Early-life determinants of the age at menarche

by

Erica Christine Jansen

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2016

Doctoral Committee:

Professor Eduardo Villamor, Chair
Assistant Professor Nancy Fleischer
Assistant Professor Alison Mondul
Associate Professor Laura Rozek

Acknowledgements

I would like to extend my sincerest gratitude to many people who have supported me and this research. First to my committee members Alison Mondul, Nancy Fleischer, and Laura Rozek. It was a great pleasure and honor working with each one of you. Thank you so much for supporting and challenging me in my work. I would like to offer a special thanks to my advisor and chair, Eduardo Villamor. I learned so much through your instruction and guidance (and your own attention to detail!), and for that I will forever be grateful. Thank you so much for always taking the time for me and for giving me many opportunities to learn and grow as an epidemiologist. I would also like to acknowledge colleagues in Colombia, Oscar Herrán, Constanza Marín, and Mercedes Mora-Plazas. This work would simply not be possible without all of your hard work.To all of my colleagues in SPH- especially other "Villamor groupies" including Kerry Flanagan, Wenchao Li, Sonia Robinson, and those from my cohort including Rachel Gicquelais, Alicia Kraay, and Kyu Han Lee- I cannot thank you enough for all of your support and friendship. It was so much fun learning from you and with you! Finally, I want to recognize my family and loved ones who have been so supportive throughout this process. To my parents, Ted and Sue- I could not ask for two better people. You are two of the most hard-working, caring, and resilient people I know, and I will always strive to be more like you. To my siblings, Kevin and Lydia- thanks for always taking an interest in my work and for your continued encouragement and love. And to Chris- words cannot express howgrateful I am to you for your daily support. Your always positive attitude and your willingness to help out in any way are admirable and so appreciated!

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BMI	Body mass index
CI	Confidence interval
DANE	Departmento Administrativo Nacional de Estadistica (National Department of Statistics)
ENDS	Encuesta Nacional de Demografia y Salud (Demographic and HealthSurvey)
ENSIN	Encuesta Nacional de la Situacion Nutricional (National Nutrition Survey)
FFQ	Food frequency questionnaire
HR	Hazard ratio
ICBF	Instituto Colombiano de Bienestar Familiar (Colombian Institute of Family Welfare)
IGF-1	Insulin-like growth factor-1
IQR	Interquartile range
PUFA	Polyunsaturated fatty acid
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
UK	United Kingdom
US	United States
USDA	United States Department of Agriculture

Chapter 1

Introduction

Overview

Menarche, the first menstrual period, is a recognizable marker of puberty. The timing of menarche has important public health ramifications because an early age at menarche is associated with breast and endometrial cancers, obesity, type II diabetes, cardiovascular disease, and all-cause mortality (1-4). Secular trends and between-country variability in age at menarche suggest that the onset of puberty is responsive to changing environmental conditions. Nevertheless, the specific environmental factors that influence age at menarche remain largely unidentified. In this dissertation we first examine sociodemographic influences on recent trends in age at menarche using nationally-representative data from Colombia. Next, because exposures occurring during the prenatal period are thought to play a role in the timing of sexual maturation (5), we evaluate prenatal factors related to season and altitude that are not well understood in relation to menarche. We finally consider the role of childhood diet. In particular, higher animal food and/or animal protein intake might be related to an earlier age at menarche (6). Nevertheless, individual food items such as red meat have not been sufficiently examined. In summation, the overarching aim of this work is to gain a more complete understanding of the sociodemographic correlates related to recent trends in menarche in a population undergoing the nutrition transition, and to identify environmental predictors of menarche that may be amenable to public health intervention.

Specific Aims

This work aims to describe recent trends and correlates in age at menarche in Colombia, and to investigate the relations of several specific environmental predictors with age at menarche.

<u>Aim 1</u>: To describe the median age at menarche and the recent trends in Colombian girls born 1992-2000 using nationally representative data from Colombia's 2010 National Nutrition Survey (ENSIN). We will also assess the relation of menarche with the contextual sociodemographic factors urbanicity, wealth index, and ethnicity. Finally, we will ascertain whether the recent trends in menarche are homogenous with respect to levels of urbanicity, wealth index, and ethnicity.

<u>Aim 2</u>: To examine whether a higher number of gestation days exposed to the rainy season is associated with an earlier age at menarche in Colombia, using nationally representative data from the 2010 ENSIN survey. In addition, we will ascertain whether there is a positive relation between altitude of residence and age at menarche. Finally, we will determine whether the association between gestation days exposed to the rainy season and menarche is modified by altitude of residence.

<u>Aim 3</u>: To evaluate in a prospective study whether red meat intake frequency at 6-12 y of age is related to age at menarche in a group of low- and middle- income school-aged girls from Bogota, Colombia during a median 5.6 years of follow-up.

The importance of menarche in public health

The age at menarche is the age of a girl's first menstruation. Menarche occurs towards the end of the sexual maturation process, typically after the initiation of breast and pubic hair development and during the deceleration of the growth spurt (7). The initiation of menstruation is an easily identifiable and memorable event in a girl's life, making it a valuable marker of the presence of puberty in epidemiological studies.

There is wide variability in the timing of menarche between populations and a secular decline toward earlier menarche within populations. This indicates that although the timing of menarche is heritable to some degree (8), it may be sensitive to environmental and socioeconomic conditions at the population level. In higher-income countries, girls from families of higher socioeconomic status have later ages at menarche compared to girls from families of lower socioeconomic status (9). For example, a longitudinal study among 251 women from the UK found that those from the highest socioeconomic status, measured by paternal occupation, had menarche on average 7.8 months later than those of lowest socioeconomic status. In contrast, in the context of lower-income countries, socioeconomic status is inversely associated with age at menarche (7, 10). For example, recent studies in Nigeria and Bangladesh found that girls from families of higher socioeconomic status, as indicated by parental education and/or occupation, had an earlier age at menarche compared to girls from families of lower socioeconomic status (11, 12). In Nigeria, the difference in age at menarche comparing the highest socioeconomic status girls to the lowest was 9.4 months, and in Bangladesh it was 2.8 months. The age at menarche also is variable over time. In low and middle-income settings, improvements of socioeconomic, hygienic, and nutritional conditions are typically followed by declines in the timing of puberty onset. This is apparent in the documented decline in age at menarche in the last few centuries (13). For example, the mean age at menarche in Europe declined from approximately 15-17 years in the 1800s to 13-13.5 years in the mid-1900s (14), and currently is about 12-12.5 years (15). Whereas the age at menarche seems to have slowed or leveled off in some higher-income countries such as the US (13) and Greece (16), there is a continued secular decline in age at menarche in many regions of the world (e.g. Thailand, India, and South Africa (17-19)).

From a public health perspective, differences in the timing of menarche at the population level are important because they could be linked to differences in health outcomes. In adulthood, an earlier age at menarche is associated with breast and endometrial cancers, obesity, type II diabetes, cardiovascular disease, and all-cause mortality (1-4). In addition, early menarche has been related to risk factors during adolescence including alcohol and tobacco use, early sexual debut, and teenage pregnancy (20, 21).

There is not a consensus on specific cutpoints for an early menarche. Some studies have arbitrarily defined early menarche as the event occurring <12 y of age (22), while others defined it as <11 y of age (23). One likely reason that there are not standard definitions of early menarche is the wide variability in average ages at menarche between populations. Nonetheless, the finding that earlier ages at menarche are related to adverse health outcomes is not unique to particular regions or resource settings. For example, although much of the research linking an earlier age at menarche with cardiometabolic outcomes later in life has been from higher income and Western settings, studies in Taiwan and Argentina found that girls with earlier ages at menarche had higher risk of metabolic syndrome, measured by waist circumference, blood glucose, triglycerides, cholesterol, and blood pressure (22, 24). Similarly, the association between an earlier menarche and higher risk of breast cancer is not specific to high income settings, evidenced by studies in Tunisia and Bangladesh (25, 26). Thus, although a downward trend in the age at menarche may be a sign of overall improvements in socioeconomic and nutritional conditions, a decline in the age at menarche at the population level deserves public health recognition because it can act as an early indicator for ensuing increases in teenage pregnancy, breast cancer, obesity, and type II diabetes (27).

Considering that changes in age at menarche at the population level have public health ramifications, there should be increased surveillance of this endpoint, especially in low and middle-income countries that may be currently undergoing the epidemiologic and nutrition transition. Colombia, a nation of 48 million people, is classified as a middle income country (28). A high proportion (over 70%) of the population currently resides in urban areas; urban population growth was primarily driven by armed conflicts starting in the 1950s and industrialization of major economic centers in the 1970s (29). Increases in urbanization and economic development have coincided with an ongoing nutrition transition in Colombia. This refers to shifts in diet and physical activity characterized by higher rates of sedentary behavior and diets higher in sugar, fat, and animal source foods(30). One outcome typically associated with the nutrition transition, obesity, is most evident among certain groups in the Colombian population, including women, those in urban areas and those of highest socioeconomic status; although obesity prevalence is increasing at a faster rate in lower socioeconomic groups compared to higher socioeconomic groups (31). It is unknown how the nutrition transition has affected the timing of menarche among Colombian girls; although an increase in the prevalence of adolescent pregnancy from 13% in 1990 to 22% in 2005 may be suggestive of an earlier average age at menarche at the population level (32). Examining the age at menarche on a national scale provides valuable information on the effects of the nutrition transition in Colombia and allows us to identify subgroups in the population whose age at menarche is declining fastest and may be at the highest risk of teenage pregnancy and breast cancer.

Environmental predictors of the timing of menarche

Considering that the timing of menarche is responsive to environmental influences, it is relevant to investigate environmental exposures that could be most amenable to public health interventions. Although changes in socioeconomic and sanitary conditions are related to declines in the age of pubertal onset at the population level, these factors alone are not sufficient to explain all of the observed variability in menarche, and they do not address the biological mechanisms that link particular environmental factors with the timing of puberty. Nevertheless, a number of environmental exposures have been investigated in the literature as potential predictors of an earlier age at menarche, including higher intrauterine androgen exposures (33), lower physical activity levels (34), environmental toxicant ingestion such as bisphenol A (35), higher animal protein intake during childhood (36), early-life psychosocial factors like child abuse (37), and lower maternal breastfeeding (38). However, inconsistent or contradictory findings exist for most of these relations. In addition, many early life exposures have not yet been well-examined.

Prenatal influences on age at menarche

Some authors propose that the timing of menarche could be set very early in life, due to gestational programming effects that affect the tempo of sexual maturation (5). In support, there is some evidence to suggest that intrauterine exposures are related to the timing of menarche (33, 39). For example, the ratio of the length of the second to the fourth finger, thought to be a marker of prenatal androgen exposure has been positively related to menarche among Colombian girls

(33). To further illustrate, a prospective study in Denmark showed that maternal smoking during pregnancy was associated with an earlier age at menarche (40). In contrast, there has been no relation observed between some prenatal exposures, such as gestational diabetes, with menarcheal age (39).

Seasonal variation is one prenatal environmental factor that could potentially affect the health of the developing fetus. For example, seasonal changes in sunlight availability affect the endogenous production of vitamin D (41) and photoperiod-mediated melatonin production (42). Seasonal changes also result in differences in infectious disease rates (43), as the causative agents have differential survival depending on environmental conditions. In addition, food availability or diversity can also vary seasonally (44). Higher exposure to particular seasonal factors such as undernutrition or infection during the prenatal period could act as a prediction of extrauterine conditions and may signal the offspring to adjust their development strategy in a way to optimize survival and reproductive potential (5). Specifically, it is proposed that undernutrition or stress during the prenatal period could be related to accelerations in the timing of menarche, particularly if there is a mismatch in the nutritional conditions (e.g. overnutrition) during childhood. There have been a few studies examining the relation of season of birth with age at menarche, although with mixed results. A recent study among Polish women found that those born in the summer months had earlier ages at menarche compared to those born during other months of the year (45). In contrast, studies in the UK, US, Denmark, and Italy reported no association between season of birth and age at menarche (46-49). Nonetheless, these studies were all within the context of temperate climates. It may be particularly relevant from a public health standpoint to examine associations between season during gestation and age at menarche in a tropical climate, because many regions with tropical climates are also low and middle income settings where seasonal differences such as food shortages could affect health more drastically.

Another environment-related factor that has the potential to affect human health is altitude. As elevation increases, oxygen availability, temperature, and humidity decreases whereas ultraviolet radiation increases (50). In regions of high altitude, oxygen deprivation during development could be linked to adaptive responses that compensate for the increased energy requirements necessary for higher lung and chest development by delaying the timing of puberty (51). In support, studies in Peru and Bolivia found that girls born in altitudes >3000 m had older ages at menarche compared to girls living at lower elevations (52-54). However, previous studies were limited by potential residual confounding due to socioeconomic status, making it challenging to disentangle true altitude effects from large differences in socioeconomic status.

Colombia provides a valuable setting for exploring the questions related to season and altitude considered above. First, Colombia is located close to the equator which allows a unique opportunity to evaluate the prenatal season question in a tropical climate. Secondly, the Andes mountain range runs through central Colombia, meaning that there is a wide range of altitudes in which Colombians reside. This provides adequate variability to observe an association between altitude and menarche, which may have been a limitation in other studies (55). Considering that the prenatal period is a critical window of environmental susceptibility, gaining new insights into how perinatal climate-related factors affect the timing of menarche could have important implications for pregnant women.

Childhood nutritional influences on age at menarche

Of the childhood environmental factors affecting age at menarche, nutrition may be among the most relevant. Nutritional influences on age at menarche are plausible from a biological standpoint because availability of energy, protein and nutrients essential for sustaining pregnancy and healthy offspring may act as a signal on the body to initiate puberty. Changes in energy balance could be one important signal of the capability for reproduction. According to the "Frisch hypothesis," a critical body fat percentage must be achieved prior to the initiation of puberty. The notion was conceived in the 1970s, when Frisch et al. noted that whereas age at menarche was highly variable across human populations, attained weight at menarche seemed relatively homogeneous (56, 57). Further research led them to hypothesize that onset of puberty in girls was triggered only when total body fat reached about 17% (58). Although this hypothesis initially sparked controversy (59), many longitudinal studies have since reported an inverse association between childhood adiposity and age at menarche (60, 61).

