Maternal and Child Health Journal (2019) 23:356–368
https://doi.org/10.1007/s10995-018-2650-7

Early Menstrual Factors Are Associated with Adulthood Cardio-Metabolic Health in a Survey of Mexican Teachers

Erica C. Jansen[1] · Dalia Stern[2] · Karen E. Peterson[1] · Martin Lajous[3,4] · Ruy López-Ridaura[3]

Published online: 30 January 2019

Abstract

Objectives To evaluate whether age at menarche and time to menstrual regularity were related to cardio-metabolic risk factors in Mexican women. *Methods* The study population comprised 54,921 women from the 2008–2010 wave of the Mexican Teacher's Cohort. A modified Poisson approach was used; exposures were age at menarche and time to menstrual regularity (< 1 year vs. ≥1 year), and outcomes were prevalent obesity, type 2 diabetes, high blood pressure, and high cholesterol. *Results* Mean (SD) age of women was 42.1 (7.6) years, and mean (SD) menarcheal age was 12.5 (1.5) years. Compared to women with menarche age 13 years, those with menarche < 9 years had a 65% (95% CI 43–90%); 27% (95% CI 4–55%); and 23% (95% CI 1–49%) higher prevalence of obesity, high blood pressure, and high cholesterol, respectively. For diabetes, there was a U-shaped association; compared to menarche age 13 years, those with menarche < 9 years had an 89% higher prevalence of diabetes (95% CI 39–156%), and those with menarche ≥ 17 years had a 65% higher prevalence (95% CI 16–134%). Among women with regular cycles (n = 43,113), a longer time to menstrual regularity was associated with diabetes (PR = 1.11 with 95% CI 1.02–1.22), high blood pressure (PR = 1.11 with 95% CI 1.06–1.17), and high cholesterol (PR = 1.09 with 95% CI 1.04–1.14). *Conclusions for practice* Mexican women with earlier and later ages at menarche and/or longer time to menstrual regularity may have higher risk of cardio-metabolic disease in adulthood.

Keywords Menarche · Time to menstrual regularity · Obesity · Type 2 diabetes · High blood pressure · High cholesterol

Significance

What is already known on this subject? Existing studies from mostly European, US, or Asian populations have reported that an earlier age at menarche predicts cardio-metabolic risk in adulthood, yet evidence from Hispanic populations is lacking. Further, there is inconsistent evidence on whether later age at menarche is also associated with cardio-metabolic health in adulthood. Finally, whether the time from menarche to regular menstrual cycling is independently related to cardio-metabolic outcomes has not been examined.

What this study adds? Using a large dataset of Mexican schoolteachers, we found that an earlier age at menarche was predictive of obesity, diabetes, high blood pressure, and high cholesterol, and a later age at menarche was predictive of diabetes prevalence only. Further, among women who ever had regular menstrual cycles, a longer time from menarche to regular menstrual cycling was associated with slightly higher prevalence of adverse cardio-metabolic health outcomes, even after accounting for age at menarche.

Introduction

Early identification and prevention of cardio-metabolic disease is a public health priority in Mexico and other countries in nutritional transition, where rates of

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10995-018-2650-7) contains supplementary material, which is available to authorized users.

✉ Ruy López-Ridaura
rlridaura@insp.mx

1 Department of Nutritional Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA

2 CONACyT-Center for Research on Population Health, National Institute of Public Health, Cuernavaca, Mexico

3 Center for Research on Population Health, National Institute of Public Health, Cuernavaca, Mexico

4 Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA

overweight, obesity and diabetes are extremely high and likely to increase in coming years (Meza et al. 2015; Palloni et al. 2015). The timing of menarche, a female's first menstrual period, is one early life factor that could predict cardio-metabolic risk later in life (Prentice and Viner 2013). Studies among women from Europe (Canoy et al. 2015; Peters et al. 2015), Asia (Lim et al. 2016; Won et al. 2016), the US (Dreyfus et al. 2015, 2012; Glueck et al. 2013), and Brazil (Mueller et al. 2014) have reported associations between age at menarche and cardio-metabolic risk factors including obesity, metabolic syndrome, and diabetes; although the nature and extent of these associations have not been consistent. For instance, some studies in the US and UK reported that both an earlier and a later age at menarche were positively related to diabetes and metabolic syndrome (Canoy et al. 2015; Dreyfus et al. 2012), whereas other studies conducted in the US (Dreyfus et al. 2015), Korea (Lim et al. 2016), and Brazil (Mueller et al. 2014) found that only an earlier age at menarche was associated with higher diabetes-related risk and metabolic syndrome. In addition, at least one US study found much stronger associations between earlier menarche and insulin resistance-related conditions among White women than among African American women (Dreyfus et al. 2015), highlighting the potential for differences by race/ethnicity. Whether age at menarche is an early determinant of cardio-metabolic risk factors in later life among Mexican women has not been determined.

Other characteristics of early menstruation might also be informative about later disease risk. The time to menstrual regularity is the amount of time it takes from the occurrence of the first menstrual period to when the menstrual cycles occur with predictable frequency (if ever). Given the fact that menstrual cycle regularity in adulthood is a predictor of cardio-metabolic abnormalities (Rostami Dovom et al. 2016), it is plausible that a longer time to menstrual regularity could be an early indication of metabolic abnormalities and predisposition to later adverse cardio-metabolic health. To our knowledge, this study question has not been previously addressed.

To address these gaps in the literature, we utilized data from the Mexican Teacher's Cohort. We first evaluated associations between early life characteristics and menstrual factors. However, our primary aims were to evaluate whether early menstrual factors-age at menarche and time to menstrual regularity-were related to cardio-metabolic risk factors present in adulthood.

Methods

Study Design and Population

The Mexican Teachers' Cohort (MTC) is a prospective study established in 2006 when 28,345 female teachers aged ≥ 35 years in the Mexican states of Jalisco and Veracruz responded to a baseline questionnaire. The cohort was expanded in 2008–2010 to teachers aged ≥ 25 years from 10 additional Mexican states, to include a total of 115,315 participants. Detailed methods are described elsewhere (Lajous et al. 2017). The study was approved by the institutional review board at the National Institute of Public Health in Mexico, and informed consent was obtained from all participants.

A total of 106,493 women responded to the 2008–2010 questionnaire. We excluded women with missing information for menarche (n = 1709). In addition, we excluded women with missing information for correlates including region of residency (n = 11,669), birth weight (n = 29,321), breastfed as an infant (n = 29,694), number of older siblings (n = 29,196), body silhouette before menarche (n = 4500), and three proxies for childhood SES: occupation of the household head (n = 25,010), participant or parents spoke an indigenous language/dialect (n = 1253), and frequency of meat consumption as a child (n = 23,300). The percentage of missing correlate data ranged between 1% (indigenous language spoken) and 28% (birthweight). In the analyses with obesity as the outcome, we further excluded women without information on current height and/or weight (n = 4262). In the time to menstrual regularity analyses, we additionally excluded women who reported never having regular menstrual cycles (n = 6221) or who did not answer the question (n = 840), yielding a final analytic sample of 43,113 women.

