

# Sexual maturation and metabolic profile among adolescents and children of the Health Worker Cohort Study in Mexico

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## Abstract

**Objective.** Our objective was to investigate the associations between level and timing of sexual development with metabolic profile in a cohort of Mexican adolescents in central Mexico. **Material and Methods.** Baseline data from children between the ages of 7 and 17 years ( $n = 582$ ) who participated in the Health Worker Cohort Study, was used. The study participants included children of workers at the Mexican Institute of Social Security (IMSS) and the National Institute of Public Health, both located in Cuernavaca, in addition to children of workers at the Universidad Autónoma del Estado de México in Toluca who were enrolled between March 2004 and April 2006. Multiple linear regressions with robust estimates of variance, were used adjusting for specific covariates. **Results.** Both pubertal boys and girls, compared to their pre-pubertal counterparts, had higher body mass index (girls:  $4.59 \text{ kg/m}^2$ ,  $p < 0.0001$ ; boys:  $1.12 \text{ kg/m}^2$ ,  $p = 0.05$ ) and percent body fat (girls:  $3.61$ ,  $p < 0.0001$ ; boys:  $1.48$ ,  $p = 0.0001$ ). A significant difference in level of insulin resistance (homeostasis model assessment, HOMA) was detectable among girls ( $0.92$ ,  $p < 0.0001$ ). **Conclusions.** Timing and levels of sexual development were significantly associated with adverse differences in several critical anthropometric and metabolic parameters.

Key words: sexual maturation; metabolism; adolescents; Mexico

## Resumen

**Objetivo.** Investigar las asociaciones entre etapa y momento de inicio del desarrollo sexual y perfil metabólico en una cohorte de adolescentes mexicanos. **Material y métodos.** Se usó la información basal de los jóvenes entre 7 y 17 años de edad ( $n = 582$ ), que participaron en el Estudio de cohorte de trabajadores de la salud. Los participantes del estudio fueron los hijos e hijas de los trabajadores del Instituto Mexicano del Seguro Social (IMSS) y del Instituto Nacional de Salud Pública en Cuernavaca, Morelos, así como los hijos e hijas de los trabajadores de la Universidad Autónoma del Estado de México en Toluca. Se realizaron regresiones lineales múltiples con estimadores de varianza robustos, ajustando por covariables específicas. **Resultados.** Se encontró un índice de masa corporal mayor en los niños y niñas en la etapa de pubertad, comparado con los de pre-pubertad (niñas:  $4.59 \text{ kg/m}^2$ ,  $p < 0.0001$ ; niños:  $1.12 \text{ kg/m}^2$ ,  $p = 0.05$ ) y un mayor porcentaje de grasa corporal (niñas:  $3.61$ ,  $p < 0.0001$ ; niños:  $1.48$ ,  $p = 0.0001$ ). Se encontró una diferencia significativa en el indicador de resistencia a la insulina (HOMA, por sus siglas en inglés) en las niñas ( $0.92$ ,  $p < 0.0001$ ). **Conclusiones.** La etapa y el momento de inicio del desarrollo sexual se asociaron significativamente con diferencias adversas en varios parámetros metabólicos y antropométricos críticos.

Palabras clave: madurez sexual; metabolismo; adolescentes; México

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Puberty is a stage of rapid physiologic changes that may impact metabolic outcomes later in life. During adolescence, over the course of pubertal development, various metabolic and physiologic changes occur in parameters such as insulin sensitivity<sup>1,2</sup> and lipid levels.<sup>3</sup> In a recent euglycemic clamp study of 357 children, it was found that insulin sensitivity decreased with the onset of puberty (Tanner stage II), reached a nadir at Tanner stage III, and returned to near pre-pubertal levels by Tanner stage V.<sup>1</sup>