Particular foods and/or nutrients may also be implicated in the timing of menarche, either as a precursor to changes in energy balance or as an independent predictor of pubertal timing. Childhood protein and/or animal food intake is one macronutrient group that has been examined in epidemiologic studies for its potential role on the timing of puberty. Some evidence indicates that intake of animal foods such as milk during childhood may be related to earlier onset of puberty. Gunther and colleagues reported that protein intake from cow milk and dairy products was related to earlier pubertal growth spurt and peak height velocity among 112 German boys and girls (62). Similarly, a prospective study of 134 Iranian girls found that those with milk intake $\geq$34 g/day at 9 y of age had higher odds of early menarche than girls with milk intake <34 g/day (63). Using data from the National Health and Nutrition Examination Survey, Wiley et al. found that higher milk consumption at 5-12 y among 2057 US girls was associated with an earlier age at menarche (64). In other studies, dairy intake has not been related to onset of puberty (65).

Meat intake has also been implicated in the timing of puberty. In a cohort study of 3298 girls from Southwest England, those with the highest meat intake at 3 and 7 y of age had greater odds of menarche at 12.5 y than girls in the lowest meat intake category (66). Of note, protein intake at age 10 y was not related to menarche, which could indicate an age-specific effect. In a small study of girls from the US, animal protein intake at 3-8 y of age was related to earlier menarche (67). Similarly, among German girls, intakes of total and animal protein at 5-6 y of age were related to early age at menarche (62). Another investigation of 230 US girls found that girls who consumed meat at age 9-15 y had menarche an average 6 months earlier than girls with a vegetarian diet at baseline (68), although the estimates were not adjusted for potential confounders. In contrast, Carwile et al. reported no association between meat intake at age 9 y and age at menarche in 5583 US girls after adjustment for sociodemographic and nutritional potential confounders (65). One possible explanation for this discrepancy is differences in the timing of dietary assessments because intake around the time of puberty onset may be less relevant than earlier childhood diet (65, 66).

Relatively few studies have examined childhood intake of specific animal food groups in relation to menarche, including red meat. This is surprising given the focus on red meat intake during adulthood as a risk factor for cardiovascular disease and cancer (69). A recent investigation found that red meat intake during adolescence was related to higher breast cancer risk (70). Considering that early menarche is a predictor of breast cancer (1), it is possible that red meat intake during childhood could be associated with an earlier menarche.

An examination of childhood diet, red meat sources in particular, with the age at menarche is highly relevant from a public health standpoint because it could provide evidence of the relative importance of childhood diet in relation to puberty, and it may have implications for potential public health intervention. This research question is also salient within the context of Colombia because red meat intake is expected to increase in populations experiencing a nutrition transition (71).

Summary of Chapters

In summation, this dissertation work aims to add knowledge on the early life determinants of menarche in a few instrumental ways. Describing the age at menarche is useful for monitoring the effects of changing environmental and socioeconomic conditions on child populations and to identify populations who may be most vulnerable to the adverse health outcomes of an earlier menarche. Thus, in the second chapter, we will describe the trends and correlates in age at menarche in the Colombian population, a country currently undergoing the epidemiologic and nutrition transition. We also seek to evaluate a few specific environmental predictors of an earlier age at menarche that are currently understudied and may be amenable to public health intervention. In the third chapter, we examine how the perinatal exposures of season and altitude are related to the age at menarche, using data from Colombia's 2010 National Nutrition Survey. In the fourth chapter we focus on how childhood red meat intake is associated with the timing of puberty in the context of a longitudinal study among 456 schoolgirls from Bogota, Colombia. Finally, we summarize the chapters and consider the public health relevance of the findings in chapter five.

REFERENCES

1. Horn J, Opdahl S, Engstrom MJ, Romundstad PR, Tretli S, Haugen OA, Bofin AM, Vatten LJ, Asvold BO. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. Cancer Causes Control: CCC 2014;25(7):881-9. doi: 10.1007/s10552-014-0388-0.
2. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. Am J Epidemiol 2014;180(1):29-40. doi: 10.1093/aje/kwu113.
3. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Fournier A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;127(2):442-51. doi: 10.1002/ijc.25050.
4. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, Hu FB. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. American Journal of Epidemiology 2010;171(3):334-44. doi: 10.1093/aje/kwp372.
5. Gluckman PD, Beedle AS, Hanson MA, Low FM. Human growth: evolutionary and life history perspectives. Nestle Nutr Inst Workshop Ser 2013;71:89-102. doi: 10.1159/000342572.
6. Villamor E, Jansen EC. Nutritional Determinants of the Timing of Puberty. Annu Rev Public Health 2016. doi: 10.1146/annurev-publhealth-031914-122606.
7. Tanner JM. Fetus into Man. Second Edition ed. Cambridge: Harvard University Press, 1990.
8. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, He C, Chasman DI, Esko T, Thorleifsson G, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. Nature 2014;514(7520):92-7. doi: 10.1038/nature13545.
9. Deardorff J, Abrams B, Ekwaru JP, Rehkopf DH. Socioeconomic status and age at menarche: an examination of multiple indicators in an ethnically diverse cohort. Annals of Epidemiology 2014;24(10):727-33. doi: 10.1016/j.annepidem.2014.07.002.
10. Cole TJ. Secular trends in growth. Proc Nutr Soc 2000;59(2):317-24.
11. Hossain MG, Islam S, Aik S, Zaman TK, Lestrel PE. Age at menarche of university students in Bangladesh: secular trends and association with adult anthropometric measures and socio-demographic factors. Journal of Biosocial Science 2010;42(5):677-87. doi: 10.1017/S0021932010000210.
12. Onyiriuka AN, Egbagbe EE. Anthropometry and menarcheal status of adolescent nigerian urban senior secondary school girls. International Journal of Endocrinology and Metabolism 2013;11(2):71-5. doi: 10.5812/ijem.8052.
13. Kaplowitz P. Pubertal development in girls: secular trends. Curr Opin Obstet Gynecol 2006;18(5):487-91. doi: 10.1097/01.gco.0000242949.02373.09.
14. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med 1982;306(17):1033-5. doi: 10.1056/NEJM198204293061707.
15. Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the Health Behaviour in School-aged Children Study. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 2012;50(6):621-6. doi: 10.1016/j.jadohealth.2011.10.254.

16. Papadimitriou A, Fytanidis G, Douros K, Bakoula C, Nicolaidou P, Fretzayas A. Age at menarche in contemporary Greek girls: evidence for levelling-off of the secular trend. Acta Paediatr 2008;97(6):812-5. doi: 10.1111/j.1651-2227.2008.00806.x.
17. Jaruratanasirikul S, Chanpong A, Tassanakijpanich N, Sriplung H. Declining age of puberty of school girls in southern Thailand. World J Pediatr 2014;10(3):256-61. doi: 10.1007/s12519-014-0472-2.
18. Jones LL, Griffiths PL, Norris SA, Pettifor JM, Cameron N. Age at menarche and the evidence for a positive secular trend in urban South Africa. Am J Hum Biol 2009;21(1):130-2. doi: 10.1002/ajhb.20836.
19. Pathak PK, Tripathi N, Subramanian SV. Secular trends in menarcheal age in India-evidence from the Indian human development survey. PLoS One 2014;9(11):e111027. doi: 10.1371/journal.pone.0111027.
20. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. Pediatrics 2005;116(6):1451-6. doi: 10.1542/peds.2005-0542.
21. Vaughan EB, Van Hulle CA, Beasley WH, Rodgers JL, D'Onofrio BM. Clarifying the associations between age at menarche and adolescent emotional and behavioral problems. Journal of Youth and Adolescence 2015;44(4):922-39. doi: 10.1007/s10964-015-0255-7.
22. Chang CJ, Lai MM, Lin CC, Liu CS, Li TC, Li CI, Lin WY. Age at menarche and its association with the metabolic syndrome in Taiwan. Obes Res Clin Pract 2015. doi: 10.1016/j.orcp.2015.10.003.
23. Mueller NT, Jacobs DR, Jr., MacLehose RF, Demerath EW, Kelly SP, Dreyfus JG, Pereira MA. Consumption of caffeinated and artificially sweetened soft drinks is associated with risk of early menarche. Am J Clin Nutr 2015;102(3):648-54. doi: 10.3945/ajcn.114.100958.
24. Figueroa Sobrero A, Evangelista P, Kovalskys I, Digon P, Lopez S, Scaiola E, Perez N, Dieuzeide G, Walz F, Mazza C. Cardio-metabolic risk factors in Argentine children. A comparative study. Diabetes Metab Syndr 2015. doi: 10.1016/j.dsx.2015.10.003.
25. Ahmed K, Asaduzzaman S, Bashar MI, Hossain G, Bhuiyan T. Association Assessment among Risk Factors and Breast Cancer in a Low Income Country: Bangladesh. Asian Pac J Cancer Prev 2015;16(17):7507-12.
26. Msolly A, Gharbi O, Ben Ahmed S. Impact of menstrual and reproductive factors on breast cancer risk in Tunisia: a case-control study. Med Oncol 2013;30(1):480. doi: 10.1007/s12032-013-0480-4.
27. McCormack VA, Boffetta P. Today's lifestyles, tomorrow's cancers: trends in lifestyle risk factors for cancer in low- and middle-income countries. Ann Oncol 2011;22(11):2349-57. doi: 10.1093/annonc/mdq763.
28. 2016. Internet: http://data.worldbank.org/country/colombia.
29. Alvarez-Berrios NL, Pares-Ramos IK, Aide TM. Contrasting patterns of urban expansion in Colombia, Ecuador, Peru, and Bolivia between 1992 and 2009. Ambio 2013;42(1):29-40. doi: 10.1007/s13280-012-0344-8.
30. The Nutrition Transition: Diet and Disease in the Developing World. San Diego, California: Academic Press, 2002.
31. Kasper NM, Herran OF, Villamor E. Obesity prevalence in Colombian adults is increasing fastest in lower socio-economic status groups and urban residents: results from

two nationally representative surveys. Public Health Nutr 2014;17(11):2398-406. doi: 10.1017/S1368980013003418.
32. Sarmiento OL, Ramirez A, Kutschbach BS, Pinzon PL, Garcia S, Olarte AC, Mosquera T, Atalah E, Ojeda G, Forero Y. Nutrition in Colombian pregnant women. Public Health Nutr 2012;15(6):955-63. doi: 10.1017/S1368980011003399.
33. Oberg AS, Villamor E. Low digit ratio predicts early age at menarche in Colombian schoolgirls. Paediatr Perinat Epidemiol 2012;26(5):448-55. doi: 10.1111/j.1365-3016.2012.01310.x.
34. Malina RM, Spirduso WW, Tate C, Baylor AM. Age at menarche and selected menstrual characteristics in athletes at different competitive levels and in different sports. Med Sci Sports 1978;10(3):218-22.
35. Buttke DE, Sircar K, Martin C. Exposures to endocrine-disrupting chemicals and age of menarche in adolescent girls in NHANES (2003-2008). Environ Health Perspect 2012;120(11):1613-8. doi: 10.1289/ehp.1104748.
36. Cheng G, Remer T, Prinz-Langenohl R, Blaszkewicz M, Degen GH, Buyken AE. Relation of isoflavones and fiber intake in childhood to the timing of puberty. Am J Clin Nutr 2010;92(3):556-64. doi: 10.3945/ajcn.2010.29394.
37. Boynton-Jarrett R, Wright RJ, Putnam FW, Lividoti Hibert E, Michels KB, Forman MR, Rich-Edwards J. Childhood abuse and age at menarche. J Adolesc Health 2013;52(2):241-7. doi: 10.1016/j.jadohealth.2012.06.006.
38. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. BMC Public Health 2010;10:736. doi: 10.1186/1471-2458-10-736.
39. Epplein M, Novotny R, Daida Y, Vijayadeva V, Onaka AT, Le Marchand L. Association of maternal and intrauterine characteristics with age at menarche in a multiethnic population in Hawaii. Cancer Causes Control 2010;21(2):259-68. doi: 10.1007/s10552-009-9457-1.
40. Ernst A, Kristensen SL, Toft G, Thulstrup AM, Hakonsen LB, Olsen SF, Ramlau-Hansen CH. Maternal smoking during pregnancy and reproductive health of daughters: a follow-up study spanning two decades. Hum Reprod 2012;27(12):3593-600. doi: 10.1093/humrep/des337.
41. Luque-Fernandez MA, Gelaye B, VanderWeele T, Ferre C, Siega-Riz AM, Holzman C, Enquobahrie DA, Dole N, Williams MA. Seasonal variation of 25-hydroxyvitamin D among non-Hispanic black and white pregnant women from three US pregnancy cohorts. Paediatr Perinat Epidemiol 2014;28(2):166-76. doi: 10.1111/ppe.12103.
42. Reiter RJ, Tan DX, Korkmaz A, Rosales-Corral SA. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. Hum Reprod Update 2014;20(2):293-307. doi: 10.1093/humupd/dmt054.
43. Rodriguez-Martinez CE, Rodriguez DA, Nino G. Respiratory syncytial virus, adenoviruses, and mixed acute lower respiratory infections in children in a developing country. J Med Virol 2015;87(5):774-81. doi: 10.1002/jmv.24139.
44. M'Kaibi FK, Steyn NP, Ochola S, Du Plessis L. Effects of agricultural biodiversity and seasonal rain on dietary adequacy and household food security in rural areas of Kenya. BMC Public Health 2015;15:422. doi: 10.1186/s12889-015-1755-9.