Exposures: Menarche and Time to Menstrual Regularity

From the 2008–2010 self-administered questionnaire, we obtained information on age at menarche and time to menstrual regularity. Women were asked to report the age of their first menstrual cycle to the nearest year (range < 9 to > 18 years). Menarche ages ≤ 9 years (y) were collapsed into one category as were menarche ages ≥ 17. Women were also asked how long it took for their period to occur at regular intervals. Six multiple-choice answers were possible: < 1 year, 1–2 years, 3–4 years, ≥ 5 years, never, and "I do not remember." As women who reported never having regular menstrual cycles may have had underlying metabolic conditions present in childhood (e.g. 18% reported having polycystic ovaries compared to 8% of women who had regular cycles within 1 years), we excluded those women from analysis. Among women who reported ever having regular periods, we categorized them into two groups: <1 years to regular menstrual cycling and ≥ 1 years to regular menstrual cycling.

Outcomes: Adult Cardio-Metabolic Disease Markers

Participants self-reported height (cm) and weight (kg) in the same 2008–2010 questionnaire. Standardized technician measurements were well correlated with self-reported weight (r = 0.92) and height (r = 0.86) in a subset of 3413 participants (Ortiz-Panozo et al. 2017). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined BMI ≥ 30 kg/m^2. Women also self-reported if they have ever been diagnosed by a physician with type 2 diabetes, high blood pressure and high cholesterol; thus, each of these were binary outcomes.

Early Life Sociodemographic and Anthropometric Covariates

Potential confounding variables were selected a priori based on knowledge of predictors of cardio-metabolic risk and from previously reported associations with menarche in other populations (Al-Sahab et al. 2011; Jansen et al. 2015). They include the following: year of birth, region of residence at birth, birth weight, breastfed as an infant, number of older siblings, occupation of the household head during infancy, participant or parents spoke an indigenous language/dialect, frequency of meat consumption as a child, and body size before menarche. Covariates were categorized as shown in Table 1.

Statistical Analysis

Associations Between Early Life Characteristics and Menstrual Factors

We first estimated average age ± SD of menarche according to categories of early life sociodemographic and anthropometric characteristics. We also conducted adjusted multivariable regression analysis with age at menarche as the continuous outcome and all sociodemographic and anthropometric variables as mutually-adjusted predictors. To evaluate associations between sociodemographic and anthropometric characteristics and time to menstrual regularity, we compared the proportion of women who took ≥ 1 year for menstrual cycles to become regular by categories of the sociodemographic and anthropometric correlates, as well as age at menarche. In adjusted analysis, we used a modified Poisson regression approach with time to menstrual cycling as a dichotomous outcome to compute prevalence ratios and 95% confidence intervals (CI). We chose the modified Poisson regression approach due to our non-rare outcome (Barros and Hirakata 2003).

Primary Analysis

To evaluate associations between age at menarche or time to menstrual regularity and adulthood cardio-metabolic risk factors, we used a modified Poisson regression approach. We ran separate models for each of the dichotomous outcomes. Adjusted models included all potential confounders except for birthweight, as adjusting for both birthweight and premenarcheal body size was deemed unnecessary. Models for time to menstrual regularity were also adjusted for age at menarche.

Due to the high degree of missingness in potential confounders, sensitivity missing-indicator analyses were conducted to assess robustness of the estimates. In this method, a category for missing values is created in each potential confounder, with the assumption that missing values are missing completely at random and that the participants within the indicator variable are unconditionally exchangeable (Toh et al. 2012). We also performed supplemental analyses in which we compared the mean values of sociodemographic and anthropometric characteristics among women with no missing information to women with at least one missing variable. To assess potential misclassification of self-reported diagnosis of diabetes, hypertension, and high cholesterol, we ran models where the outcome was receipt of treatment for these outcomes. Finally, sensitivity analyses adjusting for self-reported polycystic ovaries (PCO) in all models were conducted. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

The mean ± SD age of the women at baseline (2008–2010) was 42.1 ± 7.6 years (y). Seventy-six percent of the sample were pre-menopausal, 15% were postmenopausal, and 9% were of unknown status. The mean ± SD age at menarche was 12.5 ± 1.5 years. After mutual adjustment, an earlier age at menarche was associated with being born more recently, not being breastfed as a child, higher frequency of meat consumption as a child, a larger pre-menarcheal body size, being born in Mexico City, having fewer older siblings, and growing up in a household that did not rely on manual work or farming (Table 1).

Among the women who reported that their menstrual cycle became regular, 31.1% of women said it took ≥ 1 year. In mutually-adjusted analysis of early life factors and time to menstrual regularity, a longer time to menstrual regularity was associated with being born in Mexico City, lower

Table 1 Early life sociodemographic and anthropometric correlates of age at menarche among 54,921 Mexican teachers

Early life sociodemographic and anthropometric correlates	N	Mean ± SD age at menarche, years	Multivariable adjusted difference in menarche, years (95% CI)[a]
Year of birth			
1926–1944	195	13.13 ± 1.63	0.38 (0.14, 0.62)
1945–1949	606	12.77 ± 1.54	Reference
1950–1954	1956	12.71 ± 1.52	− 0.07 (− 0.21, 0.07)
1955–1959	6403	12.63 ± 1.53	− 0.16 (− 0.29, − 0.04)
1960–1964	15,814	12.57 ± 1.51	− 0.22 (− 0.34, − 0.10)
1965–1969	12,687	12.51 ± 1.48	− 0.26 (− 0.38, − 0.14)
1970–1974	7698	12.40 ± 1.49	− 0.35 (− 0.47, − 0.23)
1975–1979	6843	12.31 ± 1.47	− 0.43 (− 0.56, − 0.31)
≥1980	2719	12.23 ± 1.43	− 0.47 (− 0.60, − 0.34)
P-trend[b]		< 0.0001	< 0.0001
Region of residence at birth			
North	10,557	12.52 ± 1.48	0.13 (0.08, 0.17)
Central	12,707	12.56 ± 1.51	0.16 (0.12, 0.20)
Mexico City	9540	12.35 ± 1.50	Reference
South	22,117	12.52 ± 1.50	0.09 (0.06, 0.13)
P value		< 0.0001	< 0.0001
Birthweight			
Less than normal	3551	12.51 ± 1.60	− 0.01 (− 0.06, 0.04)
Normal	49,629	12.50 ± 1.49	Reference
Higher than normal	1741	12.37 ± 1.59	− 0.08 (− 0.15,− 0.01)
P-trend		0.002	0.29
Breastfed as an infant			
Yes	48,456	12.52 ± 1.50	Reference
No	6465	12.33 ± 1.53	− 0.10 (− 0.14, − 0.06)
P value		< 0.0001	< 0.0001
Number of older siblings			
0	14,048	12.37 ± 1.51	Reference
1	11,325	12.48 ± 1.53	0.11 (0.07, 0.14)
2	8295	12.52 ± 1.48	0.11 (0.07, 0.15)
3	6153	12.54 ± 1.50	0.09 (0.05, 0.14)
4	4650	12.61 ± 1.46	0.15 (0.10, 0.20)
5 or more	10,450	12.60 ± 1.48	0.10 (0.07, 0.14)
P trend		< 0.0001	< 0.0001
Occupation of the household head			
Retail or private sector employee	16,734	12.44 ± 1.49	Reference
Manual worker or farmer	19,853	12.67 ± 1.49	0.12 (0.09, 0.15)
Government employee or teacher	12,749	12.33 ± 1.50	− 0.08 (− 0.11, − 0.04)
Other	5585	12.47 ± 1.52	− 0.01 (− 0.06, 0.03)
P value		< 0.0001	< 0.0001
Parents or participant spoke indigenous language			
Yes	3848	12.67 ± 1.50	0.10 (0.05, 0.15)
No	51,073	12.49 ± 1.50	Reference
P value		< 0.0001	< 0.001
Frequency of meat consumption as a child			
Never or < 1 time per month	2645	12.84 ± 1.55	Reference
1–3 times per month	8620	12.62 ± 1.51	− 0.14 (− 0.20, − 0.07)
1 time per week	15,881	12.55 ± 1.48	− 0.19 (− 0.25, − 0.13)

