included studies, using an electronic form. The forms were compared and disagreements were solved by consensus. Study quality was not assessed. But, we extracted information on the following methodological characteristics that could be source of heterogeneity among

the studies<sup>33</sup>: year of publication, sample size, country of data collection, study design, type of population studied (e.g. population-base, hospital or professional category), early and late menarche age categories, source of information on menarche age, age at assessment of blood pressure, length of recall of information on age at menarche, losses to follow-up, control for confounding, blood pressure measurement (e.g. techniques and methods of measurement, type of equipment), definition of hypertension, and effect measures.

Separate analyses were performed for the studies that reported the mean difference in systolic or diastolic blood pressure and for those that reported the odds ratio for hypertension (or high blood pressure, at least >130/85mmHg), comparing women who presented early menarche with those having menarche at an older age. Initially, studies were combined using fixed effects models and heterogeneity was assessed using Q test and  $I^2$ . If the Q test was statistically significant or  $I^2$  was >50%, estimates were pooled using random effects models<sup>34</sup>. Meta-regression was used to assess the contribution of co-variables (sample size, study design, early and later menarche age categories, adjustment for confounders) to the heterogeneity among the studies. The percentage of the variance of the heterogeneity that was explained by the co-variables was estimated. If the inclusion of the co-variable increased the heterogeneity, the estimate on the change in the measure of heterogeneity was truncated to zero. Funnel plot and Egger test were employed to investigate the possibility of publication bias. The analyses were carried out using the software Stata® version 12.1 for Windows.

## **Results**

We identified 21,088 records and, after duplicates were excluded, 14,322 titles and abstracts were evaluated. Of these, 47 texts were selected for full-text reading and 13 manuscripts were included in our review. Additionally, we included four of six papers, which were identified in the search of reference lists and studies citing the manuscripts identified in the electronic search. Therefore, 17 studies<sup>9,12-15,26-32,35-39</sup> were included in the meta-analysis. Figure 1 shows the study selection flow chart.

Table 1 presents the main characteristics of the included studies. Two were published before 2007, 11 were carried out in high income countries, 11 were cohort studies, and

one was a birth cohort. Thirteen studies defined early menarche as age less than or equal to 11 years.

The length of recall of age at menarche was heterogeneous, ranging from less than one year to over 40 years. Eight studies adjusted the estimates for confounding factors.

Figure 2 shows that in 13 of 17 studies, early menarche increased the odds of hypertension, and four of these 13 studies had confidence intervals that included the reference. In the pooled analysis, early menarche increased the odds of hypertension/high arterial pressure [pooled random effects OR: 1.25 (95% CI: 1.17-1.34;  $p < 0.001$ )]. Heterogeneity was high ( $I^2$  84.6%).

For systolic and diastolic blood pressure, the heterogeneity was also high and the pooled random mean difference was 0.80 mmHg (95% CI: -1.52 to 3.12;  $p = 0.50$ ) ( $I^2$  87.5%) and 0.14 mmHg (95% CI: -1.17 to 1.46;  $p = 0.83$ ) ( $I^2$  84.3%) between early and later menarche categories, for systolic and diastolic blood pressure, respectively (Figures 2).

Table 2 shows that those studies whose sample size was  $\geq 1500$  reported a higher effect measure than those with smaller samples, but the difference between the categories was not statistically significant. This variable explained 15.5% of the heterogeneity among studies. Study design explained 19.4% of the heterogeneity and the cohort studies reported higher odds of hypertension than the cross-sectional ones with a statistically significant difference [pooled random effects OR: 1.29 (95% CI: 1.21-1.38;  $p < 0.001$ )  $I^2$  86.0%]. Those studies that considered an age at menarche  $\leq 11$  as early menarche, reported higher odds for hypertension/high blood pressure, compared to those that considered menarche at an age  $\leq 13$  as early menarche. Early menarche categorization explained 39.7% of the heterogeneity among the studies. The pooled random effect odds ratio was higher among those studies that adjusted the estimates for confounding variables [pooled random effects OR: 1.28 (95% CI: 1.20-1.37;  $p < 0.001$ )  $I^2$  55.9%].

When the analysis was restricted to those studies that defined early menarche as age  $\leq 11$  years old, with cohort design, and sample size  $\geq 1500$ , the pooled effect for systolic blood pressure was 1.69 mmHg (95% CI: -0.18; 3.56;  $p = 0.077$ ) and 1.34 mmHg (95% CI: 0.80; 1.88;  $p < 0.001$ ) for diastolic blood pressure.