45. Klis K, Jarzebak K, Borowska-Struginska B, Mulawa A, Zurawiecka M, Wronka I. Season of birth influences the timing of first menstruation. Am J Hum Biol 2015. doi: 10.1002/ajhb.22783.
46. Boldsen JL. Season of birth and recalled age at menarche. J Biosoc Sci 1992;24(2):167-73.
47. Maisonet M, Christensen KY, Rubin C, Holmes A, Flanders WD, Heron J, Ong KK, Golding J, McGeehin MA, Marcus M. Role of prenatal characteristics and early growth on pubertal attainment of British girls. Pediatrics 2010;126(3):e591-600. doi: 10.1542/peds.2009-2636.
48. Jongbloet PH, Kersemaekers WM, Zielhuis GA, Verbeek AL. Menstrual disorders and month of birth. Ann Hum Biol 1994;21(6):511-8.
49. Cagnacci A, Pansini FS, Bacchi-Modena A, Giulini N, Mollica G, De Aloysio D, Vadora E, Volpe A, Emilia-Romagna Operative Group for the M. Season of birth influences the timing of menopause. Hum Reprod 2005;20(8):2190-3. doi: 10.1093/humrep/dei040.
50. Geografia de Colombia. Bogota, Colombia: Instituto Geografico Agustin Codazzi, 2014.
51. Frisancho AR. Developmental functional adaptation to high altitude: review. Am J Hum Biol 2013;25(2):151-68. doi: 10.1002/ajhb.22367.
52. Gonzales GF, Villena A. Body mass index and age at menarche in Peruvian children living at high altitude and at sea level. Hum Biol 1996;68(2):265-75.
53. Freyre EA, Ortiz MV. The effect of altitude on adolescent growth and development. J Adolesc Health Care 1988;9(2):144-9.
54. Greksa LP. Age of menarche in Bolivian girls of European and Aymara ancestry. Ann Hum Biol 1990;17(1):49-53.
55. Matchock RL, Susman EJ, Brown FM. Seasonal rhythms of menarche in the United States: correlates to menarcheal age, birth age, and birth month. Womens Health Iss 2004;14(6):184-92. doi: 10.1016/j.whi.2004.07.007.
56. Frisch RE. Weight at menarche: similarity for well-nourished and undernourished girls at differing ages, and evidence for historical constancy. Pediatrics 1972;50(3):445-50.
57. Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of critical body weights and adolescent events. Science 1970;169(3943):397-9.
58. Frisch RE. Fatness of girls from menarche to age 18 years, with a nomogram. Hum Biol 1976;48(2):353-9.
59. Trussell J. Statistical flaws in evidence for the Frisch hypothesis that fatness triggers menarche. Hum Biol 1980;52(4):711-20.
60. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. Pediatrics 2007;119(3):e624-30. doi: 10.1542/peds.2006-2188.
61. Song Y, Ma J, Wang HJ, Wang Z, Hu P, Zhang B, Agardh A. Trends of age at menarche and association with body mass index in Chinese school-aged girls, 1985-2010. Journal of Pediatrics 2014;165(6):1172-7 e1. doi: 10.1016/j.jpeds.2014.08.013.
62. Gunther AL, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. J Nutr 2010;140(3):565-71. doi: 10.3945/jn.109.114934.
63. Ramezani Tehrani F, Mirmiran P, Gholami R, Moslehi N, Azizi F. Factors influencing menarcheal age: results from the cohort of tehran lipid and glucose study. Int J Endocrinol Metab 2014;12(3):e16130. doi: 10.5812/ijem.16130.

64. Wiley AS. Milk intake and total dairy consumption: associations with early menarche in NHANES 1999-2004. PLoS One 2011;6(2):e14685. doi: 10.1371/journal.pone.0014685.
65. Carwile JL, Willett WC, Wang M, Rich-Edwards J, Frazier AL, Michels KB. Milk Consumption after Age 9 Years Does Not Predict Age at Menarche. J Nutr 2015. doi: 10.3945/jn.115.214270.
66. Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, Emmett PM. Diet throughout childhood and age at menarche in a contemporary cohort of British girls. Public Health Nutr 2010;13(12):2052-63. doi: 10.1017/S1368980010001461.
67. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiol 2000;152(5):446-52.
68. Kissinger D, Sanchez A. The association of dietary factors with age at menarche. Nutrition Research 1987;7:471-9.
69. Norat T, Scoccianti C, Boutron-Ruault MC, Anderson A, Berrino F, Cecchini M, Espina C, Key T, Leitzmann M, Powers H, et al. European Code against Cancer 4th Edition: Diet and cancer. Cancer Epidemiol 2015;39 Suppl 1:S56-66. doi: 10.1016/j.canep.2014.12.016.
70. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Adolescent meat intake and breast cancer risk. Int J Cancer 2015;136(8):1909-20. doi: 10.1002/ijc.29218.
71. Popkin BM. Contemporary nutritional transition: determinants of diet and its impact on body composition. Proc Nutr Soc 2011;70(1):82-91. doi: 10.1017/S0029665110003903.

Chapter 2

Trends and correlates of age at menarche in Colombia: results from a nationally representative survey

Erica C. Jansen, Oscar F. Herrán, and Eduardo Villamor

ABSTRACT

Surveillance of age at menarche could provide useful information on the impact of changing environmental conditions on child health. Nevertheless, nationally-representative data are exceedingly rare. The aim of this study was to examine trends and sociodemographic correlates of age at menarche of Colombian girls. The study sample included 15 441 girls born between 1992 and 2000 who participated in the Colombian National Nutrition Survey of 2010. We estimated median menarcheal age using Kaplan-Meier time-to-event analyses. Hazard ratios with 95% confidence intervals were estimated with Cox regression models. The median age at menarche was 12.6 years. There was an estimated decline of 0.54 years/decade ($P<0.001$) over the birth years; this decline was only observed among girls from urban areas, and was more pronounced among girls from wealthier versus poorer families. Higher family wealth was related to earlier menarcheal ages whereas Indigenous ethnicity was associated with later ages at menarche. In conclusion, a negative trend in age at menarche is ongoing in Colombia, especially in groups most likely to benefit from socioeconomic development.

INTRODUCTION

Age at menarche, a measureable indicator of puberty onset, is a sensitive marker of environmental and socioeconomic conditions at the population level (1). In lower-income countries, socioeconomic status is inversely associated with age at menarche, and improvements of socioeconomic conditions are typically followed by declines in the timing of puberty onset (2, 3). For example, recent studies in Nigeria and Bangladesh found that girls from families of higher socioeconomic status, as indicated by parental education and/or occupation, had an earlier age at menarche compared to girls from families of lower socioeconomic status (4, 5).

Monitoring age at menarche at the country level could be highly relevant to document the effects of environmental conditions on child health because an earlier timing of puberty is related to adverse health outcomes during adolescence such as teenage pregnancy (6-8), lower final height (9), and higher risk of adult disease risk and all-cause mortality (10-12). Nevertheless, availability of data on age at menarche at the national level is exceedingly rare (13). The Colombian National Nutrition Survey of 2010 for the first time included a question on age at menarche among girls. Whereas a previous investigation documented a negative trend in age at menarche in this country (14), the study sample was not representative. The availability of nationally-representative data on menarche in Colombia constitutes an unprecedented opportunity to examine recent trends and correlates of the timing of puberty in a country undergoing rapid political and economic transformations. The aim of this study was to examine recent trends and socioeconomic correlates of age at menarche of Colombian girls born between 1992 and 2000, using data from a nationally-representative survey.

METHODS

Study Population

The Colombian National Nutrition Survey (ENSIN) was conducted in 2010 by the Colombian Institute of Family Welfare (Instituto Colombiano de Bienestar Familiar, ICBF) in conjunction with the Colombian Demographic and Health Survey (ENDS). Briefly, a multistage stratified sampling scheme was employed to select participants representing 99% of the Colombian population. All municipalities from the thirty-two departments in the country were grouped into strata based on similar geographic and sociodemographic characteristics. One municipality was randomly chosen from each stratum with the probability of being chosen proportional to the population size. Clusters of about ten households were randomly selected within strata and all household members were invited to participate. A total 50 670 households were included, representing 4987 clusters from 258 strata.

Trained personnel administered questionnaires to the head of each household to obtain demographic information as well as wealth measures. Anthropometric measurements were collected on each member of the family with standardized techniques and calibrated instruments. Research personnel measured height with a stadiometer (Diseños Flores SR. Ltda, Lima, Perú) to the nearest millimeter, and weight with SECA 872 scales to the nearest 100 grams. Girls aged 10 to less than 18 years were asked to recall the age in years and months when their first menstrual period had occurred or if it had not yet occurred.

2.2. Data Sources

The survey included 188 599 people; 16 940 were girls 10 to <18 years of age. We excluded 1499 girls with missing information on menarche or who answered “don’t know” to the question on age at menarche. The final sample comprised 15 441 girls born 1992-2000.

The primary outcome was age at menarche, estimated in decimal years. The exposures were year of birth, race/ethnicity, urbanicity, and wealth index. Other covariates included maternal education level and country region. Race/ethnicity was categorized as Indigenous, Afro-Colombian (survey response options black/mulato/Afro-Descendant, *raizal*, or *Palenquero*), or Mestizo-Caucasian (all others). Urbanicity was categorized as urban, small village, or disperse rural area. A continuous index representing household wealth was quantified by principal component analysis of various socioeconomic indicators including household assets, type of flooring, number of bedrooms per person and mode of transportation. This variable was categorized into quintiles.

Ethical Considerations

Participation consent was obtained prior to enrolment by the ICBF. The Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan determined that analyses of these anonymized data were exempt from review.

Statistical Analysis

Analyses were conducted with the use of the complex survey design routines of Stata statistical software package version 13 (StataCorp, College Station, TX, USA). We utilized time-to-event analytic techniques including the Kaplan-Meier method and Cox proportional hazards models because these methods properly account for right-censoring in the data (15) due to the inclusion of both pre- and post-menarcheal girls. These methods allow to combine information on menarcheal age from post-menarcheal girls with the last known age when menarche had not occurred from pre-menarcheal girls in the estimation of the population median age at menarche. In addition, proportional hazards modelling provides interpretable probability ratios of menarche by categories of predictors. This cannot be achieved with other methods, including the "status quo," which is used to estimate the median age at menarche of a population (16).

We estimated the weighted median age at menarche by categories of predictors using Kaplan-Meier cumulative probabilities from birth. For girls who had not yet experienced menarche, the censoring time was age at interview, estimated as date of interview minus birthdate. Cox proportional hazards models were used to estimate hazard ratios of menarche, accounting for the complex survey design. For ordinal predictors, we conducted tests for linear trend by introducing into the model a variable representing ordered categories as a continuous covariate. For nominal characteristics, we conducted Type III Wald Tests. Adjusted hazard ratios and 95% confidence intervals (95% CI) were estimated with a model that included all predictors, maternal education, and region. To address issues of potential reverse causation and potential outcome misclassification among the oldest girls, we conducted supplemental analysis of the sociodemographic correlates of menarche, restricting to girls 10-14 y at the time of the survey.

We examined the relation of year of birth and age at menarche overall and stratified by levels of urbanicity, wealth, and race/ethnicity. Birth years 1998 through 2000 were combined because <10% of girls born after 1998 had experienced menarche at the time of interview and statistical power was very low for years 1999 and 2000 separately. Trends in age at menarche over time (years/decade) were estimated as the slope of linear regression models with median age at menarche as the outcome and year of birth as the predictor. The statistical significance of these trends was determined using tests for linear trend for year of birth in multivariable Cox proportional hazards models. Interactions were tested with the use of Type III Wald tests in Cox regression. All tests incorporated the complex survey design.

RESULTS

The mean ± SD age of girls at the time of the interview was 13.9 ± 2.3 years. The weighted proportion (%) of girls with menarche was 0, 3.5, 16.6, 48.9, 78.5, 94.2, 98.7, 99.9, and 99.8 for girls ages 9, 10, 11, 12, 13, 14, 15, 16, and 17 years respectively. Thirty-three percent of participants had not experienced menarche and were censored.

The weighted estimated median age at menarche was 12.6 years (IQR 12.0 to 13.5 years). Age at menarche was inversely related to year of birth (**Table 1.1**). The difference in median age at menarche between girls born in 1992 and those born between 1998 and 2000 was 5.04 months, with an estimated decline of 0.54 y/decade ($P<0.001$).

Next, we examined the associations of contextual sociodemographic characteristics with age at menarche. In bivariate analysis, age at menarche was inversely associated with the girls' wealth index (**Table 1.1**). In addition, age at menarche was positively related to Indigenous ethnicity and living in non-urban areas. After multivariable adjustment, urbanicity was not significantly associated with menarche, while the associations with the other indicators were slightly attenuated. Indigenous girls had a later age at menarche than Mestizo-Caucasian girls (HR 0.86 95% CI 0.78 to 0.96; $P=0.003$), whereas being in the highest quintile of wealth was related to an earlier age at menarche (HR 1.55 95% CI 1.40 to 1.72; $P<0.001$) than being in the lowest. Estimates remained essentially unchanged when restricted to girls aged 10-14 y at the time of the survey (**Table 1.2**).

The association between year of birth and age at menarche varied significantly by urbanicity and wealth. While there was little decline in age at menarche over the birth years in small villages or rural areas (0.17 y/decade; $P=0.55$), in urban areas there was an estimated decline of 0.60 y/decade ($P<0.001$) (**Figure 1.1;** P, test for interaction=0.04). Similarly, among girls in the lowest quintile of wealth, there was no substantial decline in menarche over time (0.10 y/decade; P= 0.90); whereas there was a negative trend of 0.65 y/decade (P<0.001) among girls in wealth quintiles 2 through 4, and a decline of 0.58 y/decade (P<0.001) among girls in the highest quintile of wealth (**Figure 1.2**; P, test for interaction=0.02). Finally, the trend in age at menarche by year of birth was similar between Mestizo-Caucasian (0.63 y/decade, P<0.001) and Afro-Colombian girls (0.53 y/decade, P=0.21), but lower among Indigenous girls (0.11 y/decade, P=0.50). Nevertheless, the interaction was not statistically significant (**Figure 1.3,** P, test for interaction=0.30).

DISCUSSION

While there are no other recent nationally-representative estimates in the region to compare; our estimate of median age at menarche in Colombia (12.6 years), is younger than figures recently reported in Argentina (12.8 y, (17)), but older than figures from Chile (12.4 y, (18)), and Brazil (12.1 y, (19)). Age at menarche in Colombia is comparable to recent estimates from Canada (12.7 y, (20)) and China (12.5 y, (21)); but older than in the US (mean 12.3 y, (6)) and Italy (mean 12.4 y,(22)). Menarcheal ages in urban Turkey (13.1 y, (23)), rural India (13.0 y, (24), and rural Gambia (14.9 y, (25)) are older than Colombia's. The decline in age at menarche of girls in Colombia born 1992 to 2000 (≈0.54 y/decade) is very close to the estimated decline of 0.55 y/decade of Colombian women born 1941 to 1989 (14); which suggests that the timing of sexual maturation in this country has not stabilized. This decline probably reflects ongoing socioeconomic changes considering that it was observed only in urban areas and was more pronounced in higher versus lower socioeconomic status groups.

There persists a socioeconomic gradient in age at menarche in Colombia, apparent from our finding that higher wealth index was linearly related to earlier age at menarche. Similar associations have been recently reported in Brazil (26) and Argentina (17); and generally corroborate the notion that age at menarche is still a sensitive indicator of the "material and moral condition" of these societies (27). While ethnic differences in adult height have been reported in Colombian population samples, with Afro-Colombians being taller than other groups (28), we found no differences in age at menarche between Afro-Colombians and Mestizo-Caucasians. Similarly, the trend toward earlier menarche did not differ between these groups. Differences in birth cohorts and in the representativeness of the populations under study may explain discrepancies with previous studies. We noted that menarche of Indigenous girls was delayed compared to that of Mestizo-Caucasians. Poorer socioeconomic and nutritional conditions among Indigenous groups compared to Mestizo-Caucasians (28) could explain this difference. It might also be related to differences in the chronological perception and reporting of this event, but we had no data to explore this possibility.