Table 1 (continued)

Early life sociodemographic and anthropometric correlates	N	Mean ± SD age at menarche, years	Multivariable adjusted difference in menarche, years (95% CI)[a]
2–4 times per week	22,510	12.41 ± 1.49	− 0.28 (− 0.34, − 0.22)
5–6 times per week	3611	12.35 ± 1.55	− 0.34 (− 0.42, − 0.27)
≥ 1 time per day	1654	12.44 ± 1.54	− 0.27 (− 0.36, − 0.18)
P-trend		< 0.0001	< 0.0001
Body size before menarche[c]			
Figure 1 (slimmest)	23,420	12.63 ± 1.51	0.23 (0.20, 0.27)
Figure 2	12,375	12.55 ± 1.45	0.16 (0.12, 0.20)
Figure 3	9747	12.38 ± 1.46	Reference
Figure 4	6104	12.20 ± 1.51	− 0.17 (− 0.21, − 0.11)
Figure 5	1288	12.33 ± 1.51	− 0.01 (− 0.09, 0.08)
Figure 6	816	12.26 ± 1.56	− 0.06 (− 0.17, 0.05)
Figure 7	886	12.27 ± 1.66	− 0.05 (− 0.15, 0.05)
Figure 8	228	12.25 ± 1.72	− 0.06 (− 0.26, 0.13)
Figure 9 (largest)	57	12.60 ± 1.96	0.29 (− 0.09, 0.68)
P-trend		< 0.0001	< 0.0001

CI confidence interval

Data come from the Mexican Teachers' Cohort, a prospective study of 115,315 female teachers', initiated in 2006–2008 among women from two states and expanded in 2008 to include women from 10 additional states across Mexico. After exclusions, the final study population included 54,921 women (complete case analysis)

[a]From a linear regression model adjusted for all other covariates, with the exception that in the model for birthweight, the variables for breastfeeding and pre-menarcheal body size were not included because they are potential intermediates on the causal pathway

[b]For ordinal predictors, a P test for trend was obtained by including in the linear regression model a continuous variable representing the ordinal categories of the predictor. For nominal correlates, a type III Wald test was used

[c]Based on 9 pictorial figures, with 1 corresponding to the slimmest figure and 9 to the largest figure

birthweight, not being breastfed as a child, smaller number of older siblings, lower frequency of meat consumption as a child, larger body size before menarche, and later age at menarche (Table 2).

In 2008–2010, 24.1% of the women were obese, 4.9% had type 2 diabetes, 14.8% had high blood pressure, and 16.8% had high cholesterol. The age at menarche was inversely and monotonically associated with prevalence of obesity (Table 3). After adjustment for potential confounders, women whose menarche occurred at 9 or less y of age had a 65% higher prevalence of obesity than women with menarche at age 13 y (95% CI 43–90%; P < 0.0001). After adjustment for potential confounders, every year later of menarche was associated with 0.38 lower BMI (95% CI 0.35–0.40; P-trend < 0.0001). There was a U-shaped association between age at menarche and diabetes (Fig. 1), with the highest prevalence of diabetes among those with the earliest and latest ages at menarche. After confounder adjustment, women with menarche ≤ 9 years had an 89% higher prevalence of diabetes (95% CI 43–90%; P < 0.0001) and women with menarche ≥ 17 years had a 65% higher prevalence of diabetes (95% CI 16–134%; P = 0.005) than women with menarche at 13 years. Earlier ages at menarche were associated with higher prevalence of high blood pressure and high cholesterol in adulthood, although these associations were of lower magnitude than those with obesity and diabetes. After adjustment for confounders, women with a menarche ≤ 9 years of age had a 27% higher prevalence of high blood pressure than women with a menarche of 13 y (95% CI 4–55%; P = 0.02). Similarly, women with a menarche ≤ 9 years of age had a 23% higher prevalence of high cholesterol than women with a menarche of 13 years (95% CI 1–49%; P = 0.04).

Taking longer to reach menstrual regularity was positively associated with prevalence of diabetes, high blood pressure, and high cholesterol (Table 4). In adjusted analysis, women who took ≥ 1 y after menarche to have regular menstrual cycles had a 13% higher prevalence of diabetes (95% CI 3–23%; P-trend < 0.0001), an 11% higher prevalence of high blood pressure (95% CI 6–17%; P-trend < 0.0001), and an 11% higher prevalence of high cholesterol (95% CI 6–16%; P-trend < 0.001) than women who experienced regular menstrual cycles < 1 year after menarche. Time to menstrual regularity was not associated with prevalence of obesity in adulthood. Supplemental analysis investigating associations between categories of time to menstrual

Table 2 Early life correlates of greater time to menstrual regularity (≥ 1 year) among 43,113 Mexican teachers