Mexican-Americans have higher rates of obesity<sup>4</sup> and metabolic syndrome (MS),<sup>5</sup> which are predictive of type 2 diabetes and poor cardiovascular health in adulthood.<sup>6</sup> Adolescents in Mexico experience a similarly high prevalence of obesity and metabolic syndrome. A recent study reported a prevalence of MS from 10.6% to 19.6% among a group of Mexican adolescents depending on the definition used.<sup>7</sup> Further, compared to Caucasian children, Hispanic children have lower insulin sensitivity and higher insulin secretion throughout childhood and adolescence.<sup>8</sup> The elevated prevalence of obesity in this population, combined with lower insulin sensitivity and the high prevalence of low high density lipoprotein (HDL) and high triglycerides puts Mexican adolescents at a higher risk for metabolic syndrome. The exact mechanism responsible for the pubertal drop in insulin sensitivity remains unknown. Moreover, the impact these changes in insulin sensitivity might have on the risk of developing metabolic syndrome is also not known.

Timing of sexual maturation is another important factor when assessing metabolic parameters in pubertal children. Mexican-American adolescents generally experience earlier sexual maturation than their Caucasian peers.<sup>9</sup> Multiple studies have found that early sexual maturation is associated with a higher risk of obesity and MS.<sup>10-13</sup> This association may convey additional risk of developing metabolic disorders among Mexican-American and Mexican adolescents who experience earlier sexual maturation,<sup>9</sup> and have lower insulin sensitivity,<sup>8</sup> a higher prevalence of obesity,<sup>4</sup> lower HDL, and higher triglycerides<sup>10</sup> than their Caucasian peers.

Thus, it is important to examine both timing of sexual development and pubertal stage when studying differences in metabolic parameters among adolescent populations, particularly those at high risk of developing diabetes and MS. To the best of the authors' knowledge no such study has been reported in a large cohort of Mexican or Mexican-American adolescents. To provide such information, our objective was to measure a comprehensive panel of metabolic parameters and assess their associations with timing of sexual development

and pubertal stage among 551 participants enrolled in a large cohort study of Mexican adolescents.

## Materials and Methods

### Study population

The study population consisted of a sample of children and adolescents who participated, along with their parents, in the Health Worker cohort study. The study participants included children of workers at the Mexican Institute of Social Security (IMSS, per its abbreviation in Spanish) and the National Institute of Public Health, both located in Cuernavaca, in addition to children of workers at the Universidad Autonoma del Estado de Mexico in Toluca, the capital of the neighboring state. All participants are being followed in an on going cohort study of life style and health and were enrolled between March 2004 and April 2006. The specifics regarding the study design, methodology and baseline characteristics of participants have been detailed elsewhere,<sup>7</sup> and the ethical committees of all participating institutions approved the study protocol and consent forms for the cohort study.

A total of 1 349 children and adolescents aged 7-17 years old were enrolled in the Health Worker cohort study. In order to examine the differences in metabolic profile by level of sexual development, we restricted our analysis to participants aged 7-17 who reported being in Tanner stages I-IV (n=1 000). Those in Tanner stage V were excluded from this analysis since sexual development ends during Tanner V and we wished to eliminate children from our sample who had completed development prior to our study. Most participants had complete clinical data at the time of this analysis; however, only 551 of these participants had fasting insulin and glucose data in addition to percent body fat. To examine the differences in metabolic profile associated with timing of sexual maturation we expanded our sexual development criteria to include those in Tanner stages I-V, but further restricted the age range to those 7-14. The age restriction was done in order to eliminate children who had already completed sexual development at the time of enrollment, for whom we could not determine the timing of their development. Sexual development is completed during Tanner stage V. According to Sun et. al. the median age at entry to Tanner stage V,<sup>5</sup> for Mexican-American girls was 14.70. Therefore, excluding those 14 and older was a conservative approach that ensured that we only included those in our analysis for whom timing of puberty could be established with some confidence. Of these participants, 425 met these inclusion criteria and had complete glucose and insulin data.

## Assessment of pubertal stage and metabolic parameters

We classified pubertal stage based on Tanner staging. Tanner staging uses the appearance of secondary sexual characteristics that include four separate indexes: breast development and pubic hair for girls and testicular development and pubic hair for boys.<sup>14</sup> Participants were shown sex-specific pictures of adolescents in each stage and asked to identify which picture most accurately matched their current stage of sexual development. Breast stage for girls and testicular development stage for boys were used in this analysis. For both sexes, those in Tanner I were classified as pre-pubertal, those in Tanner II-IV were classified as pubertal, and those in Tanner V were classified as post-pubertal.