Supplementary figures 1 to 3 shows that there was some asymmetry in the funnel plots, but the Egger tests were not statistically significant [hypertension/high blood pressure –  $p = 0.05$ ; systolic blood pressure –  $p = 0.561$ ; diastolic blood pressure –  $p = 0.302$ ).

## **Discussion**

### **Main finding of this study**

Early menarche was associated with a higher odds of hypertension in adulthood. Systolic and diastolic blood pressure levels were also higher among women who presented early menarche, but the confidence intervals included the reference. Therefore, the higher mean systolic and diastolic blood pressure among women who presented early menarche may have been due to chance. Heterogeneity among studies was high and it was observed that part of this heterogeneity derived from differences among the studies regarding sample size, study design, and categorization of age at menarche.

### **What is already known on this topic**

It has been reported an inverse association between age at menarche and blood pressure/prevalence of hypertension<sup>9,13,32,48</sup>.

Heys and colleagues<sup>13</sup> observed an increase in the odds ratio for high blood pressure in women with early menarche (<12.5 years), compared to those with late menarche ( $\geq 14$  years) (OR: 1.11; 95% CI: 1.09-1.65), even after adjusting for age, schooling and parity. Other study<sup>9</sup> also found a tendency to increase the prevalence of hypertension with a reduction in the age of menarche.

A previously published systematic review<sup>8</sup> observed that six studies reported that early sexual maturation was associated with an increased risk of high blood pressure among men and women.

### **What this study adds**

Those that defined early age at menarche as less than or equal to 11 years old<sup>9,12,14,15,26,27,29-31,35-37</sup> reported a stronger association than the ones that used higher ages as cut-off point. Such specificity in the association suggests that early menarche is associated with high blood pressure.

One explanation for the association between early menarche and hypertension could be that early menarche is associated with a higher risk of obesity<sup>40</sup> and adiposity in

adulthood<sup>41,42</sup>. In turn, obesity is associated with higher blood pressure levels<sup>43-46</sup>. Hence, the association observed in the present review might be mediated by body composition in adulthood. However, none of the studies included in this meta-analysis estimated the indirect effect of body composition in the association between early menarche and hypertension.

Besides adiposity, other mechanisms may explain this association. One such mechanism is the speed of maturational development, because blood pressure during puberty increases mainly due to the peak of growth<sup>47</sup>, which is higher among women who mature early, possibly having long-term effects on blood pressure<sup>48</sup>. Moreover, early exposure to high levels of estrogen due to early menarche can increase the risk of developing hypertension. Evidence suggests that blood pressure tends to increase in situations where serum levels of estrogen are higher, such as in the third trimester of pregnancy, use of oral contraceptive, or estrogen-based hormone replacement therapy<sup>49</sup>. On the other hand, we did not observe an association of early menarche with systolic and diastolic blood pressure. We only observed an association between early age at menarche and hypertension. This finding could be due to an effect of age at menarche only at the extremes of the blood pressure distribution, having no impact on the distribution of the variable. Besides the smaller number of studies assessing mean pressure, most of the studies identified (seven out of eight) in this meta-analysis did not adjust the estimates for anti-hypertensive medication use or exclude from the analysis women who took such medication, which may have underestimated the associations. Therefore, further studies on this subject should control the estimates for medication use or exclude women taking anti-hypertensive medications.

In addition, certain methodological characteristics may have underestimated the association. When the analysis was restricted to those studies that defined early menarche as age  $\leq 11$  years, with cohort design, and sample size  $\geq 1500$ , the pooled effect was larger [pooled effect – systolic blood pressure: 1.69 mmHg [(95% CI: -0.18; 3.56)  $I^2$  72.3%,  $p$ : 0.08].; pooled effect – diastolic blood pressure: 1.34 mmHg [(95% CI: 0.80; 1.88)  $I^2$  0%,  $p < 0.001$ ], suggesting that the heterogeneity in definition of early menarche may have underestimated the association. Furthermore, the stronger association among those studies that used a more strict definition of early menarche reinforces the evidence that early menarche may be associated with higher systolic



blood pressure. Because the confidence interval included the nullity, we cannot exclude that this association was due to chance.

In spite of a certain asymmetry in funnel plot, we believe that the observed association between early menarche and hypertension was not due to publication bias. The magnitude of the association was similar among the studies that assessed over 1500 women and <1500 women, which is the opposite of what would be expected if such bias was present<sup>50</sup>.