Early life sociodemographic and anthropometric correlates	N	Proportion of women with time to menstrual regularity ≥ 1 year	Unadjusted Prevalence Ratio (95% CI)[a]	Adjusted Prevalence Ratio (95% CI)[b]
Year of birth				
1926–1949	616	32.3	1.10 (0.95, 1.26)	1.10 (0.96, 1.26)
1950–1954	1550	29.5	Reference	Reference
1955–1959	5070	30.9	1.05 (0.96, 1.14)	1.05 (0.97, 1.15)
1960–1964	12,624	30.9	1.05 (0.97, 1.14)	1.07 (0.98, 1.16)
1965–1969	9994	31.4	1.07 (0.98, 1.16)	1.07 (0.98, 1.16)
1970–1974	5903	32.1	1.09 (1.00, 1.19)	1.07 (0.99, 1.17)
1975–1979	5250	29.9	1.02 (0.93, 1.11)	1.01 (0.93, 1.11)
≥ 1980	2106	31.7	1.08 (0.97, 1.19)	1.07 (0.97, 1.18)
P-trend[c]			< 0.0001	0.76
Region of residence at birth				
North	8511	25.4	0.79 (0.75, 0.82)	0.80 (0.76, 0.83)
Central	10,148	28.8	0.69 (0.66, 0.73)	0.70 (0.67, 0.73)
Mexico City	7716	36.6	Reference	Reference
South	16,738	32.8	0.89 (0.86, 0.93)	0.89 (0.85, 0.92)
P value			< 0.0001	< 0.0001
Birthweight				
Less than normal	2716	33.4	1.03 (1.02, 1.14)	1.06 (1.00, 1.12)
Normal	39,056	31.0	Reference	Reference
Higher than normal	1341	28.6	1.04 (0.85, 1.01)	0.95 (0.87, 1.03)
P-trend			< 0.0001	0.01
Breastfed as an infant				
Yes	68,094	30.9	Reference	Reference
No	5019	32.4	1.05 (1.02, 1.09)	1.04 (1.00, 1.09)
P-trend			< 0.0001	0.05
Number of older siblings				
0	10,898	33.2	Reference	Reference
1	8901	31.5	0.95 (0.91, 0.99)	0.95 (0.91, 0.99)
2	6560	30.3	0.91 (0.87, 0.95)	0.91 (0.87, 0.96)
3	4822	30.4	0.91 (0.87, 0.95)	0.92 (0.88, 0.97)
4	3664	30.3	0.91 (0.86, 0.96)	0.92 (0.87, 0.97)
5 or more	8268	29.0	0.87 (0.84, 0.91)	0.89 (0.85, 0.93)
P-trend			< 0.0001	< 0.0001
Occupation of the household head				
Retail or private sector employee	13,305	31.2	Reference	Reference
Manual worker or farmer	1541	30.5	0.98 (0.95, 1.01)	0.99 (0.96, 1.03)
Government employee or teacher	9994	32.1	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)
Other	4323	30.4	0.98 (0.93, 1.03)	0.99 (0.94, 1.05)
P value			0.06	0.55
Parents or participant spoke indigenous language				
Yes	2850	34.1	1.11 (1.05, 1.17)	1.04 (0.98, 1.10)
No	40,263	30.9	Reference	Reference
P value			0.002	0.18
Frequency of meat consumption as a child				
Never or < 1 time per month	1983	34.7	Reference	Reference
1–3 times per month	6743	33.0	0.95 (0.89, 1.02)	0.94 (0.88, 1.01)
1 time per week	12,399	30.8	0.89 (0.83, 0.95)	0.88 (0.83, 0.94)
2–4 times per week	17,865	30.5	0.88 (0.82, 0.94)	0.87 (0.81, 0.93)

Table 2 (continued)

Early life sociodemographic and anthropometric correlates	N	Proportion of women with time to menstrual regularity ≥ 1 year	Unadjusted Prevalence Ratio (95% CI)[a]	Adjusted Prevalence Ratio (95% CI)[b]
5–6 times per week	2862	30.4	0.88 (0.81, 0.95)	0.87 (0.80, 0.95)
≥ 1 time per day	1261	27.3	0.79 (0.71, 0.88)	0.80 (0.72, 0.89)
P-trend			< 0.0001	< 0.0001
Body size before menarche[d]				
Figure 1	18,560	31.1	1.02 (0.98, 1.07)	1.03 (0.99, 1.07)
Figure 2	9809	30.2	0.99 (0.95, 1.04)	1.00 (0.95, 1.04)
Figure 3	7584	30.4	Reference	Reference
Figure 4	4688	32.5	1.07 (1.01, 1.13)	1.07 (1.01, 1.13)
Figure 5	980	33.7	1.11 (1.01, 1.22)	1.11 (1.01, 1.22)
Figure 6	611	32.9	1.08 (0.96, 1.22)	1.09 (0.97, 1.22)
Figure 7	667	32.5	1.07 (0.95, 1.20)	1.09 (0.97, 1.22)
Figure 8 or 9	214	36.5	1.20 (1.00, 1.44)	1.21 (1.01, 1.44)
P-trend			0.02	0.03
Age at menarche, years				
≤ 9	442	33.5	1.08 (0.94, 1.23)	1.07 (0.93, 1.22)
10	2620	31.9	1.03 (0.96, 1.09)	1.01 (0.94, 1.07)
11	7884	30.6	0.98 (0.94, 1.03)	0.97 (0.92, 1.07)
12	12,946	28.9	0.93 (0.89, 0.97)	0.92 (0.88, 0.96)
13	8628	31.1	Reference	Reference
14	6124	31.1	1.00 (0.95, 1.05)	1.00 (0.96, 1.05)
15	3622	35.7	1.15 (1.09, 1.21)	1.14 (1.08, 1.20)
16	557	42.7	1.38 (1.24, 1.52)	1.35 (1.22, 1.49)
≥17	290	50.7	1.63 (1.45, 1.84)	1.60 (1.43, 1.80)
P-trend			< 0.0001	< 0.0001

CI confidence interval

Data come from the Mexican Teachers' Cohort, a prospective study of 115,315 female teachers', initiated in 2006–2008 among women from two states and expanded in 2008 to include women from 10 additional states across Mexico. After exclusions, the final study population included 43,113 women (complete case analysis)

[a]Estimates were obtained using a modified Poisson regression approach, with time to menstrual regularity (< 1 or ≥ 1 year) as a dichotomous outcome and early life characteristics as categorical variables. A Poisson distribution with a log link and robust error variance were specified for each model

[b]Adjusted for all other covariates except for age at menarche because it is a potential intermediate on the causal pathway. In the model for birthweight, the variables for breastfeeding and pre-menarcheal body size were not included because they are potential intermediates on the causal pathway

[c]For ordinal predictors, a P test for trend was obtained by including in the modified Poisson regression model a continuous variable representing the ordinal categories of the predictor. For nominal correlates, a type III Wald test was used

[d]Based on 9 pictorial figures, with 1 corresponding to the slimmest figure and 9 to the largest figure

regularity and cardio-metabolic risk factors showed that longer time to menstrual regularity was linearly associated with high blood pressure, high cholesterol, and diabetes, but not obesity (Online Resource 3). Analysis that included women who never had regular menstrual cycles showed similar trends (data not shown).

Sensitivity analyses using missing indicators for missing covariates did not substantially alter findings (available upon request). Furthermore, a comparison of mean values of sociodemographic and anthropometric characteristics among women with no missing information compared to women with at least one missing covariate did not reveal notable differences (Online Resources 1 and 2). In sensitivity analysis that replaced self-reported diabetes, high blood pressure, or high cholesterol with whether or not the woman had received treatment for these conditions, associations were either similar or slightly strengthened. Finally, sensitivity analyses accounting for PCO did not alter estimates.