There are some limitations to consider in these analyses. The fact that this is a cross-sectional survey means that that the urbanicity and wealth index of the girls at the time of the survey might not be reflective of the urbanicity and wealth index status before the occurrence of menarche. Bias may also occur if error in the recall of menarcheal age varied according to the sociodemographic correlates under study. Although the validity of recalled age at menarche has not been investigated in this country, validation studies in comparable settings indicate that the short-term recall of menarche is reliable (29, 30). Furthermore, in supplemental analysis restricting to girls 10-14 y at the time of the survey, estimates were not substantially different than those with the full sample including older girls who may not recall menarche as reliably. Another limitation of the study is the presence of missing data, which could result in selection bias if the probability of inclusion in the analysis was related to both age at menarche and the predictors examined. Percentages of eligible girls excluded due to missing menarche information ranged from 9.3% in the Eastern region to 3.4% in Bogotá. Some girls in the sample were from the same families and we were unable to incorporate this household clustering in the estimation of variances. Nevertheless, the within-household component of the variances is likely negligible compared to that arising from clustering of households as sampling units (31), which was fully accounted for. Finally, the survey was limited by not having asked the age at menarche of women ≥18 years of age. This prevented us from examining longer-term trends. It also precluded an analysis of age at menarche in women who had attained final height.

In sum, a negative trend in age at menarche is still ongoing in Colombia, especially in urban areas and higher socioeconomic groups. These groups may be in greatest need of public health interventions aimed to reduce teenage pregnancy and breast cancer. Continued monitoring of age at menarche and its sociodemographic determinants in Colombia is warranted.

ACKNOWLEDGEMENTS

The following organizations participated in the Colombian National Nutrition Survey and the National Demographic and Health Survey (ENDS): Ministry of Health and Social Protection (Ministerio de Salud y Protección Social), National Institute of Health (Instituto Nacional de Salud), Profamilia, Association of Nutrition and Dietetic Schools (Asociación de Facultades de Nutrición y Dietética), Administrative Department of Recreational Sport, Physical Activity, and Use of Free Time (Departamento Administrativo del Deporte la Recreación, la Actividad Física y el Aprovechamiento del Tiempo Libre), National Administrative Department of Statistics (Departamento Administrativo Nacional de Estadística), Panamerican Health Organization (Organización Panamericana de la Salud), World Food Program (Programa Mundial de Alimentos), International Organization for Migration (Organización Internacional para las Migraciones), and United States Agency for International Development (USAID).

Table 1.1 Menarche of Colombian girls born 1992 to 2000 according to sociodemographic characteristics

	N[1]	Median age at menarche, years[2]	Unadjusted hazard ratio[3] (95% CI)	Adjusted hazard ratio[4] (95% CI)
Overall	15441	12.6		
Year of birth				
1992	969	13.0	1.00	
1993	1804	12.8	1.09 (1.00, 1.19)	
1994	1952	12.8	1.13 (1.04, 1.24)	
1995	1911	12.5	1.26 (1.16, 1.37)	
1996	1964	12.5	1.35 (1.23, 1.47)	
1997	1975	12.5	1.28 (1.15, 1.41)	
1998-2000[5]	4828	12.6	1.16 (1.02, 1.30)	
P trend[6]			<0.001	
Race/ethnicity				
Mestizo-Caucasian	11889	12.6	1.00	1.00
Indigenous	1836	13.0	0.71 (0.66, 0.77)	0.86 (0.78, 0.96)
Afro-Colombian	1716	12.7	0.98 (0.91, 1.05)	1.07 (0.97, 1.18)
P			<0.001	0.003
Urbanicity				
Urban centre	10293	12.5	1.00	1.00
Small village	3237	13.0	0.77 (0.72, 0.82)	0.97 (0.89, 1.05)
Disperse population	1911	13.0	0.76 (0.71, 0.82)	1.01 (0.93, 1.10)
P			<0.001	0.68
Wealth index, quintiles[7]				
Q1- poorest	5220	13.0	1.00	1.00
Q2	3764	12.8	1.17 (1.09, 1.25)	1.15 (1.07, 1.24)
Q3	2852	12.5	1.34 (1.25, 1.43)	1.31 (1.20, 1.42)
Q4	2059	12.3	1.47 (1.37, 1.59)	1.41 (1.28, 1.55)
Q5- wealthiest	1546	12.2	1.57 (1.46, 1.71)	1.55 (1.40, 1.72)
P trend			<0.001	<0.001

[1] Totals may be less than 15 441 due to missing values.
[2] From Kaplan-Meier survival probabilities
[3] From Cox proportional hazards models with age at menarche as the outcome and each predictor as the covariate. Girls who had not experienced menarche were censored on the date of interview.
[4] From a Cox proportional hazards model with age at menarche as the outcome and predictors that included indicator variables for all variables presented in the model in addition to maternal education and region.

[5] Sample sizes for years 1998, 1999, and 2000 were, respectively, 1899, 2038, and 891. The years were combined because <10% of girls born after 1998 had experienced menarche at the time of interview.
[6] For ordinal variables, tests for linear trend are from Cox proportional hazards models in which a variable representing ordinal categories was introduced as a continuous predictor. For race/ethnicity and urbanicity, P values are from Type III Wald tests. All tests incorporated the complex survey design.
[7] The wealth index is a composite measure of household's cumulative living standard. It is calculated from the ownership of home assets, materials used in housing construction, and type of water supply and sanitation facilities.

Table 1.2 Menarche of Colombian girls aged 10-14 y at time of survey, according to sociodemographic characteristics

	N[1]	Median age at menarche, years[2]	Unadjusted hazard ratio[3] (95% CI)	Adjusted hazard ratio[4] (95% CI)
Total	9896	12.5		
Year of birth				
1995	1074	12.4	1.00	
1996	1964	12.5	1.01 (0.92, 1.10)	
1997	1975	12.5	0.96 (0.86, 1.07)	
1998-2000[5]	4865	12.6	0.86 (0.75, 0.97)	
P, trend[6]			0.02	
Race/ethnicity				
Mestizo-Caucasian	7565	12.5	1.00	1.00
Indigenous	1206	13.0	0.67 (0.58, 0.79)	0.84 (0.70, 1.00)
Afro-Colombian	1125	12.6	0.91 (0.82, 1.02)	1.03 (0.91, 1.16)
P			<0.001	0.11
Urbanicity				
Urban centre	6481	12.3	1.00	1.00
Small village	2167	12.9	0.71 (0.63, 0.78)	0.98 (0.86, 1.11)
Disperse population	1248	13.0	0.69 (0.62, 0.77)	0.96 (0.84, 1.10)
P			<0.001	0.83
Wealth index, quintiles[7]				
Q1- poorest	3450	13.0	1.00	1.00
Q2	2418	12.8	1.20 (1.08, 1.33)	1.12 (1.00, 1.26)
Q3	1828	12.3	1.55 (1.40, 1.72)	1.40 (1.23, 1.59)
Q4	1261	12.2	1.63 (1.44, 1.84)	1.45 (1.26, 1.67)
Q5- wealthiest	939	12.0	1.89 (1.67, 2.15)	1.63 (1.40, 1.90)
P trend			<0.001	<0.001

1 Totals may be less than 9,896 due to missing values.
2 From Kaplan-Meier survival probabilities
3 From Cox proportional hazards models with age at menarche as the outcome and each predictor as the covariate. Girls who had not experienced menarche were censored on the date of interview.
4 From a Cox proportional hazards model with age at menarche as the outcome and predictors that included indicator variables for all characteristics presented in the table in addition to maternal education and region.
5 Sample sizes for years 1998, 1999, and 2000 were, respectively, 1899, 2038, and 891. The years were combined because <10% of girls born after 1998 had experienced menarche at the time of interview.
6 For ordinal variables, tests for linear trend are from Cox proportional hazards models in which a variable representing ordinal categories was introduced as a continuous predictor. For

race/ethnicity and urbanicity, P values are from Type III Wald tests. All tests incorporated the complex survey design.
[7] The wealth index is a composite measure of household's cumulative living standard. It is calculated from the ownership of home assets, materials used in housing construction, and type of water supply and sanitation facilities.

Figure 1.1 Median ages at menarche by year of birth in Colombia, stratified by urbanicity; Colombian National Nutrition Survey 2010, n=15 441.

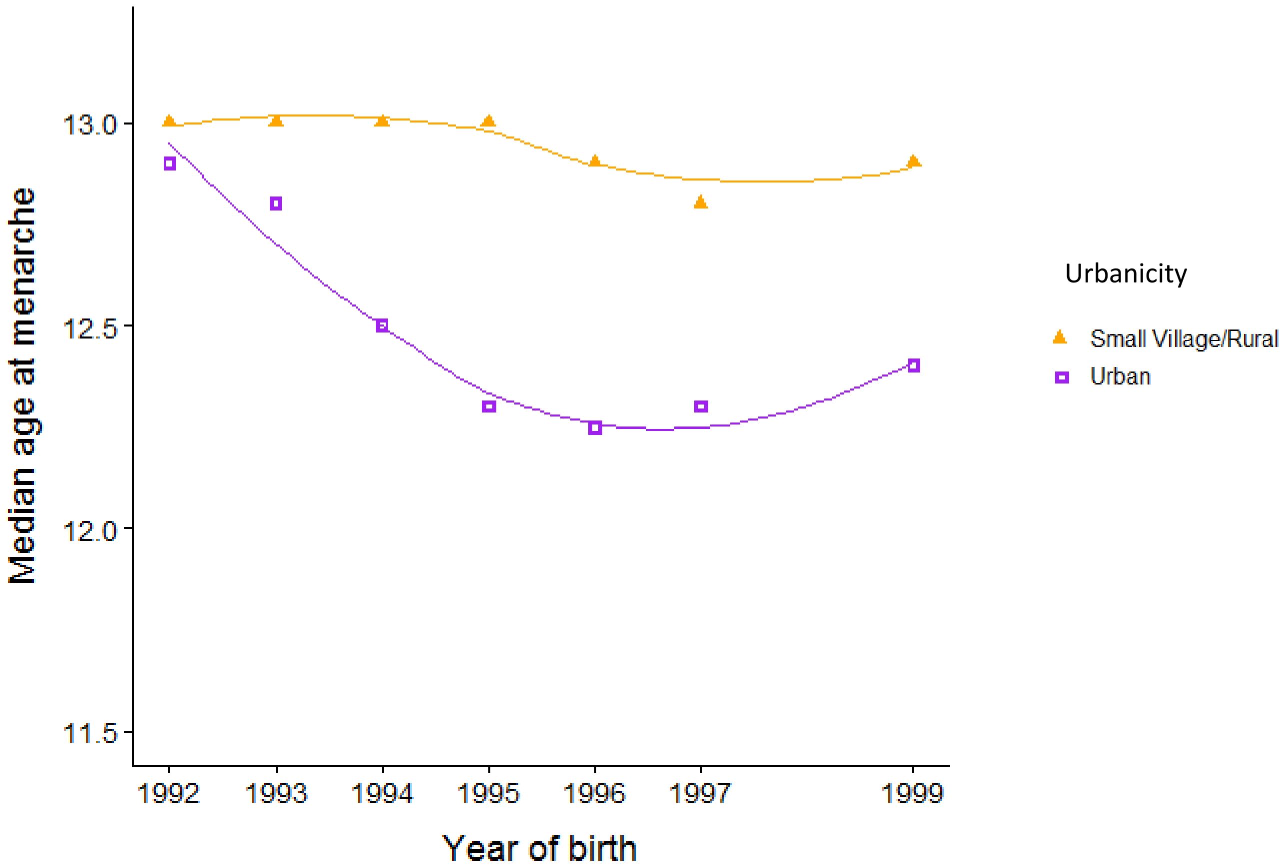


Figure 1.2 Median ages at menarche by year of birth in Colombia, stratified by wealth index; Colombian National Nutrition Survey 2010, n=15 441.