The definition of hypertension varied among the studies, but the observed association was not due to this heterogeneity in the definition of hypertension. Even among those studies that used the most recent criteria to define hypertension<sup>51</sup>, early menarche was associated with a higher odds of hypertension [1.31 (95% CI: 1.20; 1.43)  $I^2$  64.4%,  $p$ : 0.038].

In this systematic review and meta-analysis, we observed an association between early menarche and risk of hypertension. Evidence indicates that the body composition of adulthood is an important mediator of this association<sup>14,28</sup>. Therefore, suggesting that by blocking the development of obesity, the mechanism of action of early menarche will be blocked. Consequently, this is further evidence on the public health importance of combating obesity.

### **Limitations of this study**

The exclusion of six studies (Supplementary Table 1) that did not report quantitative data on the association of early menarche with hypertension or mean blood pressure could have biased the pooled effect away from the null, if the excluded studies did not find statistically significant associations. On the other hand, four of these studies reported that early age at menarche was associated with a high risk of hypertension or blood pressure. And, if these studies had been included in this review the pooled effect would be higher with a lower  $p$ -value. Therefore, the observed associations were not due to the exclusion of potentially eligible studies. Furthermore, late menarche was not evaluated in this review, although some papers have found that it is also associated with poor health outcomes<sup>26,31</sup>.

## **Conclusion**

In conclusion, besides the high heterogeneity among studies, the present review and meta-analysis suggests that early menarche is associated with hypertension among adult women.

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## **Authors contributions**

SB: conception and design of the study, acquisition of data, analysis and interpretation data, drafting the article, final approval of the version to be submitted; CLM: acquisition of data, analysis and interpretation data, revising it critically for important intellectual content, final approval of the version to be submitted; RH, JD, ACS: acquisition of data, revising it critically for important intellectual content, final approval of the version to be submitted; BLH: conception and design of the study, analysis and interpretation data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted.

**Conflict of interest:** Jill Dreyfus worked on this project as a student at the University of Minnesota and is currently employed as a Principal Research Scientist at Premier, Inc.

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## **Figure Legends**

**Figure 1** - Age at menarche and blood pressure flow diagram

**Figura 2** – (a) Random effects meta-analysis of odds ratio in studies that evaluating hypertension and age at menarche categorical. (b) Random effects meta-analysis of mean difference in studies that evaluating continuous systolic blood pressure and age at menarche categorical. (c) Random effects meta-analysis of mean difference in studies that evaluating continuous diastolic blood pressure and age at menarche categorical.



**Table 1** – Summary of studies included in meta-analyses

First author/ Year	Sample	Study design	Origin	Age of assessment	Menarche		Adjustment	HTN definition
					Early	Late		
Cui, 2006	37965	Cohort	Japan	40-79	≤13	≥17	No	History of HTN
Hardy, 2006 <sup>c</sup>	738	Cohort	England	53	≤12 <sup>a</sup>	≥13 <sup>a</sup>	Childhood and adult SES, BW, BMI at 7 years, MES at 53 years	BP≥130/85mmHg
					12.25 <sup>b</sup>	14.58 <sup>b</sup>	BMI and height at 7 years	-
Heys, 2007	7108	Cohort	China	50-94	<12.5	≥14.5	Age, EDU, PREG	BP≥130/85mmHg or treatment of previously diagnosed HTN
Kivimäki, 2008	794	Cohort	Finland	30-39	≤11.9	≥14	No	-
Santos, 2008	1207	Cross-sectional	Portugal	40 or more	<12	≥12	Age, MS, EDU, OC, SES, TPA, AC, SS	BP>130/80mmHg
He, 2009	101415	Cohort	USA	30-55	≤12	≥15	No	History of HTN
	100547			24-44			No	History of HTN
Lakshman, 2009	15807	Cohort	England	40-80	08-11	15-18	Age, EDU, OC, OCU, HRT, parity	Medication use
Mendoza, 2010	1975	Cross-sectional	Spain	45-78	<11	≥11	No	Medication use
Stöckl, 2011	1536	Cross-sectional	Germany	32-81	<12	>15	No	Diagnostic of HTN, medication use or BP>140/90mmHg
Aker, 2012	1423	Cross-sectional	India	29-56	<12	>13	Age, EDU, MS, TP, OCU, PREG	Diagnostic of HTN, medication use or BP≥130/85mmHg
Mueller, 2012	34022	Cohort	Singapore	45-74	≤12	≥17	No	Ever had/being physician report for high BP
Glueck, 2013	268	Longitudinal	USA	30-46	≤10	≥16	No	BP≥130/85mmHg or medication use prescribed by a physician