Table 3 Prevalence of cardiovascular disease risk factors among 54,921 Mexican teachers according to age at menarche

Cardio-metabolic risk factor	Age of menarche, years	N	Prevalence of outcome	Unadjusted prevalence ratio (95% CI)[a]	Adjusted prevalence ratio (95% CI)[b]
Obesity					
	≤ 9	542	38.9	1.69 (1.27, 2.26)	1.65 (1.43, 1.90)
	10	3081	36.2	1.53 (1.29, 1.80)	1.50 (1.39, 1.61)
	11	9277	29.0	1.36 (1.19, 1.55)	1.30 (1.23, 1.38)
	12	15,170	23.8	1.18 (1.04, 1.34)	1.09 (1.04, 1.15)
	13	10,131	21.7	Reference	Reference
	14	7033	19.6	1.04 (0.89, 1.22)	0.92 (0.86, 0.98)
	15	4317	18.7	0.93 (0.78, 1.13)	0.88 (0.82, 0.96)
	16	730	16.7	0.79 (0.43, 1.43)	0.78 (0.65, 0.94)
	≥ 17	378	24.9	1.07 (0.72, 1.57)	1.10 (0.89, 1.35)
	P, trend[c]			< 0.0001	< 0.0001
Diabetes					
	≤ 9	569	7.9	1.75 (1.31, 2.35)	1.89 (1.39, 2.56)
	10	3341	6.7	1.49 (1.28, 1.74)	1.49 (1.28, 1.75)
	11	9993	5.4	1.19 (1.06, 1.34)	1.28 (1.13, 1.44)
	12	16,453	4.7	1.03 (0.93, 1.15)	1.10 (0.98, 1.23)
	13	11,006	4.5	Reference	Reference
	14	7670	4.5	1.00 (0.88, 1.15)	0.99 (0.86, 1.13)
	15	4690	4.1	0.90 (0.77, 1.06)	0.87 (0.74, 1.03)
	16	785	5.4	1.18 (0.87, 1.61)	1.09 (0.79, 1.49)
	≥ 17	414	8.2	1.82 (1.30, 2.53)	1.65 (1.16, 2.34)
High BP					
	≤ 9	569	18.1	1.19 (0.97, 1.45)	1.27 (1.04, 1.55)
	10	3341	18.3	1.20 (1.09, 1.31)	1.22 (1.11, 1.34)
	11	9993	15.1	0.99 (0.92, 1.06)	1.05 (0.98, 1.13)
	12	16,453	14.2	0.93 (0.88, 0.99)	0.98 (0.92, 1.05)
	13	11,006	15.2	Reference	Reference
	14	7670	13.5	0.89 (0.82, 0.96)	0.88 (0.81, 0.95)
	15	4690	14.4	0.94 (0.86, 1.03)	0.92 (0.84, 1.01)
	16	785	14.4	0.94 (0.78, 1.14)	0.88 (0.73, 1.07)
	≥ 17	414	14.7	0.97 (0.75, 1.25)	0.93 (0.72, 1.20)
	P, trend			< 0.0001	< 0.0001
High cholesterol					
	≤ 9	569	18.5	1.12 (0.92, 1.36)	1.23 (1.01, 1.49)
	10	3341	17.0	1.03 (0.94, 1.13)	1.08 (0.98, 1.18)
	11	9993	17.0	1.03 (0.97, 1.10)	1.09 (1.02, 1.17)
	12	16,453	15.8	0.96 (0.91, 1.02)	1.01 (0.95, 1.07)
	13	11,006	16.5	Reference	Reference
	14	7670	15.5	0.94 (0.88, 1.01)	0.93 (0.87, 1.00)
	15	4690	15.9	0.96 (0.89, 1.05)	0.94 (0.86, 1.02)
	16	785	16.6	1.01 (0.84, 1.20)	0.94 (0.79, 1.13)
	≥ 17	414	19.1	1.16 (0.93, 1.45)	1.13 (0.90, 1.42)
	P, trend			< 0.0001	< 0.0001

CI confidence interval, *BP* blood pressure

Data come from the Mexican Teachers' Cohort, a prospective study of 115,315 female teachers', initiated in 2006–2008 among women from two states and expanded in 2008 to include women from 10 additional states across Mexico. After exclusions, the final study population included 54,921 women (complete case analysis)

Table 3 (continued)

[a]Estimates were obtained using a modified Poisson regression approach, with cardio-metabolic risk factor as a dichotomous outcome and age at menarche as a categorical variable. A Poisson distribution with a log link and robust error variance were specified for each model

[b]Adjusted for birth cohort, region of birth, occupation of household head during childhood, indigenous language spoken, breastfed as an infant, frequency of meat consumption as a child, body size before menarche, and number of older siblings

[c]A P test for trend was obtained by including age at menarche in the modified Poisson regression model as a continuous variable