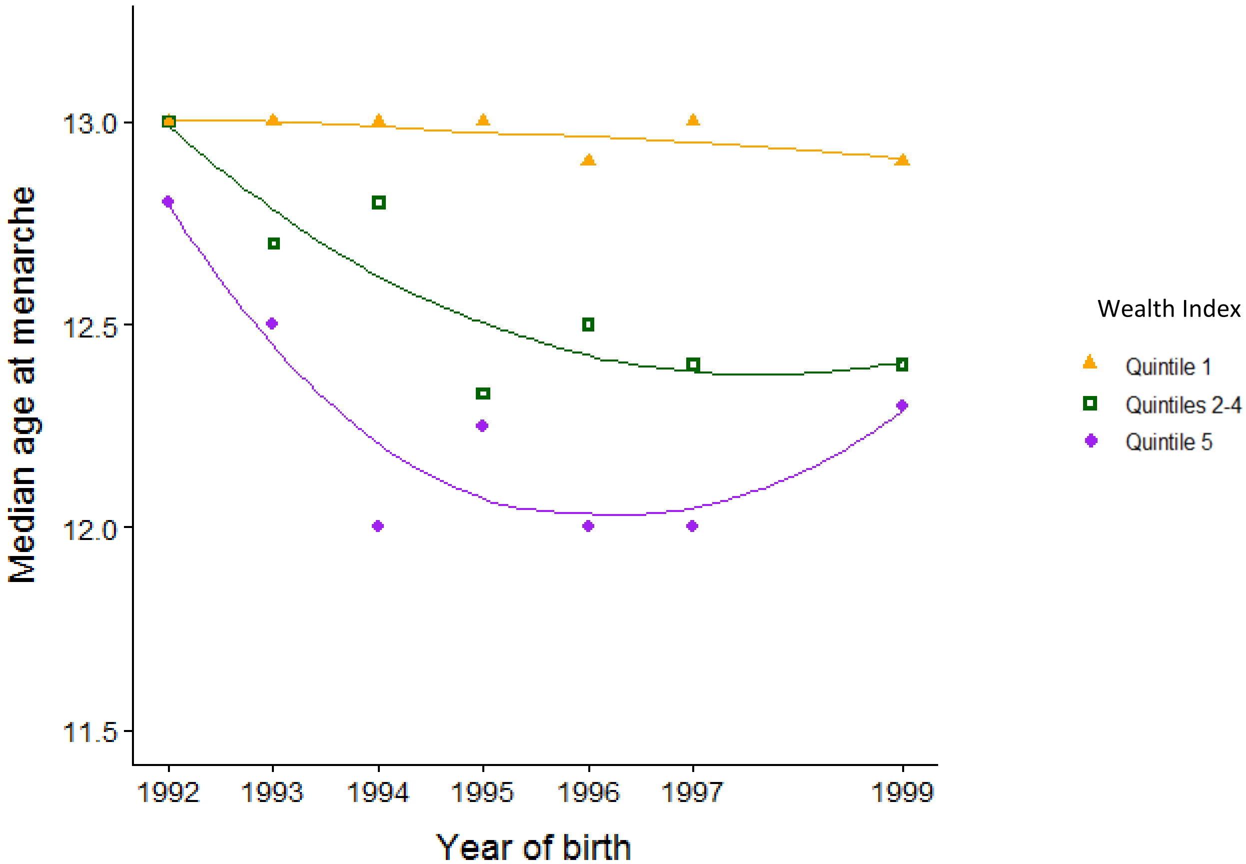
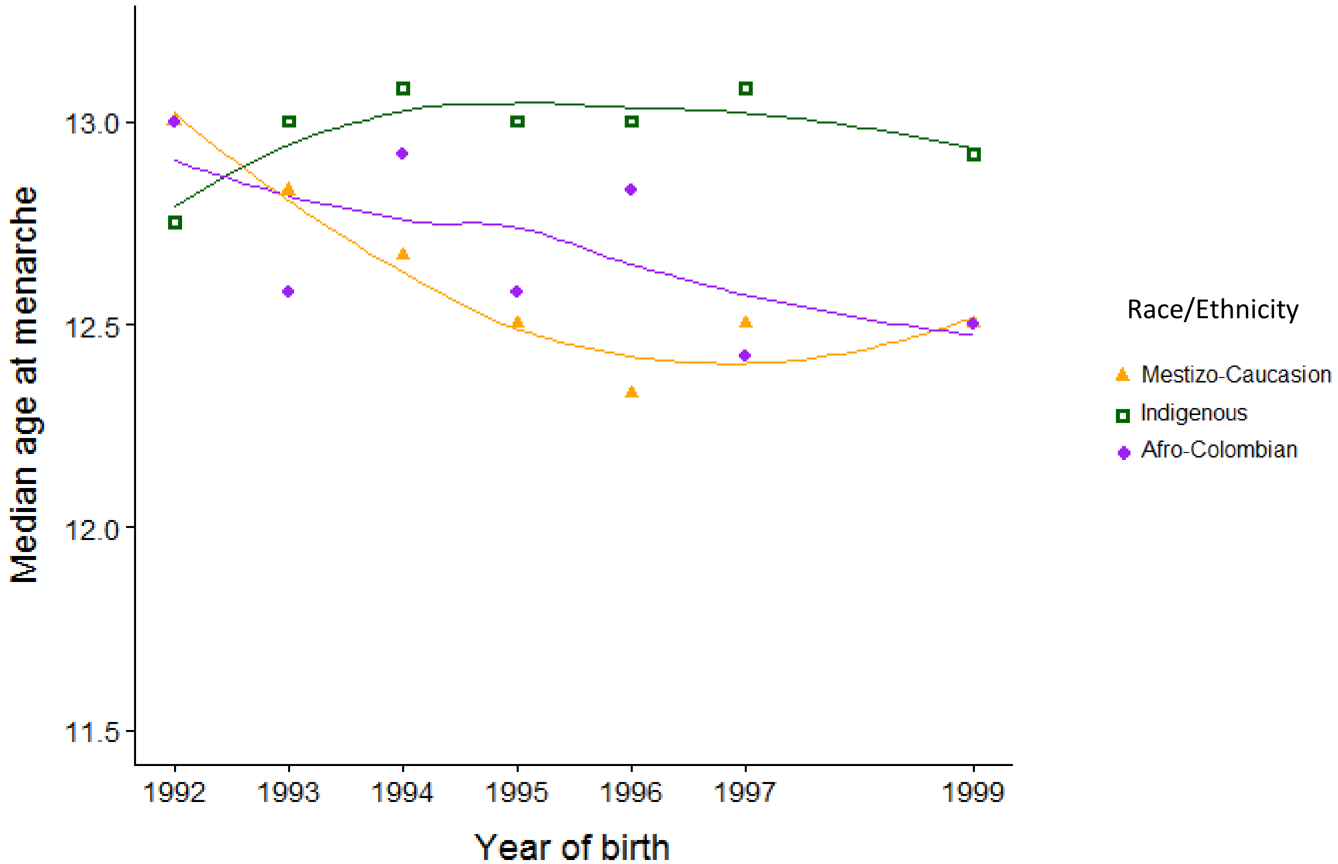


Figure 1.3 Median ages at menarche by year of birth in Colombia, stratified by race/ethnicity; Colombian National Nutrition Survey 2010, n=15 441.



REFERENCES

1. Deardorff J, Abrams B, Ekwaru JP, Rehkopf DH. Socioeconomic status and age at menarche: an examination of multiple indicators in an ethnically diverse cohort. Annals of Epidemiology 2014;24(10):727-33. doi: 10.1016/j.annepidem.2014.07.002.
2. Tanner JM. Fetus into Man. Second Edition ed. Cambridge: Harvard University Press, 1990.
3. Cole TJ. Secular trends in growth. Proc Nutr Soc 2000;59(2):317-24.
4. Hossain MG, Islam S, Aik S, Zaman TK, Lestrel PE. Age at menarche of university students in Bangladesh: secular trends and association with adult anthropometric measures and socio-demographic factors. Journal of Biosocial Science 2010;42(5):677-87. doi: 10.1017/S0021932010000210.
5. Onyiriuka AN, Egbagbe EE. Anthropometry and menarcheal status of adolescent nigerian urban senior secondary school girls. International Journal of Endocrinology and Metabolism 2013;11(2):71-5. doi: 10.5812/ijem.8052.
6. Vaughan EB, Van Hulle CA, Beasley WH, Rodgers JL, D'Onofrio BM. Clarifying the associations between age at menarche and adolescent emotional and behavioral problems. Journal of Youth and Adolescence 2015;44(4):922-39. doi: 10.1007/s10964-015-0255-7.
7. Glynn JR, Kayuni N, Gondwe L, Price AJ, Crampin AC. Earlier menarche is associated with a higher prevalence of Herpes simplex type-2 (HSV-2) in young women in rural Malawi. Elife 2014;3:e01604. doi: 10.7554/eLife.01604.
8. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. Pediatrics 2005;116(6):1451-6. doi: 10.1542/peds.2005-0542.
9. Yousefi M, Karmaus W, Zhang H, Roberts G, Matthews S, Clayton B, Arshad SH. Relationships between age of puberty onset and height at age 18 years in girls and boys. World Journal of Pediatrics 2013;9(3):230-8. doi: 10.1007/s12519-013-0399-z.
10. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. Am J Epidemiol 2014;180(1):29-40. doi: 10.1093/aje/kwu113.
11. Horn J, Opdahl S, Engstrom MJ, Romundstad PR, Tretli S, Haugen OA, Bofin AM, Vatten LJ, Asvold BO. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. Cancer Causes Control: CCC 2014;25(7):881-9. doi: 10.1007/s10552-014-0388-0.
12. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, Hu FB. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. American Journal of Epidemiology 2010;171(3):334-44. doi: 10.1093/aje/kwp372.
13. Sommer M. Menarche: a missing indicator in population health from low-income countries. Public Health Reports 2013;128(5):399-401.
14. Villamor E, Chavarro JE, Caro LE. Growing up under generalized violence: an ecological study of homicide rates and secular trends in age at menarche in Colombia, 1940s-1980s. Economics and Human Biology 2009;7(2):238-45. doi: 10.1016/j.ehb.2009.03.002.

15. Kleinbaum D, Klein M. Survival Analysis: A Self-Learning Text. 3rd ed. New York, New York: Springer Science and Business Media, 2012.
16. Henneberg M, Louw GJ. Average menarcheal age of higher socioeconomic status urban Cape coloured girls assessed by means of status quo and recall methods. American Journal of Physical Anthropology 1995;96(1):1-5. doi: 10.1002/ajpa.1330960102.
17. Orden AB, Vericat A, Apezteguia MC. Age at menarche in urban Argentinian girls: association with biological and socioeconomic factors. Anthropologischer Anzeiger 2011;68(3):309-22.
18. Ossa XM, Munoz S, Amigo H, Bangdiwala SI. Secular trend in age at menarche in indigenous and nonindigenous women in Chile. American Journal of Human Biology 2010;22(5):688-94. doi: 10.1002/ajhb.21068.
19. Castilho SD, Pinheiro CD, Bento CA, Barros-Filho Ade A, Cocetti M. [Secular trends in age at menarche in relation to body mass index]. Arquivos Brasileiros de Endocrinologia e Metabologia 2012;56(3):195-200.
20. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. BMC Public Health 2010;10:736. doi: 10.1186/1471-2458-10-736.
21. Song Y, Ma J, Wang HJ, Wang Z, Hu P, Zhang B, Agardh A. Trends of age at menarche and association with body mass index in Chinese school-aged girls, 1985-2010. Journal of Pediatrics 2014;165(6):1172-7 e1. doi: 10.1016/j.jpeds.2014.08.013.
22. Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the Health Behaviour in School-aged Children Study. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 2012;50(6):621-6. doi: 10.1016/j.jadohealth.2011.10.254.
23. Tekgul N, Saltik D, Vatansever K. Secular trend of menarche age in an immigrant urban city in Turkey: Izmir. The Turkish Journal of Pediatrics 2014;56(2):138-43.
24. Biswas S, Koziel S, Chakraborty R, Bose K. Sibling composition and household room sharing are associated with menarcheal status among rural Bengalee girls of West Bengal, India. Human Biology 2013;85(4):607-18. doi: 10.3378/027.085.0407.
25. Prentice S, Fulford AJ, Jarjou LM, Goldberg GR, Prentice A. Evidence for a downward secular trend in age of menarche in a rural Gambian population. Annals of Human Biology 2010;37(5):717-21. doi: 10.3109/03014461003727606.
26. Roman EP, Ribeiro RR, Guerra-Junior G, Barros-Filho Ade A. [Antropometry, sexual maturation and menarcheal age according to socioeconomic status of schoolgirls from Cascavel (PR)]. Revista da Associacao Medica Brasileira 2009;55(3):317-21.
27. Tanner JM. Growth as a mirror of the condition of society: secular trends and class distinctions. Edtion ed. In: Demirjian A, ed. Human Growth: A Multidisciplinary Review. London: Taylor and Francis, 1986:3-34.
28. Acosta K, Meisel A. Anthropometric measurements by ethnicity in Colombia, 1965-1990. Economics and Human Biology 2013;11(4):416-25. doi: 10.1016/j.ehb.2013.03.006.
29. Koo MM, Rohan TE. Accuracy of short-term recall of age at menarche. Annals of Human Biology 1997;24(1):61-4.

30. Castilho SD, Nucci LB, Assuino SR, Hansen LO. [The importance of memory bias in obtaining age of menarche by recall method in Brazilian adolescents]. Arquivos Brasileiros de Endocrinologia e Metabologia 2014;58(4):394-7.
31. Lepkowski JM, Mosher WD, Groves RM, West BT, Wagner J, Gu H. Responsive Design, Weighting, andVariance Estimation in the 2006-2010 National Survey of Family Growth. Vital and Health Statistics Series 2, Data Evaluation and Methods Research 2013(158):1-52.

Chapter 3

Prenatal exposure to the rainy season and low altitude of residence are associated with earlier age at menarche in a tropical climate: results from a nationally representative study

Erica C Jansen, Oscar F Herrán, Nancy L Fleischer, Alison M Mondul, Laura S Rozek, and Eduardo Villamor

ABSTRACT

Background: Intrauterine exposure to the rainy season in the tropics may be accompanied by high rates of infection and nutritional deficiencies. It is unknown whether this exposure is related to the extrauterine timing of development. Our aim was to evaluate the relations of prenatal exposure to the rainy season and altitude of residence with age at menarche.

Methods: The study included 15,370 girls 10- <18 y old who participated in Colombia's 2010 National Nutrition Survey. Primary exposures included the number of days exposed to the rainy season during the 40 weeks preceding birth, and altitude of residence at the time of the survey. We estimated median menarcheal ages and hazard ratios with 95% CI according to exposure categories using Kaplan–Meier cumulative probabilities and Cox proportional hazards models, respectively. All tests incorporated the complex survey design.

Results: Girls in the highest quintile of gestation days exposed to the rainy season had an earlier age at menarche compared to those in the lowest (adjusted HR= 1.08; 95% CI 1.00 to 1.18, P-trend=0.03). Girls living at altitudes ≥2000 m had a later age at menarche compared to those living <1000 m (adjusted HR= 0.88; 95% CI 0.82 to 0.94, P-trend<0.001). The association between gestation days during the rainy season and menarche was mostly apparent among girls living at altitudes ≥2000 m (P, interaction= 0.04).

Conclusions: Gestation days exposed to the rainy season and altitude of residence were associated with the timing of sexual maturation among Colombian girls.

INTRODUCTION

The age at menarche, or timing of a girl's first menstrual period, is a reliable marker of puberty. An earlier age at menarche is related to adverse health outcomes including breast cancer and all-cause mortality(1, 2). The timing of menarche is relevant from a public health perspective because it could be responsive to environmental conditions occurring as early as the prenatal period(3).

In tropical climates, there is a rainy season characterized by increased precipitation, reductions in temperature and sunlight(4), higher transmission rates of some infections(5), and decreased availability of food(6). When pregnancy overlaps with the rainy season, mothers and fetuses may be at high risk of infections and nutritional deficiencies(7). Intrauterine exposure to these factors could act as a prediction of prevailing extrauterine conditions and signal the offspring to alter their development plan in a way that maximizes survival and reproductive potential(8). Accelerating the timing of sexual maturation could constitute one of those adaptations. Some studies conducted in temperate climates found associations between the season of birth and onset of puberty in the offspring (9, 10). However, this has not been investigated in tropical climates where the effects of season on health could be substantial.

Altitude of residence is another environmental factor may affect the timing of sexual maturation. Studies in Peru and Bolivia found that girls living in altitudes >3000 m had older ages at menarche compared to girls living in elevations <500 m; these observations were attributed to the lower oxygen availability at higher compared to lower elevations (11-13). Nevertheless, some argued that these variations could be explained by differences in socioeconomic status and access to nutrition rather than altitude (14).

The aim of this study was to assess whether a higher number of gestation days exposed to the rainy season was related to an earlier age at menarche. We also examined the association of altitude of residence with age at menarche. In addition, since seasonality may differ according to altitude, we ascertained whether the relation between gestation days exposed to the rainy season and age at menarche was modified by altitude of residence.