We defined early maturation as being below the lower limit of the 95% confidence interval of the mean age for a given Tanner stage and sex as indicated by the Third National Health and Nutrition Examination Survey (NHANES III) for Mexican-Americans.<sup>9</sup> We used the mean age in a Tanner stage and the standard error reported by Sun *et al.*<sup>9</sup> to calculate the lower limits of the 95% confidence intervals for the mean age in a stage. This was a modification of the method used by Wang, who classified children who were below the median age for a given gender and stage.<sup>13</sup> Rather than simply defining half of our population as early maturers we used the lower limit of the 95% confidence interval for the mean age in a stage in order to give the definition of early maturer more physiologic and clinical meaning. Specifically, the lower limits we calculated for girls were: 8 years old (Tanner I), 10.29 years old (Tanner II), 12.22 years old (Tanner III), 13.50 years old (Tanner IV), and 15.97 years old (Tanner V). The lower limits for boys were: 9 years old (Tanner I), 10.76 years old (Tanner II), 12.42 years old (Tanner III), 15.01 years old (Tanner IV), and 16.60 years old (Tanner V).

Insulin sensitivity was measured using the homeostasis model assessment (HOMA).<sup>15</sup> HOMA was calculated from the fasting insulin and glucose measurements using the standard formula:  $(\text{glucose (mmol/L)} \times \text{insulin } (\mu\text{U/mL})) / 22.5$ . Similarly, HOMA-B was used as a measure of beta-cell function and calculated using the standard formula:  $(20 \times \text{insulin } (\mu\text{U/mL})) / (\text{glucose (mmol/L)} - 3.5)$ .<sup>16</sup> Serum glucose concentration was determined by the oxidize glucose method; insulin was measured in serum by solid phase RIA (Coat-A-Count, Diagnostic Products, Los Angeles, CA, USA).<sup>17</sup> To remain consistent with previous analyses among adolescents from the National Health and Nutrition Examination Survey (NHANES)<sup>18-21</sup> and other Health Worker cohort studies,<sup>7</sup> a fasting time of eight hours or

greater was used for all assays. Serum triglyceride concentrations were analyzed with a colorimetric method after enzymatic hydrolysis with lipases. HDL/LDL was analyzed by the elimination of chylomicron and VLDL-C, LDL/HDL-C by cholesterol esterase, cholesterol oxidize, and subsequently catalase, respectively.<sup>7</sup>

Waist circumference was measured to the nearest 0.1 cm at the high point of the iliac crest at the end of normal expiration, with a steel measuring tape, which was placed under any clothing, directly touching the participant's skin. Weight was assessed with participants wearing minimal clothing by an electronic TAN-ITA scale, which was previously calibrated. Height was measured using a conventional stadiometer. Overweight and obesity classifications were based on the Centers for Disease Control and Prevention (CDC) Growth Charts for the U.S. population. Obesity was defined as being  $\geq$  the 95<sup>th</sup> percentile BMI for age and gender. Overweight was defined as being  $\geq$  the 85<sup>th</sup> percentile < 95<sup>th</sup> percentile BMI for age and gender. Normal weight was defined as being < the 85<sup>th</sup> percentile BMI for age and gender.<sup>4</sup> Percent body fat was measured by dual-energy X-ray absorptiometry (DEXA) using a Lunar DPX-GE (model: DPX-NT 73735, series: 638405U77).

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) instrument<sup>22,23</sup> which was adapted for the Mexican population. Participants were asked about their leisure activity, recreational activity, daily activity, and any physical labor associated with employment. The IPAQ section on leisure time activity included 16 items on the amounts of time spent weekly performing exercises such as walking, running and cycling. Each activity was given a value in metabolic equivalents (MET) and total METS per week were calculated. Three categories were defined:  $\leq 21$  METS per week,  $> 21$  METS per week and  $< 110$  METS per week, and  $\geq 110$  METS per week.