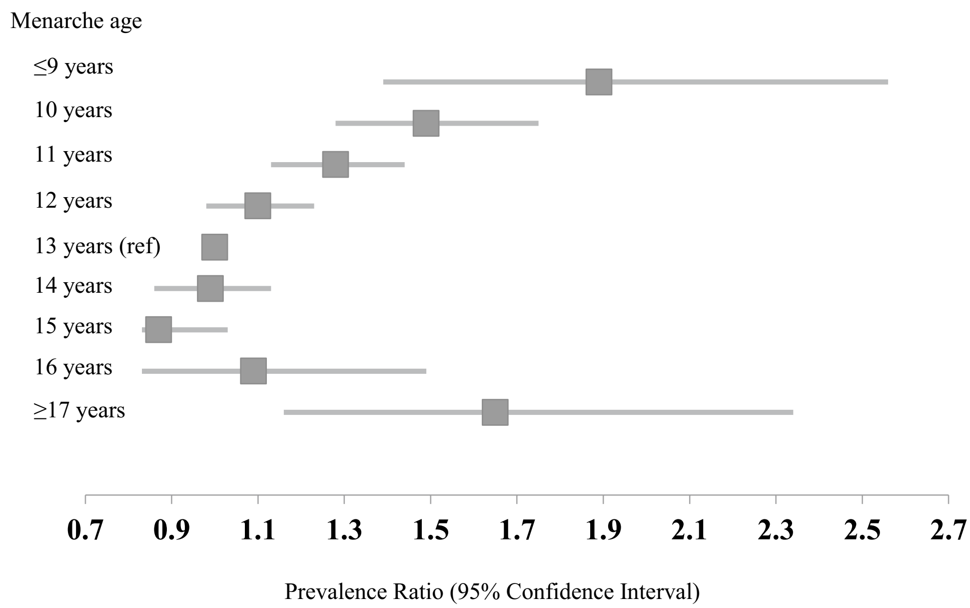

Fig. 1 Prevalence of Type 2 Diabetes by Age at Menarche among Mexican Teachers

Discussion

In this cross-sectional analysis of a large cohort of Mexican teachers, we found that self-reported age at menarche was associated with cardio-metabolic disease markers in adulthood. Specifically, we found that earlier age at menarche was associated with higher prevalence of obesity, high blood pressure, and high cholesterol in a linear fashion, while both earlier and later ages at menarche were related to higher prevalence of diabetes. Among women who reported achieving menstrual regularity, a longer time to menstrual regularity was a predictor of diabetes, high blood pressure, and high cholesterol independently of age at menarche and other confounders, although the magnitudes of these associations were modest. In this analysis, we also found that a number of early life socioeconomic and nutritional factors were associated with age at menarche and menstrual regularity; in particular, factors associated with higher SES during childhood were related to earlier age at menarche. Altogether, the findings indicate that age at menarche and, to some extent, time to menstrual regularity are salient markers of adult cardio-metabolic risk in the Mexican female population.

Our finding that an earlier age at menarche is related to higher prevalence of cardio-metabolic risk factors among Mexican women is in line with findings from other populations. Although varying statistical approaches make direct comparisons difficult, the direction and magnitude our findings were comparable to previous studies (Dreyfus et al. 2015, 2012; Lim et al. 2016; Mueller et al. 2014; Peters et al. 2015) that have linked earlier age at menarche with higher BMI, and increased risk of obesity, metabolic syndrome, and/or diabetes. For example, a meta-analysis on early puberty and cardio-metabolic risk that summarized studies-mostly from the US and UK-found that a menarche < 12 years of age was related to a twofold greater odds of obesity than menarche 12 years or later (Prentice and Viner 2013). We similarly found an almost twofold greater probability of obesity comparing women with menarche at age 13 years to those with menarche ≤ 9 years. Considering diabetes, we found an approximately 1.5 times higher probability of diabetes comparing menarche < 12 years to menarche at 13 years, while a recent study from Brazil reported a 34% greater risk of diabetes among women with a menarche < 11 years compared to menarche at 13–14 years (Mueller et al. 2014). The observed association between later age at menarche and higher prevalence of diabetes is consistent with some findings from the US (Glueck et al. 2013) and UK (Canoy et al. 2015), although it has not been noted in

Table 4 Prevalence of cardio-metabolic risk factors among 43,113 Mexican teachers according to time to menstrual regularity

Cardio-metabolic risk factor	Time to menstrual regularity	N	Prevalence of outcome	Unadjusted prevalence ratio (95% CI)[a]	Adjusted prevalence ratio (95% CI)[b]
Obesity					
	< 1 year	27,436	23.3	Reference	Reference
	≥ 1 year	12,371	23.5	1.01 (0.97, 1.05)	1.01 (0.99, 1.03)
	P value[c]			0.65	0.46
Diabetes					
	< 1 year	29,720	4.5	Reference	Reference
	≥ 1 year	13,393	5.1	1.13 (1.03, 1.23)	1.11 (1.02, 1.22)
	P value			< 0.0001	0.02
High BP					
	< 1 year	29,720	14.0	Reference	Reference
	≥ 1 year	13,393	15.6	1.11 (1.06, 1.17)	1.11 (1.06, 1.17)
	P value			< 0.0001	< 0.0001
High cholesterol					
	< 1 year	29,720	15.6	Reference	Reference
	≥ 1 year	13,393	17.3	1.11 (1.06, 1.16)	1.09 (1.04, 1.14)
	P value			< 0.0001	0.002

CI confidence interval, *BP* blood pressure

Data come from the Mexican Teachers' Cohort, a prospective study of 115,315 female teachers', initiated in 2006–2008 among women from two states and expanded in 2008 to include women from 10 additional states across Mexico. After exclusions, the final study population included 43,113 women (complete case analysis)

[a]Estimates were obtained using a modified Poisson regression approach, with cardio-metabolic risk factor as a dichotomous outcome and time to menstrual regularity as a dichotomous predictor. A Poisson distribution with a log link and robust error variance were specified for each model

[b]Adjusted for age at menarche, birth cohort, region of birth, occupation of household head during childhood, breastfed as an infant, frequency of meat consumption as a child, body size before menarche, and number of older siblings

[c]P values were from a Wald test

other countries, including Brazil (Mueller et al. 2014). One potential reason for this discrepancy is a wider range of ages at menarche and a higher sample size in our study compared to previous studies, which may have afforded us the power to detect an association. Further, there is no strict definition of late menarche, so prior studies may have masked associations by grouping a fairly wide range of ages together.

Several potential mechanisms may explain the association between early menarche and increased risk of cardio-metabolic risk factors. Earlier menarcheal age has been linked to other reproductive markers including earlier age at first birth (Sim et al. 2015) and earlier age at menopause (Mishra et al. 2017), which have been related to obesity (Patchen et al. 2016) and cardiovascular disease (Clegg et al. 2017). Girls with earlier menarche than their peers may be more likely to exhibit unhealthy behaviors (e.g., poor diet, low physical activity) (van Jaarsveld et al. 2007) that relate to higher adiposity gain and insulin resistance during the post-pubertal period (Boyne et al. 2014) and beyond. In contrast, it is possible that an earlier age at menarche is a marker for early life factors present prenatally or in childhood that are responsible for both an earlier age at menarche and later cardio-metabolic risk. Nonetheless, in our study, we found robust associations between early age at menarche and adult cardio-metabolic disease markers independent of multiple early life factors including body size before menarche and early childhood socioeconomic conditions.

Mechanisms for the associations with late menarche and adulthood diabetes may have to do with insulin resistance in adolescence. Girls with underlying metabolic disorders such as polycystic ovarian syndrome (PCOS) often have delayed puberty (Pereira et al. 2015; Rohrer et al. 2007); and would also be pre-disposed to adulthood diabetes diagnosis. Adjusting for PCO in our models did not, however, substantially attenuate the estimates (e.g. PR comparing menarche ≥ 17–13 years was 1.65 with 95% CI 1.16–2.34 in models without PCO adjustment versus 1.63 with 95% CI 1.17–2.26 in models with PCO adjustment). Another potential explanation is that delayed puberty was a sign of nutrient deprivation during childhood and, when coupled with overnutrition later in life, could predispose to insulin resistance in adulthood (Vaag et al. 2012). Future directions that include the examination of changes in weight from birth through childhood could help uncover mechanisms responsible for the associations.

Our finding that time to menstrual regularity was associated with cardio-metabolic disease in adulthood is novel, although it is corroborated by other literature. One study among approximately 1600 US women showed that women who took longer to have regular menstrual cycles had a higher probability of experiencing irregular cycles in adulthood (Rockhill et al. 1998). Further, irregular menstrual cycles among adult women have been related to metabolic disorder (Rostami Dovom et al. 2016).