Dreyfus, 2015	1791	Cohort	USA	42-59	<12	≥14 <sup>a</sup>	Age, race, PHDM, OCU, SS, PAL, AC, EDU, HTN medications	BP≥130/85mmHg or medication use
						≥12 <sup>b</sup>		-
Canoy, 2015	1217840	Cohort	England	50-64	≤10	≥17	No	Ever had/being treated for HTN
Cao, 2015	1625	Longitudinal	China	54-65	<12	≥12	Age	BP≥140/90mmHg
Day, 2015	152959	Cohort	England	40-69	08/nov	13	BW, age, age <sup>2</sup>	Ever had/being physician report for HTN
Lim, 2016	4463	Cross-sectional	Korea	28-45	<12	≥16	No	BP≥130/85mmHg or medication use

<sup>a</sup>Hypertension/high blood pressure; <sup>b</sup>Systolic and diastolic blood pressure; <sup>c</sup>Birth cohort.

Abbreviation: AC: alcohol consumption; BP: blood pressure; BW: birth weight; EDU: education level; HRT: hormone replacement therapy use; HTN: hypertension; OC: occupation; OCU: oral contraceptive use; MES at 53 years: menopausal status at 53 years; MS: marital status; PAL: physical active level; PHDM: parental history of diabetes; PREG: number of pregnancies; SS: smoking status; TP: use of tobacco products TPA: total physical active.

**Table 2** – Univariate meta-regression and pooled odds ratio of hypertension and mean differences of continuous systolic and diastolic blood pressure comparing women presenting early and late menarche, in subgroups at methodological factors.

Factors <sup>a</sup>	Hypertension			Systolic blood Pressure			Diastolic blood Pressure		
	<i>N</i>	<i>OR</i> (95% <i>CI</i> )	<i>R</i> <sup>2</sup> (%)	<i>N</i>	<i>Mean difference</i> (95% <i>CI</i> )	<i>R</i> <sup>2</sup> (%)	<i>N</i>	<i>Mean difference</i> (95% <i>CI</i> )	<i>R</i> <sup>2</sup> (%)
<b>Sample size</b>									
<1500	4	1.05 (0.87; 1.27)	15.5	4	1.48 (-0.92; 3.88)	0	4	0.12 (-1.65; 1.90)	0
≥ 1500	13	1.27 (1.19; 1.36)		4	0.22 (-3.63; 4.07)		4	0.17 (-1.93; 2.25)	
<b>Study design</b>									
Cohort	12	1.29 (1.21; 1.38)	19.4	4	2.03 (0.70; 3.36)	7.64	4	0.91 (-0.31; 2.13)	0
Cross-sectional	5	0.91 (0.65; 1.28)		4	-0.34 (-4.89; 4.20)		4	-0.43 (-2.64; 1.78)	
<b>Early age at menarche, years</b>									
≤11	13	1.33 (1.25; 1.41)	39.7	6	0.29 (-2.50; 3.07)	0	6	0.18 (-1.28; 1.63)	0
≤13	4	1.11 (0.95; 1.31)		2	3.02 (0.47; 5.57)		2	-0.06 (-4.76; 4.65)	
<b>Menarche at older age category, years</b>									
≥ 12	6	1.27 (1.17; 1.38)	0	2	0.45 (-3.01; 3.91)	0	2	0.18 (-1.74; 2.10)	0
≥ 14	11	1.24 (1.12; 1.38)		6	0.93 (-2.00; 3.86)		6	0.12 (-1.62; 1.85)	
<b>Adjustment for confounders</b>									
Yes	8	1.28 (1.20; 1.37)	0	4	1.37 (-0.03; 2.76)	0	4	0.61 (-0.78; 2.00)	0
No	9	1.20 (1.05; 1.37)		4	-0.21 (-4.54; 4.11)		4	-0.16 (-2.52; 2.20)	

<sup>a</sup>The reference category is a second in each factor.

Abbreviation: OR: odds ratio, 95% CI: 95% confidence interval, R<sup>2</sup> (%): % heterogeneity explained, N: number of studies. Mean difference expressed in mmHg.