Participants were shown a series of graded silhouettes, numbered 1-9, of men and women and asked to mark the body type that best described their mother's and father's current physical appearance. The use of this scale was previously validated for use within this population.<sup>24</sup> A selection of an image numbered four or greater was interpreted as a parent being overweight or obese. Participants were categorized as having one, two, or no overweight or obese parents.

## Statistical analysis

Multiple regression models with robust variance estimates were used to determine the means and 95% confidence intervals for BMI, waist circumference, percent body fat, insulin, glucose, HOMA, HOMA-B,

HDL, triglycerides, and low density lipoprotein (LDL) (treated as dependent variables) according to levels of sexual maturation for girls and boys, adjusting for age, percent body fat (except where percent body fat was the dependent variable), physical activity and number of obese or overweight parents. The association of being pubertal versus pre-pubertal with differences in metabolic parameters was allowed to vary by age. Student's t-tests were used to identify differences between pre-pubertal versus pubertal status.

Analyses of the association between early sexual maturation and differences in metabolic components and anthropometric parameters were carried out in a similar fashion. These analyses were restricted to participants aged 7-14 years in order to exclude individuals who could not be identified conclusively as early-maturers. The cut-point of age 14 was chosen based on the average age of entry into Tanner stage V for Mexican-American adolescent girls reported by Sun *et al.* (mean age at entry

for Tanner V for Mexican-American girls: 14.70).<sup>9</sup> While this was a conservative estimate, using this cut point gave us confidence that we were excluding from our analysis those children who had completed puberty before enrolling in the cohort and for whom we could not adequately establish timing of sexual development. To evaluate the association of early sexual maturation and the change in the metabolic components of interest we used our definitions of early versus not early. All analyses were adjusted for age, percent body fat (except where percent body fat was the dependent variable), physical activity and parental obesity or overweight. Student's t-tests were used to identify differences between early and not early maturers. Analyses were conducted using STATA 9 software.\*

\* StataCorp. Stata Statistical Software: Release 9. College Station (TX, USA): Statacorp LP, 2005.

**Table I**  
**CHARACTERISTICS OF THE STUDY POPULATION BY LEVEL AND TIMING OF SEXUAL MATURATION.\***  
**HEALTH WORKER COHORT STUDY, MARCH 2004-APRIL 2006**

Covariate	Pubertal status		<i>p</i> <sup>‡</sup>	Timing of sexual maturation		<i>p</i> <sup>‡</sup>
	Pre-pubertal	Pubertal		Early	Not early	
<i>n</i>	103	479		287	162	
Age	9 ± 1.38	13 ± 2.49	<0.0001	11 ± 2.13	11 ± 2.02	0.14
Residence						
Morelos	89 (86)	381 (80)	0.11	241 (84)	130 (80)	0.37
Toluca	14 (14)	98 (20)		46 (16)	32 (20)	
Sex						
Girls	46 (44.7)	242 (50.5)	0.28	156 (54.4)	75 (46.3)	0.10
Boys	57 (55.3)	237 (49.5)		131 (45.6)	87 (53.7)	
Mean BMI (kg/m <sup>2</sup> )	17.99 ± 4.42	20.61 ± 4.18	<0.0001	19.51 ± 3.94	19.52 ± 4.65	0.98
BMI category						
Normal	94 (91.3)	419 (87.5)	0.28	264 (92.0)	143 (88.3)	0.19
Overweight	6 (5.8)	42 (8.8)		18 (6.3)	12 (7.4)	
Obese	3 (2.9)	18 (3.8)		5 (1.7)	7 (4.3)	
Percent body fat <sup>§</sup>	26.9 ± 10.7	29.8 ± 11.4	0.02	29.1 ± 11.4	29.2 ± 11.1	0.95
METS per week	94 ± 55	106 ± 62	0.08	103 ± 58.6	94 ± 55.7	0.12
# of parents overweight or obese						
0	5 (4.9)	13 (2.7)	0.26	9 (3.1)	6 (3.7)	0.75
1	20 (19.4)	92 (19.2)		62 (21.6)	26 (16.1)	
2	78 (75.7)	374 (78.1)		216 (75.3)	130 (80.3)	