METHODS

Study population

The Colombian National Nutrition Survey (ENSIN) was conducted in 2010 by the Colombian Institute of Family Welfare (Instituto Colombiano de Bienestar Familiar, ICBF) in conjunction with the Colombian Demographic and Health Survey (ENDS). The survey methodology has been described in detail elsewhere (15). Briefly, a multistage stratified sampling scheme was employed to select participants representing 99% of the Colombian population. All municipalities from the thirty-two departments in the country were grouped into strata based on similar geographic and sociodemographic characteristics. One municipality was randomly chosen from each stratum with the probability of being chosen proportional to the population size. Clusters of about ten households were randomly selected within strata and all household members were invited to participate. A total 50,670 households were included, representing 4987 clusters from 258 strata.

Trained personnel administered questionnaires to the head of each household to obtain sociodemographic information of all family members. Girls aged 10 to less than 18 years were asked to recall the age in years and months when their first menstrual period had occurred or if it had not yet occurred. Geographic information on the households including region and altitude of residence was abstracted from the National Department of Statistics (Departmento Administrativo Nacional de Estadistica, DANE) and included in the survey datasets.

Data sources

The survey included 188,599 people; 16,940 were girls 10 to <18 years of age. We excluded 1570 girls with missing information on menarche or date of birth or who answered "don't know" to either of these questions. Thus, the final sample comprised 15,370 girls born from 1992–2000.

The primary outcome was age at menarche, estimated in decimal years from the age of occurrence reported in years and months. There were two primary exposures, gestation days exposed to the rainy season and altitude of residence at the time of the survey. For gestation days exposed to the rainy season, we assumed as the exposure period the 40 weeks prior to and including the birthdate. Each day that occurred during the rainy season within this period, according to region-specific weather patterns averaging years 1972 to 1998 (16), contributed to the summary measure. There are five geographic regions in Colombia: Andean, Pacific, Atlantic, Orinoquian, and Amazonian. Rainy seasons in the Andean and Pacific regions occur from April-May and September-November, whereas there is only one rainy season in the Atlantic (May-October), Eastern Andean piedmont (July-August), and Orinoquian (April-November) regions (17). The Amazonian region does not show much variability in rainfall throughout the year, although from December-May the precipitation is slightly higher (according to data averaging years 1964 to 2003)(18); thus, we assigned exposure to the rainy season to the gestation days that occurred between December and May in the Amazonian region. The number of gestation days exposed to the rainy season was categorized into quintiles, weighted according to the complex survey design. It was also considered as a continuous variable, per 30 days of gestation. Altitude of residence (in meters) at the time of the survey for each girl was abstracted from the ENSIN dataset and categorized into altitude of residence zones as 0-999 m, 1000-1999 m, or ≥2000 m. It was also considered as a continuous exposure, per 500 m. We assumed that altitude of residence at the time of the survey was a proxy for altitude of residence during gestation.

Other covariates were year of birth, race/ethnicity, maternal education, wealth index, and geographic region. Race/ethnicity, maternal education, and wealth index were defined as previously described (19). Although wealth index and maternal education were measured at the time of the survey, we assumed that they were proxies for the socioeconomic status (SES) of the girls' family environment during her intrauterine life.

Ethical considerations

Participation consent was obtained prior to enrolment by the ICBF. The Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan determined that analyses of these anonymized data were exempt from review.

Statistical analysis

Analyses were conducted with the use of the complex survey design routines of Stata statistical software package version 13 (StataCorp, College Station, TX, USA).

We first compared the distribution of sociodemographic predictors of age at menarche according to the primary exposures. For categorical predictors, we estimated proportions ± SE in each category of the primary exposure, and performed Rao-Scott χ^2 tests. For continuous characteristics, we estimated means ± SE. We performed tests for linear trend using linear regression models in which a variable representing ordinal categories of quintiles of gestation days exposed to the rainy season or altitude of residence zone was introduced as a continuous predictor.

In bivariate analysis, we estimated the weighted median age at menarche by exposure categories using Kaplan–Meier cumulative probabilities from birth. For girls who had not yet experienced menarche, the censoring time was age at interview, estimated as date of interview minus birthdate. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), accounting for the complex survey design. We conducted tests for linear trend by introducing into the models a variable representing ordinal categories of each exposure as a continuous covariate.

Next, we estimated adjusted HR and 95% CI with a model that included indicator variables for the gestation days exposed to rainy season quintiles in addition to year of birth, race/ethnicity, wealth index, and geographic region (Amazonian and Orinoquian regions were collapsed into one category). For altitude of residence, HR and 95% CI were adjusted for race/ethnicity, maternal education, and wealth index. We did not include geographic region due to issues of collinearity.

We also examined the relation of gestation days exposed to the rainy season and age at menarche stratified by altitude of residence zones. We used a Cox proportional hazards model that included gestation days exposed to the rainy season as a continuous exposure, altitude of residence zone as an ordinal variable, and their interaction terms. Estimates were adjusted for year of birth, race/ethnicity, and wealth index. The interaction between gestation days exposed to the rainy season and altitude of residence was tested with the use of Type III Wald tests. All tests incorporated the complex survey design.

RESULTS

The mean ± SD age of girls at the time of the interview was 13.9 ± 2.3 y. Thirty-three percent of the girls had not experienced menarche and were censored.

The weighted mean ± SE number of gestation days that occurred during the rainy season was 115.3 ± 0.4. Girls born 1992-1993 had fewer gestation days during the rainy season than girls born after 1993. Also, girls of Mestizo-Caucasian ethnicity had fewer gestation days during the rainy season compared to those of Afro-Colombian or Indigenous ethnicity (**Table 2.1**). The number of gestation days during the rainy season was non-monotonically inversely related to household wealth index. In addition, it was higher in girls from the Pacific, Amazonian, and Orinoquian regions compared to those from other geographic regions.

The weighted mean ± SE altitude of residence was 1194 ± 16 m. Girls of Afro-Colombian ethnicity were more likely to reside in the lowest altitude zone compared to girls of other ethnicities (**Table 2.2**). In addition, altitude of residence was positively related to maternal education, wealth index, and living in the Andean region.

The weighted median age at menarche was 12.6 years (IQR 12.0 to 13.5). In bivariate analysis, the number of gestation days exposed to the rainy season was related to earlier menarche (HR for Q5 to Q1= 1.09, 95% CI 1.02 to 1.18; P, trend= 0.002, **Table 2.3**). After adjustment for year of birth, ethnicity, wealth index, and geographic region, girls in the highest weighted quintile had a 8% higher probability of menarche compared to those in the lowest quintile (HR for Q5 to Q1 1.08 95% CI 1.00 to 1.18, P, trend= 0.03).

In bivariate analysis, altitude of residence was not related to age at menarche (**Table 2.3**). However, after adjustment for ethnicity, maternal education, and wealth index, altitude of residence was significantly related to later age at menarche. Girls living at an altitude ≥2000 m had a 12% lower probability of menarche compared to girls living at an altitude <1000 m (HR for ≥2000 m to <1000 m 1.12 95% CI 1.06 to 1.18; P, trend <0.001).

The association between gestation days exposed to the rainy season and age at menarche varied according to altitude of residence (**Table 2.4**). There was no association between gestation days exposed to the rainy season and menarche at an altitude of residence <2000 m, whereas there was an 8% higher hazard of menarche for every 30 gestation days exposed to the rainy season among girls living at an altitude ≥2000 m (HR= 1.08, 95% CI 1.03 to 1.14, P, interaction=0.04).

DISCUSSION

In this nationally representative sample of Colombian girls born 1992-2000, we found that a higher number of gestation days exposed to the rainy season was related to an earlier age at menarche whereas a higher altitude of residence was associated with a later age at menarche. We also noted that the relation between gestation days exposed to the rainy season and menarche was mostly apparent among girls residing in altitudes ≥2000 m.

Our finding on the relation between prenatal rainy season exposure and age at menarche in the context of a tropical climate is novel. A few studies have examined whether season of birth is associated with age at menarche in temperate regions, although results are mixed (9, 10, 20-23). One recent study among 1,697 Polish women found that those who were born during summer months (June-August) reported earlier ages at menarche than those born during other seasons of the year. Another study among 950 US women reported that those born in February had earlier ages at menarche compared to those born in December, although only when restricting the analyses to women born before 1970 (10). In contrast, studies in the UK, US, Denmark, and Italy reported no association between season of birth and age at menarche (20-23).

The rainy season in tropical climates is characterized by lower sunlight exposure(24) which could be related to vitamin D deficiencies (25) or decreases in photoperiod-mediated melatonin concentrations (26). The rainy season is also marked by higher transmission rates of infectious diseases including dengue (27), malaria (28), and respiratory infections (29). In addition, it may be linked to food shortages (30). Hence, the finding that a higher number of gestation days exposed to the rainy season was associated with an earlier menarche is consistent with the notion that adverse early-life conditions may be related to earlier onset of sexual maturation. There are a few specific pathways that may contribute to explain this association.

Lower serum vitamin D levels during middle childhood were related to an earlier age at menarche in a prospective study of girls from Bogotá, Colombia (31). Although there is no evidence for an effect of vitamin D deficiency during pregnancy on the onset of puberty, a recent study among 977 UK women showed that gestational vitamin D deficiency was related to higher adiposity in the offspring at age 4 and 6 y (32). Childhood obesity is a predictor of earlier age at menarche (33). Another potential mechanism related to decreased sunlight exposure during pregnancy involves photoperiod effects. Some studies have suggested that higher sunlight exposure in peripubertal years may trigger menarche (10). It is plausible that rhythmicity in exposure to photoperiods during pregnancy affects the development of the fetal circadian system (26), altering the offspring's response to light cycles around the time of puberty. Our finding could also have to do with a higher rate of infectious disease transmission or lower availability of food during the rainy season compared to the dry season. One consequence of these insults is reduced nutrient availability to the fetus (34). This could act as a signal to the fetus of nutrient scarcity in the extrauterine environment, leading to an acceleration in the timing of puberty as an adaptive mechanism to optimize reproductive success (35). Although human studies are lacking, experimental animal studies have supported the notion that undernutrition during pregnancy may result in accelerations in the timing of sexual maturation of the offspring (36). In addition, some epidemiological studies have linked prenatal undernutrition with higher incidence of adult obesity (37). An earlier menarche is related to increased risk of adult obesity (38).

We found that girls residing at higher altitudes had later menarche than girls living at lower altitudes independent of socioeconomic conditions. This finding is in agreement with results from studies in Peru and Bolivia (11-13). In these studies, girls residing in altitudes >3000 m had later ages at menarche than girls residing at altitudes <500 m. For example, a study among

4142 Peruvian girls found that those at an altitude of 3,400 m had a mean menarcheal age of 13.7 y, whereas girls at sea level had a mean age at menarche of 12.2 y (12). Later sexual maturation among high altitude dwellers has been explained as an energy trade-off to allow for accelerated growth of the lungs and chest (39). Thus, the observed association with altitude may not necessarily be due to exposure to a higher altitude during pregnancy, but throughout childhood.

We also found that the relation between gestation days exposed to the rainy season was mostly apparent at altitudes ≥2000 m. This could be due to higher seasonal variation at higher altitudes. For example, the seasonal incidence of respiratory infections could be more marked at higher elevations (9). It is also plausible that cooler overall temperatures at high altitudes are correlated with greater differences in seasonal behavior among pregnant women, which could affect exposure to sunlight (e.g. through clothing choices).

Our study has several strengths. The 2010 ENSIN survey provided adequate statistical power; in addition, the estimates are nationally representative. Few nation-wide studies have collected information on age at menarche. The ability to adjust for important socioeconomic variables was also a strength, particularly in the analysis of altitude. There were also limitations. We lacked information on gestational age at delivery; thus, exposure to rainy season days could have been misclassified in girls delivered pre- or post-term. If girls delivered preterm had later ages at menarche(40) and fewer gestation days during the rainy season than assigned, estimates might represent an underestimation of the true underlying effect. The lack of information on gestational age at delivery also prevented us from examining effects of rainy season exposure during each trimester of pregnancy. We did not have access to rainfall data during the specific birth years of the participants, rather we used historical data spanning from 1964 to 2003. This is another source of potential misclassification of the number of gestation days exposed to the rainy season. There is also a possibility of outcome misclassification, although research in a similar setting suggests that the short-term recall of menarche is reliable (41). Furthermore, we would not expect that the recall of menarche is differential with respect to the exposures examined. Girls <10 y were not asked about menarche. This could result in selection bias if there was a meaningful number of girls with menarche <10 y who differed with respect to exposure status from girls ≥10 y of age. However, there may be very few girls with menarche before 10 y of age; in a nationally representative survey of US girls from 1992-2002, only 0.3% had menarche before their 10^{th} birthday (42). Some girls came from the same households and this could violate the assumption of independence in the estimation of variances. Nevertheless, the within-household component of the variances is likely negligible compared to that arising from clustering of households as sampling units (43), which was fully accounted for. Causal inference may also be hindered by residual confounding of the estimates due to ethnic composition or SES. Our measures of SES were only a proxy for socioeconomic conditions during the girls' intrauterine life, since they were measured after the occurrence of the outcome. Finally, we do not have knowledge on whether altitude of residence at the time of the survey was reflective of that at birth.

In summary, a higher number of gestation days exposed to the rainy season was related to an earlier age at menarche in a nationally representative sample of Colombian girls, a finding mostly apparent among girls residing in altitudes ≥2000 m. Conversely, higher altitude of residence was related to a later age at menarche after adjustment for SES indicators. These findings support the notion that climate and geographical factors during gestation and childhood development may affect the timing of sexual maturation.

ACKNOWLEDGEMENTS

The following organizations participated in the Colombian National Nutrition Survey and the National Demographic and Health Survey (ENDS): Ministry of Health and Social Protection (Ministerio de Salud y Protección Social), National Institute of Health (Instituto Nacional de Salud), Profamilia, Association of Nutrition and Dietetic Schools (Asociación de Facultades de Nutrición y Dietética), Administrative Department of Recreational Sport, Physical Activity, and Use of Free Time (Departamento Administrativo del Deporte la Recreación, la Actividad Física y el Aprovechamiento del Tiempo Libre), National Administrative Department of Statistics (Departamento Administrativo Nacional de Estadística), Panamerican Health Organization, World Food Program, International Organization for Migration, and United States Agency for International Development (USAID).