Of note, the associations between early life correlates and age at menarche were in expected directions. Typically, the average age at menarche is highly sensitive to socioeconomic and nutritional factors within populations and to changes in these factors over time (Tanner 1992). Our study findings are indicative of a country in the midst of a nutrition transition, given the decline in average at menarche over the birth years and the fact that the higher-income groups and more urban regions had earlier average ages at menarche. These associations are expected because in regions undergoing nutritional transitions, higher-income and urban groups have higher adiposity (Popkin et al. 2012), and higher childhood adiposity is related to earlier menarche. The association with meat intake frequency is intriguing because it corroborates findings from a prospective study linking higher early childhood red meat intake with earlier age at menarche among Colombian schoolgirls (Jansen et al. 2016). Although red meat intake frequency was considered a proxy for early-life socioeconomic status in this study, the possibility that the association can be explained by the meat itself cannot be ruled out.

The study had multiple strengths. A large sample size provided us with adequate power to detect associations, and a comprehensive survey meant we could adjust for a large number of important potential confounders, including premenarcheal body size. The fact that these women were from a population that had gone through a nutrition transition over the course of their lifespan means that these findings are likely generalizable to other populations undergoing similar transitions. Further, the fact that the associations with age at menarche were highly consistent with other similar populations (Jansen et al. 2015) supports the validity of the data. There were also limitations. The high level of missingness, most notably in covariates, means there could be selection bias if those who responded were different with respect to menstrual factors and cardio-metabolic outcomes. The fact that the estimates were highly similar in the missing indicator analysis is reassuring, although we recognize the possibility of introducing missing indicator bias (which could bias estimates in either direction) if the assumption of missing completely at random is not met (Greenland and Finkle 1995). Nonetheless, the similarity in sociodemographic characteristics between the complete-case sample and the sample with at least one missing covariate suggests the missing completely at random assumption may not be violated. Another limitation is the fact that cardio-metabolic outcomes were self-reported rather than physician-assessed, although this potential misclassification of the outcome may be non-differential. The fact that age at menarche and time to menstrual regularity was recalled decades after their occurrence likely also resulted in measurement error (Cooper et al. 2006), although this would not result in recall bias if recall did not depend on cardio-metabolic health status. Finally, there is the potential for unmeasured or residual confounding, especially given that early life confounders were recalled retrospectively.

In summary, we found that age at menarche and time to menstrual regularity were each associated with cardio-metabolic health indicators in the Mexican population. Monitoring early menstrual characteristics at the population level could provide information on groups within the population at greater risk for cardio-metabolic disease. At the clinical level, asking women about their menstrual histories in addition to traditional risk factors may add further predictability of future cardio-metabolic disease risk.

Acknowledgements We gratefully acknowledge Antonio García-Anaya, and Eduardo Ortiz-Panozo for data management expertise and assistance. We thank ISSSTE (Social Security and Services Institute for Employees of the State) for technical and administrative support. We also wish to thank the participants of the Mexican Teachers' Cohort. Without their participation, this study would not have been possible. R. López-Ridaura and M. Lajous have a nonrestricted investigator-initiated grant from AstraZeneca. E. Jansen is supported by funding from the National Institute of Diabetes and Digestive and Kidney Diseases (5T32DK071212-12). This work is also supported by the American Institute for Cancer Research (05B047), and Consejo Nacional de Ciencia y Tecnología (S0008-2009-1:000000000115312).

Compliance with Ethical Standards

Conflict of interest The authors declare they have no conflict of interest.

References

Al-Sahab, B., Adair, L., Hamadeh, M. J., Ardern, C. I., & Tamim, H. (2011). Impact of breastfeeding duration on age at menarche. *American Journal of Epidemiology, 173*(9), 971–977. https://doi.org/10.1093/aje/kwq496.

Barros, A. J. D., & Hirakata, V. N. (2003). Alternatives for logistic regression in cross-sectional studies: An empirical comparison of models that directly estimate the prevalence ratio. *BMC Medical Research Methodology, 3*, 21. https://doi.org/10.1186/1471-2288-3-21.

Boyne, M. S., Thame, M., Osmond, C., Fraser, R. A., Gabay, L., Taylor-Bryan, C., & Forrester, T. E. (2014). The effect of earlier puberty on cardiometabolic risk factors in Afro-Caribbean