\* Data are means ± S.D. or *n* (percentages)

<sup>‡</sup> *p* values for the differences between pre-pubertal and pubertal children and early and not early maturers determined by student's t-test for continuous variables and  $\chi^2$  test for proportions

<sup>§</sup> Pre-pubertal (*n* = 97), pubertal (*n* = 454), early (*n* = 274), not early (*n* = 151)

BMI: body mass index

METS: metabolic equivalents

## Results

The characteristics of the sample covariates are shown in Table I by level of sexual maturation and timing of sexual maturation. The pre-pubertal children differed significantly from the pubertal children in age, mean BMI, and percent body fat. The early maturing children did not differ significantly from the non-early maturers in any of the covariates.

Being pubertal versus pre-pubertal among girls was associated with higher BMI (4.59 kg/m<sup>2</sup>,  $p<0.0001$ ), waist circumference (15.26 cm,  $p<0.0001$ ), percent body fat (3.61%,  $p<0.0001$ ), glucose (0.45 mg/dL,  $p=0.01$ ), insulin (4.47  $\mu$ U/mL,  $p<0.0001$ ), HOMA (0.92,  $p<0.0001$ ), HOMA-B (67.57,  $p<0.0001$ ), and triglycerides (10.43 mg/dL,  $p<0.0001$ ), as well as lower HDL (-3.25 mg/dL,  $p<0.0001$ ) and LDL (-3.94 mg/dL,  $p<0.0001$ ). Among boys, being pubertal versus pre-pubertal was associated

with higher BMI (1.12 kg/m<sup>2</sup>,  $p=0.05$ ), waist circumference (4.74 cm,  $p=0.01$ ), and percent body fat (1.48%,  $p=0.0001$ ), as well as lower HDL (-0.95 mg/dL,  $p=0.03$ ), triglycerides (-6.99 mg/dL,  $p=0.01$ ) and LDL (-11.20 mg/dL,  $p<0.0001$ ) (Table II).

Among girls, early versus not early sexual maturation was associated with higher BMI (1.89 kg/m<sup>2</sup>,  $p=0.00$ ), waist circumference (4.70 cm,  $p=0.00$ ), glucose (0.89 mg/dL,  $p<0.0001$ ), insulin (2.78  $\mu$ U/mL,  $p<0.0001$ ), HOMA (0.57,  $p<0.0001$ ) and HOMA-B (50.85,  $p<0.0001$ ), in addition to lower LDL (-4.343,  $p<0.0001$ ) (Table III). For boys, early sexual maturation versus not early was associated with higher glucose (0.75 mg/dL,  $p<0.0001$ ) and HDL (2.32 mg/dL,  $p<0.0001$ ) as well as lower BMI (-1.28 kg/m<sup>2</sup>,  $p=0.01$ ), waist circumference (-4.72 cm,  $p=0.01$ ), percent body fat (-0.78%,  $p=0.003$ ), triglycerides (-11.68 mg/dL,  $p<0.0001$ ) and LDL (-8.04 mg/dL,  $p<0.0001$ ) (Table III).

**Table II**  
**MEANS OF METABOLIC AND ANTHROPOMETRIC COMPONENTS BY LEVELS OF SEXUAL MATURATION IN MEXICAN ADOLESCENTS AGED 7-17. HEALTH WORKER COHORT STUDY, MARCH 2004-APRIL 2006\***

	Girls				Boys			
	Pubertal status		Difference	$p^{\ddagger}$	Pubertal status boys		Difference	$p^{\ddagger}$
	Pre-pubertal n=46	Pubertal n=232			Pre-pubertal n=51	Pubertal n=222		
BMI(kg/m <sup>2</sup> ) <sup>§</sup>	15.98 [15.09-16.88]	20.57 [20.16-20.98]	4.59	<0.001	19.18 [18.09-20.27]	20.30 [19.81-20.78]	1.12	0.05
Waist circumference (cm) <sup>§</sup>	61.70 [59.08-64.32]	76.97 [75.75-78.18]	15.26	<0.001	71.28 [67.95-74.61]	76.02 [74.60-77.44]	4.74	0.001
% Body fat <sup>§</sup>	30.58 [29.41-31.74]	34.19 [34.02-34.35]	3.61	<0.001	23.31 [21.85-24.78]	24.79 [24.64-24.94]	1.48	0.0001
Fasting glucose (mg/dL)	82.77 [82.57-82.98]	83.22 [83.08-83.36]	0.45	0.01	85.59 [85.47-85.72]	85.59 [85.44-85.74]	0.002	0.99
Fasting insulin (mU/mL)	6.75 [5.84-7.67]	11.22 [10.85-11.59]	4.47	<0.001	8.36 [7.19-9.52]	9.06 [8.61-9.52]	0.71	0.21
HOMA	1.34 [1.16-1.53]	2.27 [2.20-2.34]	0.92	<0.001	1.74 [1.50-1.97]	1.89 [1.80-1.98]	0.16	0.17
HOMA-B	133.94 [119-148.88]	201.51 [195.51-207.52]	67.57	<0.001	143.33 [123.93-162.72]	150.18 [142.90-157.46]	6.86	0.45
HDL (mg/dL) <sup>§</sup>	42.83 [42.14-43.51]	39.57 [39.28-39.87]	-3.25	<0.001	40.47 [39.47-41.46]	39.51 [39.18-39.84]	-0.95	0.03
Triglycerides (mg/dL) <sup>§</sup>	95.58 [91.35-99.80]	106.00 [104.41-107.60]	10.43	<0.001	98.84 [93.10-104.57]	91.85 [89.88-93.82]	-6.99	0.01
LDL (mg/dL) <sup>§</sup>	88.83 [87.29-90.37]	84.89 [84.28-85.51]	-3.94	<0.001	92.36 [90.43-94.30]	81.17 [80.39-81.95]	-11.20	<0.0001

\* Data are means and 95% confidence intervals adjusted by age, percent body fat, physical activity, and parental obesity

<sup>†</sup>  $p$  values are for the difference between pubertal and pre-pubertal children determined by Student's  $t$ -test

<sup>§</sup> Girls: pre-pubertal ( $n=46$ ) pubertal ( $n=231$ ), boys: pre-pubertal ( $n=51$ ) pubertal ( $n=221$ )

BMI: body mass index

HOMA: homeostasis model assessment

HOMA-B: HOMA of  $\beta$ -cell function

HDL: high density lipoprotein

LDL: low density lipoprotein



**Table III**  
**MEANS OF METABOLIC AND ANTHROPOMETRIC COMPONENTS BY TIMING OF SEXUAL MATURATION IN MEXICAN ADOLESCENTS AGED 7-14. HEALTH WORKER COHORT STUDY, MARCH 2004-APRIL 2006\***