children. *Journal of Pediatric Endocrinology and Metabolism, 27*(5–6), 453–460. https://doi.org/10.1515/jpem-2013-0324.
Canoy, D., Beral, V., Balkwill, A., Wright, F. L., Kroll, M. E., Reeves, G. K., … Young, H. (2015). Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation, 131*(3), 237–244. https://doi.org/10.1161/CIRCULATIONAHA.114.010070.
Clegg, D., Hevener, A. L., Moreau, K. L., Morselli, E., Criollo, A., Van Pelt, R. E., & Vieira-Potter, V. J. (2017). Sex hormones and cardiometabolic health: Role of estrogen and estrogen receptors. *Endocrinology*. https://doi.org/10.1210/en.2016-1677.
Cooper, R., Blell, M., Hardy, R., Black, S., Pollard, T. M., Wadsworth, M. E. J., … Kuh, D. (2006). Validity of age at menarche self-reported in adulthood. *Journal of Epidemiol Community Health, 60*, 993–997. https://doi.org/10.1136/jech.2005.043182.
Dreyfus, J., Jacobs, D. R., Mueller, N., Schreiner, P. J., Moran, A., Carnethon, M. R., & Demerath, E. W. (2015). Age at menarche and cardiometabolic risk in adulthood: The coronary artery risk development in young adults study. *The Journal of Pediatrics, 167*(2), 344–352.e1. https://doi.org/10.1016/j.jpeds.2015.04.032.
Dreyfus, J. G., Lutsey, P. L., Huxley, R., Pankow, J. S., Selvin, E., Fernández-Rhodes, L., … Demerath, E. W. (2012). Age at menarche and risk of type 2 diabetes among African-American and white women in the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia, 55*(9), 2371–2380. https://doi.org/10.1007/s00125-012-2616-z.
Ester, W. A., Houghton, L. C., Lumey, L. H., Michels, K. B., Hoek, H. W., Wei, Y., … Terry, M. B. (2017). Maternal and early childhood determinants of women's body size in midlife: Overall cohort and sibling analyses. *American Journal of Epidemiology, 185*(5), 385–394. https://doi.org/10.1093/aje/kww222.
Glueck, C. J., Morrison, J. A., Wang, P., & Woo, J. G. (2013). Early and late menarche are associated with oligomenorrhea and predict metabolic syndrome 26 years later. *Metabolism: Clinical and Experimental, 62*(11), 1597–1606. https://doi.org/10.1016/j.metabol.2013.07.005.
Greenland, S., & Finkle, W. D. (1995). A critical look at methods for handling missing covariates in epidemiologic regression analyses. *American Journal of Epidemiology, 142*(12), 1255–1264. https://doi.org/10.1093/aje/kwi188.
Jansen, E. C., Herrán, O. F., & Villamor, E. (2015). Trends and correlates of age at menarche in Colombia: Results from a nationally representative survey. *Economics and Human Biology*. https://doi.org/10.1016/j.ehb.2015.09.001.
Jansen, E. C., Marín, C., Mora-Plazas, M., & Villamor, E. (2016). Higher childhood red meat intake frequency is associated with earlier age at menarche. *Journal of Nutrition*. https://doi.org/10.3945/jn.115.226456.
Lajous, M., Ortiz-Panozo, E., Monge, A., Santoyo-Vistrain, R., García-Anaya, A., Yunes-Díaz, E., … López-Ridaura, R. (2017). Cohort profile: The mexican teachers' cohort (MTC). *International Journal of Epidemiology, 46*(2), e10. https://doi.org/10.1093/ije/dyv123.
Lim, S. W., Ahn, J. H., Lee, J. A., Kim, D. H., Seo, J. H., & Lim, J. S. (2016). Early menarche is associated with metabolic syndrome and insulin resistance in premenopausal Korean women. *European Journal of Pediatrics, 175*(1), 97–104. https://doi.org/10.1007/s00431-015-2604-7.
Meza, R., Barrientos-Gutierrez, T., Rojas-Martinez, R., Reynoso-Noverón, N., Palacio-Mejia, L. S., Lazcano-Ponce, E., & Hernández-Ávila, M. (2015). Burden of type 2 diabetes in Mexico: Past, current and future prevalence and incidence rates. *Preventive Medicine, 81*, 445–450. https://doi.org/10.1016/j.ypmed.2015.10.015.
Mishra, G. D., Pandeya, N., Dobson, A. J., Chung, H. F., Anderson, D., Kuh, D., … Weiderpass, E. (2017). Early menarche, nulliparity and the risk for premature and early natural menopause. *Human Reproduction, 32*(3), 679–686. https://doi.org/10.1093/humrep/dew350.
Mueller, N. T., Duncan, B. B., Barreto, S. M., Chor, D., Bessel, M., Aquino, E. M., … Schmidt, M. (2014). Earlier age at menarche is associated with higher diabetes risk and cardiometabolic disease risk factors in Brazilian adults: Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Cardiovascular Diabetology, 13*(1), 22. https://doi.org/10.1186/1475-2840-13-22.
Ortiz-Panozo, E., Yunes-Díaz, E., Lajous, M., Romieu, I., Monge, A., & López-Ridaura, R. (2017). Validity of self-reported anthropometry in adult Mexican women. *Salud Pública de México, 59*(3), 266–275.
Palloni, A., Beltrán-Sánchez, H., Novak, B., Pinto, G., & Wong, R. (2015). Adult obesity, disease and longevity in Mexico. *Salud Publica de Mexico, 57 Suppl 1*(01), S22–S30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26172231.
Patchen, L., Leoutsakos, J.-M., & Astone, N. M. (2016). Early Parturition: Is young maternal age at first birth associated with obesity? *Journal of Pediatric and Adolescent Gynecology*. https://doi.org/10.1016/j.jpag.2016.12.001.
Pereira, K. C. X., Pugliese, B. S., Guimarães, M. M., & Gama, M. P. (2015). Pubertal development in children diagnosed with diabetes mellitus type 1 before puberty. *Journal of Pediatric and Adolescent Gynecology, 28*(1), 66–71. https://doi.org/10.1016/j.jpag.2014.08.009.
Peters, S. A. E., Huxley, R. R., & Woodward, M. (2015). Women's reproductive health factors and body adiposity: Findings from the UK Biobank. *International Journal of Obesity (2005), 40*(August 2015), 1–6. https://doi.org/10.1038/ijo.2015.254.
Popkin, B. M., Adair, L. S., & Ng, S. W. (2012). Global nutrition transition and the pandemic of obesity in developing countries. *Nutrition Reviews, 70*(1), 3–21. https://doi.org/10.1111/j.1753-4887.2011.00456.x.
Prentice, P., & Viner, R. M. (2013). Pubertal timing and adult obesity and cardiometabolic risk in women and men: A systematic review and meta-analysis. *International Journal of Obesity, 37*(8), 1036–1043. https://doi.org/10.1038/ijo.2012.177.
Rockhill, B., Moorman, P. G., & Newman, B. (1998). Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). *Cancer Causes and Control, 9*(4), 447–453. https://doi.org/10.1023/A:1008832004211.
Rohrer, T., Stierkorb, E., Heger, S., Karges, B., Raile, K., Schwab, K. O., & Holl, R. W. (2007). Delayed pubertal onset and development in German children and adolescents with type 1 diabetes: Cross-sectional analysis of recent data from the DPV diabetes documentation and quality management system. *European Journal of Endocrinology, 157*(5), 647–653. https://doi.org/10.1530/EJE-07-0150.
Rostami Dovom, M., Ramezani Tehrani, F., Djalalinia, S., Cheraghi, L., Gandavani, B. S., & Azizi, F. (2016). Menstrual cycle irregularity and metabolic disorders: A population-based prospective study. *PLoS ONE, 11*(12), e0168402. https://doi.org/10.1371/journal.pone.0168402.
Sim, J. H., Chung, D., Lim, J. S., Lee, M. Y., Chung, C. H., Shin, J. Y., & Huh, J. H. (2015). Maternal age at first delivery is associated with the risk of metabolic syndrome in postmenopausal women: From 2008 to 2010 Korean National Health and Nutrition Examination Survey. *PLoS ONE, 10*(5), e0127860. https://doi.org/10.1371/journal.pone.0127860.
Tanner, J. M. (1992). Growth as a measure of the nutritional and hygienic status of a population. *Hormone Research, 38 Suppl 1*,

106–115. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1295807.

Toh, S., García Rodríguez, L. A., & Hernán, M. A. (2012). Analyzing partially missing confounder information in comparative effectiveness and safety research of therapeutics. *Pharmacoepidemiology and Drug Safety*. https://doi.org/10.1002/pds.3248.

Vaag, A. A., Grunnet, L. G., Arora, G. P., & Brøns, C. (2012). The thrifty phenotype hypothesis revisited. *Diabetologia, 55*(8), 2085–2088. https://doi.org/10.1007/s00125-012-2589-y.

van Jaarsveld, C. H. M., Fidler, J. A., Simon, A. E., & Wardle, J. (2007). Persistent impact of pubertal timing on trends in smoking, food choice, activity, and stress in adolescence. *Psychosomatic Medicine, 69*(8), 798–806. https://doi.org/10.1097/PSY.0b013e3181576106.

Won, J. C., Hong, J. W., Noh, J. H., & Kim, D.-J. (2016). Association between age at menarche and risk factors for cardiovascular diseases in Korean women. *Medicine, 95*(18), e3580. https://doi.org/10.1097/MD.0000000000003580.