	Girls				Boys			
	Timing of sexual maturation		Difference	p <sup>‡</sup>	Timing of sexual maturation		Difference	p <sup>‡</sup>
	Early n=150	Not Early n=74			Early n=124	Not Early n=77		
BMI (kg/m <sup>2</sup> ) <sup>§</sup>	19.98 [19.44-20.52]	18.09 [17.26-18.91]	1.89	0.0001	18.77 [18.17-19.38]	20.06 [19.19-20.92]	-1.28	0.01
Waist circumference (cm) <sup>§</sup>	74.62 [72.96-76.27]	69.92 [67.35-72.49]	4.70	0.002	70.62 [68.81-72.44]	75.34 [72.82-77.87]	-4.72	0.002
% Body fat <sup>§</sup>	32.70 [32.42-32.98]	33.05 [32.64-33.46]	-0.35	0.17	24.45 [24.10-24.79]	25.23 [24.89-25.57]	-0.78	0.003
Fasting glucose (mg/dL)	84.02 [83.95-84.08]	83.13 [83.02-83.23]	0.89	<0.0001	86.35 [86.27-86.43]	85.60 [85.50-85.71]	0.75	<0.0001
Fasting insulin (mU/mL)	11.25 [10.72-11.77]	8.47 [7.66-9.29]	2.78	<0.0001	8.53 [7.94-9.12]	9.02 [8.12-9.93]	-0.49	0.35
HOMA	2.28 [2.17-2.38]	1.70 [1.54-1.87]	0.57	<0.0001	1.80 [1.68-1.91]	1.87 [1.69-2.05]	-0.07	0.48
HOMA-B	207.51 [198.61-216.42]	156.66 [142.89-170.44]	50.85	<0.0001	140.07 [129.99-150.16]	144.51 [129.43-159.59]	-4.43	0.61
HDL (mg/dL) <sup>#</sup>	39.93 [39.50-40.36]	39.91 [39.25-40.56]	0.03	0.95	41.22 [40.74-41.70]	38.90 [38.21-39.58]	2.32	<0.0001
Triglycerides (mg/dL) <sup>#</sup>	104.82 [102.77-106.88]	103.68 [100.55-106.82]	1.14	0.54	88.27 [85.93-90.61]	99.95 [96.19-103.71]	-11.68	<0.0001
LDL (mg/dL) <sup>#</sup>	83.38 [82.49-84.26]	87.71 [86.26-89.16]	-4.33	<0.0001	80.05 [78.79-81.32]	88.10 [86.50-89.69]	-8.04	<0.0001

\* Data are means and 95% confidence intervals adjusted by age, percent body fat, physical activity, and parental obesity

<sup>‡</sup> p values are for the difference between early and not early maturers determined by Student's t-test

<sup>§</sup> Girls: early (n=149) not early (n=74), boys: early (n=124) not early (n=77)

<sup>#</sup> Girls: early (n=148) not early (n=73), boys: early (n=121) not early (n=74)

BMI: body mass index

HOMA: homeostasis model assessment

HOMA-B: HOMA of  $\beta$ -cell function

HDL: high density lipoprotein

LDL: low density lipoprotein

## Discussion

In this cross-sectional survey of 582 Mexican adolescents in Cuernavaca and Toluca, Mexico we observed significant differences in metabolic profiles according to levels of sexual development. Among girls, being pubertal (as opposed to pre-pubertal) was associated with unfavorable levels of BMI, waist circumference, percent body fat, fasting insulin, fasting glucose, HOMA, HDL, and triglycerides. Among boys, being pubertal (as compared

to pre-pubertal) appeared to be associated with adverse levels of BMI, waist circumference, percent body fat and HDL. Early versus not early sexual maturation was associated with higher levels of BMI, waist circumference, HOMA, HOMA-B, fasting insulin, and fasting glucose among girls, in addition to lower LDL. For boys, early versus not early sexual maturation was associated with lower levels of BMI, waist circumference, percent body fat, fasting glucose, triglycerides, and LDL, in addition to higher HDL.

These findings indicated differences by sex in the associations between the measured metabolic parameters and level of sexual maturation. In general, the differences in metabolic components associated with increasing levels of sexual maturation were smaller among boys than among girls. A difference in the average fasting glucose, fasting insulin, HOMA, and HOMA-B for pre-pubertal versus pubertal girls was detected; however, no differences were detected for boys. Our inability to detect differences in HOMA by pubertal level in boys may corroborate Ball's finding that among overweight Hispanic children with a family history of type 2 diabetes the pubertal drop in insulin sensitivity is not detectable.<sup>25</sup> While only a small percentage of the children in our study were overweight, roughly 90% of our entire cohort reported having at least one parent who was obese or overweight. Since obesity is the main determinant of insulin resistance, then our findings suggest that it is the shared genetic and obesogenic environment rather than the obesity of the child which may be instrumental in masking or eliminating the pubertal drop in insulin sensitivity in our population. Both genetic predisposition and the environment may be impacting insulin sensitivity before either puberty or obesity can occur. This finding is largely unprecedented in the literature and warrants further investigation. In particular, longitudinal data with more exact information regarding timing of sexual maturation is needed to verify these findings and explore possible mechanisms.

The observed decrease in HDL between pubertal and pre-pubertal children has been previously described. Morrison *et al.* reported that the observed drop in total cholesterol across adolescence is due to reductions in HDL.<sup>3</sup> While the expected drop in HDL was observed in both boys and girls, a rise in triglycerides was not uniformly observed for both sexes. Boys displayed a decrease in triglycerides while girls displayed the expected increase in triglycerides. This is a new finding that indicates that the changes in lipid profile associated with puberty are different than those associated with age and that they vary by sex.

The differences in anthropometric parameters for both boys and girls, observed in this study appear to reflect the normal reported patterns of growth.<sup>13</sup> BMI, waist circumference and percent body fat were lower, on average, for boys and girls who were pre-pubertal versus pubertal. Since this data was cross-sectional it was not possible to interpret this finding as implying either that increased BMI is necessary for sexual maturation or that sexual maturation causes increased BMI. However, the association between increased BMI and puberty was consistent with the existing literature, particularly regarding girls.<sup>13</sup>

The greater magnitude of the differences in BMI, waist circumference, and percent body fat by level of sexual maturation among girls was most likely due to differences in growth patterns between the sexes. On average, girls experience greater increases in fat mass relative to lean mass during adolescence, and boys experience greater increases in lean mass relative to fat mass.<sup>13</sup> This is probably part of the mechanism underlying the fact that, on average, adult women have 22% body fat compared to adult men who, on average, have only 15% body fat.<sup>26</sup> Although in our study, percent body fat was, on average, lower for girls who were pre-pubertal versus pubertal, this cannot be interpreted as implying a causal relationship or being supportive of a particular direction of causality. However, this observation was consistent with the existing literature.<sup>26</sup>

The association of early sexual maturity with obesity and metabolic syndrome is fairly well established for girls.<sup>10-12</sup> Therefore, it is not surprising that our findings show that higher BMI, waist circumference, fasting insulin, fasting glucose, HOMA, and HOMA-B are associated with early sexual maturation among girls. Wang reported that early sexual maturation was inversely associated with BMI for boys and our results are consistent with this;<sup>13</sup> however, our study is, to the best of our knowledge, the first to examine insulin sensitivity with respect to timing of sexual maturation among boys. Among the boys in our study population, early versus not early sexual maturation was associated with lower BMI, waist circumference, and percent body fat. In our study population, lower HOMA was associated with early versus not early sexual maturation among boys, but this decrease was not detectable at the 0.05 significance level. Early sexual maturation has been reported to be associated with adverse changes in serum lipids,<sup>12</sup> but our results indicate that early maturation is associated with lower LDL for girls and boys.

The cross-sectional design of this study makes it difficult to examine a potential causal relation of sexual maturation and early sexual maturation with metabolic outcomes such as insulin resistance and/or lipid profile, as temporality of events cannot be established using this type of data. The follow-up data on this cohort should shed more light on whether the differences that we have reported between early and not early maturers do impart excess risk for type 2 diabetes or the metabolic syndrome. Also, this cohort was drawn from the children and adolescent relatives of working, seemingly healthy individuals. While these children cannot be considered representative of the Mexican population as a whole, they may be considered representative of middle to low income adolescents residing in the urban areas of central Mexico.

These limitations notwithstanding, our results provide important information about the association between level of sexual development and early sexual maturation and differences in metabolic profile in a population at high risk for obesity, metabolic syndrome, and diabetes. Our results may corroborate the hypothesis that among Hispanic children with a family history of type 2 diabetes the pubertal drop in insulin sensitivity is not detectable. Furthermore, this is the first study of this type to be conducted among such a large group of Mexican adolescents. We also report for the first time on the differences in a comprehensive panel of metabolic parameters between early versus not early maturing boys. The follow-up analysis may further support and strengthen the argument that early intervention is important in reducing the risks for obesity, metabolic syndrome, and type 2 diabetes for Mexican children and adolescents who exhibit early sexual development.

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