Table 2.1. Sociodemographic characteristics according to weighted quintiles of gestation days exposed to the rainy season among Colombian girls born 1992-2000[1]

Characteristic	Q1[2] n=2656	Q2 n=3157	Q3 n=2517	Q4 n=2926	Q5 n=4114	P[3]
Year of birth, %						0.01
1992-1993	26.4 ± 1.1	19.9 ± 1.0	17.6 ± 1.0	17.1 ± 1.0	19.0 ± 0.9	
1994-1995	20.6 ± 0.9	20.7 ± 0.8	17.8 ± 0.8	19.8 ± 0.9	21.2 ± 0.8	
1996-1997	20.0 ± 0.8	20.5 ± 0.8	19.1 ± 0.8	20.1 ± 0.9	20.2 ± 0.8	
1998-2000	21.1 ± 0.8	19.8 ± 0.7	19.4 ± 0.8	20.5 ± 0.8	19.2 ± 0.7	
Race/ethnicity, %						<0.001
Mestizo-Caucasian	23.0 ± 0.5	20.8 ± 0.5	18.2 ± 0.5	19.3 ± 0.5	18.8 ± 0.5	
Indigenous	12.5 ± 1.6	18.5 ± 1.7	19.7 ± 1.7	24.3 ± 1.8	24.9 ± 1.9	
Afro-Colombian	15.6 ± 1.1	16.4 ± 1.1	20.8 ± 1.2	23.3 ± 1.2	24.0 ± 1.3	
Maternal education, years	7.8 ± 0.08	7.6 ± 0.07	7.8 ± 0.08	7.9 ± 0.08	7.8 ± 0.07	0.41
Wealth index[4]	2.9 ± 0.04	2.7 ± 0.04	3.0 ± 0.04	3.0 ± 0.04	2.6 ± 0.04	0.006
Geographic región						<0.001
Andean	29.5 ± 0.7	21.2 ± 0.6	19.9 ± 0.7	20.4 ± 0.6	9.0 ± 0.5	
Pacific	0.3 ± 0.1	25.0 ± 0.8	12.3 ± 0.6	15.1 ± 0.7	47.4 ± 0.9	
Atlantic	23.7 ± 1.0	8.5 ± 0.7	25.8 ± 1.0	28.4 ± 1.0	13.7 ± 0.8	
Amazonian	2.2 ± 0.5	28.7 ± 1.8	13.7 ± 1.3	12.6 ± 1.2	42.8 ± 1.7	
Orinoquian	23.7 ± 1.9	26.4 ± 2.2	0.0	2.5 ± 0.4	47.5 ± 2.4	

[1] Values are weighted proportions or means ± SE
[2] Weighted quintiles of gestation days that occurred during rainy season, based on region of residence and date of birth

[3] For categorical characteristics, P values are from Rao-Scott χ^2 tests. For continuous characteristics, tests for trend are from a linear regression model in which a variable representing weighted quintiles of gestation days exposed to the rainy season was introduced as a continuous predictor.

[4] The wealth index is a composite measure of the household's living standard. It is constructed from principal component analysis of a number of household assets including type of flooring, number of bedrooms, type of toilet, and mode of transportation.

Table 2.2 Sociodemographic characteristics according to altitude of residence among Colombian girls born 1992-2000[1]

Characteristic	Altitude of residence 0-999 m n=9982	1000-1999 m n=3378	≥2000 m n=2010	P[2]
Year of birth, %				0.78
1992-1993	46.7 ± 1.3	26.9 ± 1.2	26.4 ± 1.3	
1994-1995	48.5 ± 1.1	27.1 ± 1.1	24.4 ± 1.1	
1996-1997	47.9 ± 1.1	26.0 ± 1.0	26.1 ± 1.2	
1998-2000	47.9 ± 1.1	27.0 ± 1.0	25.0 ± 1.0	
Race/ethnicity, %				<0.001
Mestizo-Caucasian	43.9 ± 0.8	27.8 ± 0.8	28.3 ± 0.8	
Indigenous	48.7 ± 3.0	26.4 ± 3.6	24.9 ± 3.4	
Afro-Colombian	76.4 ± 1.9	19.7 ± 1.8	4.0 ± 0.9	
Maternal education, years	7.6 ± 0.05	7.6 ± 0.08	8.3 ± 0.09	<0.001
Wealth index	2.5 ± 0.03	2.8 ± 0.05	3.5 ± 0.04	<0.001
Geographic region				<0.001
Andean	25.9 ± 0.8	34.5 ± 1.0	39.6 ± 1.1	
Pacific	93.9 ± 0.9	4.7 ± 0.8	1.5 ± 1.5	
Atlantic	50.6 ± 1.7	35.7 ± 1.8	13.7 ± 1.4	
Amazonian	99.1 ± 0.9	0.9 ± 0.9	0.0	
Orinoquian	100.0	0.0	0.0	

[1] Values are weighted proportions or means ± SE
[2] For categorical characteristics, P values are from Rao-Scott χ^2 tests. For continuous characteristics, tests for trend are from a linear regression model in which a variable representing altitude of residence zone was introduced as a continuous predictor.

Table 2.3 Age at menarche according to gestation days exposed to the rainy season and altitude of residence among Colombian girls born 1992-2000

	n	Median age at menarche, years[1]	Unadjusted hazard ratio (95% CI)[2]	Adjusted hazard ratio (95% CI)[3]
Gestation days exposed to rainy season, weighted quintiles				
Q1, median=75 days	2656	12.8	1.00	1.00
Q2, median=97 days	3157	12.7	1.03 (0.96, 1.11)	1.02 (0.95, 1.11)
Q3, median=112 days	2517	12.6	1.05 (0.97, 1.13)	1.02 (0.94, 1.10)
Q4, median=137 days	2926	12.5	1.11 (1.04, 1.20)	1.08 (1.00, 1.17)
Q5, median=177 days	4114	12.6	1.09 (1.02, 1.18)	1.08 (1.00, 1.18)
P, trend[4]			0.002	0.03
Per 30 days			1.03 (1.01, 1.04)	1.02 (1.00, 1.04)
P			0.008	0.10
Altitude of residence				
0-999 m	9982	12.6	1.00	1.00
1000-1999 m	3378	12.8	0.92 (0.88, 0.98)	0.88 (0.83, 0.93)
≥2000 m	2010	12.5	0.98 (0.91, 1.04)	0.88 (0.82, 0.94)
P, trend			0.27	<0.001
Per 500 m			1.00 (0.98, 1.01)	0.97 (0.96, 0.99)
P			0.52	<0.001

[1] From Kaplan-Meier survival probabilities
[2] From Cox proportional hazards models with age at menarche as the outcome and indicator variables for weighted quintiles of gestation days during the rainy season as the predictor or a continuous variable for days of exposure

[3] Estimates for gestation days exposed to the rainy season were from a Cox proportional hazards model adjusted for year of birth, race/ethnicity, wealth index, and geographic region. Estimates for altitude of residence were from a Cox proportional hazards model adjusted for race/ethnicity, maternal education, and wealth index.
[4] From a Cox proportional hazards model in which a variable representing ordinal categories of the exposure was introduced as a continuous predictor.

Table 2.4 Age at menarche per 30 gestation days exposed to the rainy season, stratified by altitude of residence among Colombian girls born 1992-2000

Altitude of residence	Unadjusted hazard ratio (95% CI)[1] per 30 gestation days exposed to the rainy season	Adjusted hazard ratio (95% CI)[2] per 30 gestation days exposed to the rainy season
0-999 m	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
1000-1999 m	1.02 (0.96, 1.07)	1.00 (0.95, 1.06)
≥2000 m	1.11 (1.05, 1.16)	1.08 (1.03, 1.14)
P, interaction	0.001	0.04

[1]From a Cox proportional hazards model with age at menarche as the outcome and predictors that included gestation days occurring during the rainy season (continuous), altitude of residence (categorical), and their interaction terms
[2]From a Cox proportional hazards model adjusted for year of birth, race/ethnicity, and wealth index

REFERENCES

1. Horn J, Opdahl S, Engstrom MJ, Romundstad PR, Tretli S, Haugen OA, Bofin AM, Vatten LJ, Asvold BO. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. Cancer Causes Control: CCC 2014;25(7):881-9. doi: 10.1007/s10552-014-0388-0.
2. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. Am J Epidemiol 2014;180(1):29-40. doi: 10.1093/aje/kwu113.
3. Cole TJ. Secular trends in growth. Proc Nutr Soc 2000;59(2):317-24.
4. Geografia de Colombia. Bogota, Colombia: Instituto Geografico Agustin Codazzi, 2014.
5. Ramirez AP, Mendoza AR, Montoya JM, Cotes K, Lopez JD, Herrera D, Rey G, de la Hoz F. [Mortality associated with peak seasons of influenza virus circulation in Bogota, Colombia, 1997-2005]. Rev Panam Salud Publica 2009;26(5):435-9.
6. Ntwenya JE, Kinabo J, Msuya J, Mamiro P, Majili ZS. Dietary patterns and household food insecurity in rural populations of Kilosa district, Tanzania. PLoS One 2015;10(5):e0126038. doi: 10.1371/journal.pone.0126038.
7. Moore SE, Cole TJ, Poskitt EM, Sonko BJ, Whitehead RG, McGregor IA, Prentice AM. Season of birth predicts mortality in rural Gambia. Nature 1997;388(6641):434. doi: 10.1038/41245.
8. Gluckman PD, Beedle AS, Hanson MA, Low FM. Human growth: evolutionary and life history perspectives. Nestle Nutr Inst Workshop Ser 2013;71:89-102. doi: 10.1159/000342572.
9. Klis K, Jarzebak K, Borowska-Struginska B, Mulawa A, Zurawiecka M, Wronka I. Season of birth influences the timing of first menstruation. Am J Hum Biol 2015. doi: 10.1002/ajhb.22783.
10. Matchock RL, Susman EJ, Brown FM. Seasonal rhythms of menarche in the United States: correlates to menarcheal age, birth age, and birth month. Womens Health Iss 2004;14(6):184-92. doi: 10.1016/j.whi.2004.07.007.
11. Gonzales GF, Villena A. Body mass index and age at menarche in Peruvian children living at high altitude and at sea level. Hum Biol 1996;68(2):265-75.
12. Freyre EA, Ortiz MV. The effect of altitude on adolescent growth and development. J Adolesc Health Care 1988;9(2):144-9.
13. Greksa LP. Age of menarche in Bolivian girls of European and Aymara ancestry. Ann Hum Biol 1990;17(1):49-53.
14. Wiley AS. An Ecology of High-Altitude Infancy: A Biocultural Perspective. USA: Cambridge University Press, 2004.
15. Encuesta Nacional de la Situacion Nutricional en Colombia 2010. Bogotá: ICBF, Instituto Colombiano de Bienestar Familiar, 2011.
16. Poveda G, Alvarez DM, Rueda OA. Hydro-climatic variability over the Andes of Colombia associated with ENSO: a review of climatic processes and their impact on one of the Earth's most important biodiversity hotspots. Clim Dynam 2011;36(11-12):2233-49. doi: 10.1007/s00382-010-0931-y.
17. Pacheco Y, Leon-Aristizabal G. Clasificación climática de la Orinoquia Colombiana a partir de los patrones de circulación atmosférica. Meteorol Colomb 2001;4:117-20.

18. Villar JCE, Ronchail J, Guyot JL, Cochonneau G, Naziano F, Lavado W, De Oliveira E, Pombosa R, Vauchel P. Spatio-temporal rainfall variability in the Amazon basin countries (Brazil, Peru, Bolivia, Colombia, and Ecuador). Int J Climatol 2009;29(11):1574-94. doi: 10.1002/joc.1791.
19. Jansen EC, Herran OF, Villamor E. Trends and correlates of age at menarche in Colombia: Results from a nationally representative survey. Econ Hum Biol 2015;19:138-44. doi: 10.1016/j.ehb.2015.09.001.
20. Jongbloet PH, Kersemaekers WM, Zielhuis GA, Verbeek AL. Menstrual disorders and month of birth. Ann Hum Biol 1994;21(6):511-8.
21. Cagnacci A, Pansini FS, Bacchi-Modena A, Giulini N, Mollica G, De Aloysio D, Vadora E, Volpe A, Emilia-Romagna Operative Group for the M. Season of birth influences the timing of menopause. Hum Reprod 2005;20(8):2190-3. doi: 10.1093/humrep/dei040.
22. Maisonet M, Christensen KY, Rubin C, Holmes A, Flanders WD, Heron J, Ong KK, Golding J, McGeehin MA, Marcus M. Role of prenatal characteristics and early growth on pubertal attainment of British girls. Pediatrics 2010;126(3):e591-600. doi: 10.1542/peds.2009-2636.
23. Boldsen JL. Season of birth and recalled age at menarche. J Biosoc Sci 1992;24(2):167-73.
24. Graham EA, Mulkey SS, Kitajima K, Phillips NG, Wright SJ. Cloud cover limits net CO2 uptake and growth of a rainforest tree during tropical rainy seasons. Proc Natl Acad Sci U S A 2003;100(2):572-6. doi: 10.1073/pnas.0133045100.
25. Parisi AV, Turnbull DJ, Downs NJ. Influence of high levels of cloud cover on vitamin D effective and erythemal solar UV irradiances. Photochem Photobiol Sci 2012;11(12):1855-9. doi: 10.1039/c2pp25160d.
26. Reiter RJ, Tan DX, Korkmaz A, Rosales-Corral SA. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. Hum Reprod Update 2014;20(2):293-307. doi: 10.1093/humupd/dmt054.
27. Polwiang S. The seasonal reproduction number of dengue fever: impacts of climate on transmission. PeerJ 2015;3:e1069. doi: 10.7717/peerj.1069.
28. Oringanje C, Meremikwu M, Ogar B, Okon A, Udoh A. Patterns of cord, placental and post-delivery maternal malaria parasitemia. Acta Obstet Gynecol Scand 2010;89(9):1206-9. doi: 10.3109/00016349.2010.484045.
29. Rodriguez-Martinez CE, Rodriguez DA, Nino G. Respiratory syncytial virus, adenoviruses, and mixed acute lower respiratory infections in children in a developing country. J Med Virol 2015;87(5):774-81. doi: 10.1002/jmv.24139.
30. Graham MA. "No somos iguales": the effect of household economic standing on women's energy intake in the Andes. Soc Sci Med 2004;58(11):2291-300. doi: 10.1016/j.socscimed.2003.08.018.
31. Villamor E, Marin C, Mora-Plazas M, Baylin A. Vitamin D deficiency and age at menarche: a prospective study. Am J Clin Nutr 2011;94(4):1020-5. doi: 10.3945/ajcn.111.018168.
32. Crozier SR, Harvey NC, Inskip HM, Godfrey KM, Cooper C, Robinson SM. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. Am J Clin Nutr 2012;96(1):57-63. doi: 10.3945/ajcn.112.037473.

33. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. Pediatrics 2007;119(3):e624-30. doi: 10.1542/peds.2006-2188.
34. Di Renzo GC, Spano F, Giardina I, Brillo E, Clerici G, Roura LC. Iron deficiency anemia in pregnancy. Womens Health (Lond Engl) 2015;11(6):891-900. doi: 10.2217/whe.15.35.
35. Uauy R, Kain J, Corvalan C. How can the Developmental Origins of Health and Disease (DOHaD) hypothesis contribute to improving health in developing countries? Am J Clin Nutr 2011;94(6 Suppl):1759S-64S. doi: 10.3945/ajcn.110.000562.
36. Khorram O, Keen-Rinehart E, Chuang TD, Ross MG, Desai M. Maternal undernutrition induces premature reproductive senescence in adult female rat offspring. Fertil Steril 2015;103(1):291-8 e2. doi: 10.1016/j.fertnstert.2014.09.026.
37. Correia-Branco A, Keating E, Martel F. Maternal undernutrition and fetal developmental programming of obesity: the glucocorticoid connection. Reprod Sci 2015;22(2):138-45. doi: 10.1177/1933719114542012.
38. Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. Int J Obes (Lond) 2013;37(8):1036-43. doi: 10.1038/ijo.2012.177.
39. Frisancho AR. Developmental functional adaptation to high altitude: review. Am J Hum Biol 2013;25(2):151-68. doi: 10.1002/ajhb.22367.
40. Hui LL, Leung GM, Lam TH, Schooling CM. Premature birth and age at onset of puberty. Epidemiology 2012;23(3):415-22. doi: 10.1097/EDE.0b013e31824d5fd0.
41. Castilho SD, Nucci LB, Assuino SR, Hansen LO. [The importance of memory bias in obtaining age of menarche by recall method in Brazilian adolescents]. Arquivos Brasileiros de Endocrinologia e Metabologia 2014;58(4):394-7.
42. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J Pediatr 2005;147(6):753-60. doi: 10.1016/j.jpeds.2005.07.016.
43. Lepkowski JM, Mosher WD, Groves RM, West BT, Wagner J, Gu H. Responsive Design, Weighting, andVariance Estimation in the 2006-2010 National Survey of Family Growth. Vital and Health Statistics Series 2, Data Evaluation and Methods Research 2013(158):1-52.

Chapter 4

Childhood red meat intake frequency is associated with earlier age at menarche

Erica C. Jansen, Constanza Marín, Mercedes Mora-Plazas, Eduardo Villamor

ABSTRACT

Background: Early age at menarche is associated with increased breast cancer risk. Red meat consumption in adolescence predicts breast cancer risk, but it is unknown whether it is also related to earlier menarche.

Objectives: We studied the association between intake of red meat at ages 5-12 y and age at menarche in a prospective study.

Methods: We assessed usual diet with a food frequency questionnaire (FFQ) in a group of 456 girls aged 8.4 ± 1.7 years and followed them for a median 5.6 y in Bogota, Colombia. Girls were asked periodically about the occurrence and date of menarche. Median age at menarche was estimated with use of Kaplan-Meier survival probabilities by categories of red meat intake frequency. Cox proportional hazards models were employed to compare the incidence of menarche by red meat intake frequency adjusting for potential sociodemographic and dietary confounders including total energy intake and intake frequency of other animal food groups (dairy, poultry, fresh water fish, tuna/sardines, eggs, and innards).

Results: Median age at menarche was 12.4 years. After adjustment for total energy intake, maternal parity, and socioeconomic status, red meat intake frequency was inversely

associated with age at menarche. Compared to girls with red meat intake <4 times per week, those consuming it ≥2 times per day had a significantly earlier age at menarche (adjusted hazard ratio [HR]=1.64; 95% CI: 1.11, 2.41; *P*-trend=0.0009). Incidentally, we found that girls with tuna/sardines intake >1 time per week had a significantly later age at menarche (HR=0.62; 95% CI: 0.42, 0.90; *P*=0.01) than those with intake <1 time per month. Intake frequency of other animal food groups was not significantly associated with age at menarche.

Conclusion: Red meat intake frequency during childhood was associated with an earlier age at menarche whereas fatty fish intake frequency was related to a later menarcheal age.

INTRODUCTION

Menarche, the first menstrual period, is a recognizable marker of puberty. In high income settings as well as lower income setting, an early age at menarche is associated with breast (1) and endometrial (2) cancers, obesity (3), type II diabetes (4), cardiovascular disease, and all-cause mortality (5). In addition, early menarche has been related to risk factors during adolescence including alcohol and tobacco use, early sexual debut, and teenage pregnancy (6, 7).

There is substantial variability in the timing of menarche across populations and a secular trend toward earlier menarche within countries (8-10). This suggests that the timing of puberty may be responsive to changes in environmental conditions. While the exact nature of these changes remains uncertain, epidemiological studies have found associations between high intake of animal protein during childhood and earlier puberty (11-17). For example, total animal protein intake between ages 3-8 y was related to earlier menarche in US (11) and German (12) girls. Intake of protein from dairy was related to earlier puberty in girls from Germany (12), Iran (15), and the US (16); whereas higher meat intake in childhood was associated with earlier menarche in British (13), Korean (14), and US (17) girls. There is some heterogeneity in this evidence, however, as a recent study in a large group of US girls found no association between dairy or meat intake at ages 9-14 y and age at menarche (18). One possible explanation for this discrepancy is differences in the timing of dietary assessments (13, 18), because intake around the time of puberty onset may be less relevant than earlier childhood diet. Relatively few studies have examined childhood intake of specific animal food groups in relation to menarche.

A recent investigation found that red meat intake during adolescence was related to higher breast cancer risk (19). Considering that early menarche is a predictor of breast cancer

(1), we hypothesized that red meat intake during childhood could be associated with an earlier menarche.

We evaluated the association between frequency of red meat intake at 5-12 y with age at menarche in a prospective study of pre-menarcheal school-aged girls from Bogotá, Colombia.

METHODS

Study Population

The study was conducted in the context of the Bogotá School Children Cohort, an ongoing longitudinal investigation of nutrition and health in school-aged children. Details concerning recruitment and data collection are published elsewhere (20). Briefly, in February 2006 we randomly sampled children from all public primary schools in Bogotá. Inclusion criteria involved being enrolled in one of the city's 361 public primary schools at the time by the beginning of the school year, and being between 5 and 12 years of age. Four thousand children were invited to participate of whom 3,202 agreed and were enrolled in the cohort. As most children in the public school system were from low- and middle-income families, the cohort represents these socioeconomic strata. Information collected at the time of enrollment included diet, anthropometry, and sociodemographic characteristics and health status.

Dietary assessment

Between May and June 2006, trained dieticians administered a thirty-eight-item food frequency questionnaire (FFQ) to a sample of 1027 mothers to 531 girls and 496 boys who attended parents' meetings at schools in order to obtain information on their children's usual intake. Details of the FFQ have been described previously (21). The FFQ was based on the most frequently consumed foods in this population according to the Colombian National Nutrition Survey 2005 and included all major sources of energy in the population. For each item, we described reference portion sizes in natural units or standard measures for commonly consumed servings among children in this population, and inquired about frequency of intake with a scale comprising 9 options: 4–5 times per day, 2–3 times per day, once per day, 5–6 times per week, 2–4 times per week, once per week, 1–3 times per month, less than once per month, or never. Energy intakes were estimated by multiplying the consumption frequency of each food by the energy contents of the specific portion using composition values from the US Department of Agriculture's Standard Reference food composition database, supplemented with data from manufacturers and published reports (Food Processor software; http://www.esha.com) and the Food Composition Table of Colombian Foods by the Colombian Institute of Family Welfare (22). A team composed of Colombian and US dietitians worked together on the nutrient composition analyses to ensure that the foods chosen from the USDA database resembled the closest to the local foods.

While the FFQ has not been formally validated, a previous investigation that included the girls in the current study provided strong evidence for its validity to measure intake frequency of animal food sources (21). In that study, principal component analyses of the FFQ clearly identified an "animal foods" dietary pattern that included frequent intake of beef, chicken, and dairy. Adherence to this pattern was strongly, positively, and linearly related to serum concentrations of vitamin B-12, a nutrient that is naturally found in animal foods only. In addition, meat intake frequency alone, as measured by the FFQ, was linearly, monotonically related to serum vitamin B-12. Among children reporting meat intake ≥2 times per day, serum vitamin B-12 was 24 pmol/L higher than in children with meat intake <4 times per week (P-trend=0.04), after adjustment for sex and intake frequency of dairy, fish, cow liver, and supplements. Because measurement errors in the FFQ and the serum vitamin B-12 values are uncorrelated, the findings indicate that the validity of the FFQ to measure animal foods is adequate.

Anthropometry

In the weeks following enrollment, trained research assistants visited the schools to obtain anthropometric measurements from the children. Weight was measured in light clothing to the nearest 0.1 kg on Tanita HS301 electronic scales (Tanita Arlington Heights, IL), and height was measured without shoes to the nearest 1 mm with wall-mounted Seca 202 stadiometers (Seca, Hanover, MD). We calculated height-for-age and BMI-for-age *z* scores, with the use of the World Health Organization sex-specific growth references for children aged 5-19 (23).

Parental and household characteristics

Information on parental and household characteristics was obtained with the use of a self-administered questionnaire that was sent to children's home during the week of enrollment. The questionnaire inquired about parental age, education level, mother's parity and age at menarche, and the child's health habits, including time watching television or playing videogames and playing outdoors. Socioeconomic status (SES) was determined from the child's home address, as the score assigned by the local government to establish the cost of public services. Maternal BMI (kg/m^2) was calculated from height and weight values that the research team measured at the time of FFQ administration, using the same methods described for the children. Measured values were available in 80% of mothers; self-reported values were used in the rest. Covariates were categorized as presented in **Table 3.1**

Follow-up

Follow-up visits occurred in June and November 2006 and once yearly thereafter. If children were absent from school on the day of the visit, they were assessed at home. At each assessment, girls were asked if they had begun menstruation and, if they had, the date of their first menstrual period. Major holidays and school vacation time were used to aid the girls' recall of the date of menarche if needed.

Written informed consent from parents or primary caregivers of all children was obtained prior to enrollment. The study protocol was approved by the Ethics Committee of the National University of Colombia Medical School. The Institutional Review Board at the University of Michigan approved use of data from the study.

Data Analysis

Sixty-six girls who had more than 5 missing responses in the FFQ were excluded. Of the remaining 465 girls with valid FFQ data, 9 had experienced menarche by the time of enrollment and were excluded. Thus, the analytic sample consisted of 456 girls.

The primary exposure was frequency of red meat intake. This was the sum of weighted intake frequencies of three separate items in the FFQ: beef/pork/veal/lamb, cold cuts (sausages/ham/bologna), and hamburger/hot dog. The frequency was categorized as <4 times per week, 4 to 6 times per week, 1 time per day, and ≥2 times per day. Because red meat is eaten as part of an animal food source pattern in this population (21), intake of other animal foods could confound the association with age at menarche; therefore, we also considered intake frequency of dairy (milk, cheese, and yogurt), poultry, freshwater fish, canned tuna or sardines (main sources of fatty fish in the population, asked together in a single FFQ item), eggs, and innards (cow's liver, spleen, lung, and tripe). Innards were treated separately because the items in the red meat category are typically more highly processed than innards. Furthermore, innards are not consumed as frequently as items in the red meat group and as a result their intake may be measured with more error than other meats'.

The outcome, age at menarche, was estimated in decimal years as date of menarche minus date of birth. Among 75 girls (16.5%) who did not recall the day of the month when menarche occurred, the 15th was imputed. In another 33 girls (7.2%) who only remembered the year of menarche, July 1st was imputed for the calculation of age at menarche. The girl's mother was the primary informant of the date of menarche in 67 participants (14.7%). Twenty-six percent of girls (n=119) did not have menarche during follow-up and were censored at the last interview date.

First, we examined the associations of baseline sociodemographic characteristics and age at menarche using time-to-event analyses. Time-to-event analytic techniques including the Kaplan-Meier method and Cox regression properly account for right-censoring in the data due to the fact that some girls did not reach menarche during follow-up. These methods allow to combine information on menarcheal age from post-menarcheal girls with the last known age during follow-up when menarche had not occurred ("censoring") from pre-menarcheal girls. We estimated median ages at menarche by categories of sociodemographic correlates using Kaplan-Meier cumulative probabilities. Values in the text are medians (IQR). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI), with decimal age as the time scale.

We next examined the distribution of the sociodemographic correlates across levels of red meat intake frequency. For continuous correlates, we estimated tests for linear trend from linear regression models in which a variable representing ordinal categories of red meat intake was introduced as a continuous predictor. We used robust estimates of the variance in these models to overcome potential deviations from the multivariate normality assumption (24). For categorical correlates, we used Cochrane-Armitage tests. We also estimated the correlations (Spearman) of red meat intake frequency with that of other animal food groups.

In bivariate analysis, we estimated median ages of menarche and HRs with 95% CI by intake frequency categories of red meat and other animal food groups using Kaplan Meier and Cox regression analyses. We conducted tests of linear trend for the associations between intake frequency of each food group and menarche by introducing into each Cox model a variable representing ordinal categories of intake frequency as a continuous predictor and performing a Wald test.

Finally, we conducted multivariable analyses of the association between red meat intake frequency and age at menarche by fitting a Cox proportional hazards model that included as covariates sociodemographic characteristics that were independent predictors of menarche, other relevant animal food groups, and total energy intake. Height-for-age and BMI-for-age *z* scores were deliberately excluded from the multivariable model because they could be mediators on the causal pathway between red meat intake and age at menarche (25). The proportional hazards assumption was verified with the use of terms for the interaction between time and covariates. This assumption was met in all models.

Because there were some missing values for socioeconomic status (0.7%), maternal parity (5.9%), red meat intake (3.7%) and tuna/sardine intake (1.1%), we conducted supplemental analyses in which these missing values were estimated using a Markov Chain Monte Carlo multiple imputation technique (26) before their inclusion in the multivariable models. Girl's baseline age, socioeconomic status, maternal parity, red meat intake, and tuna/sardine intake were included in the imputation procedures. Results from 10 multiple imputation cycles were combined with use of the PROC MIANALYZE routine of SAS Software version 9.3 (SAS Institute, Cary, NC).

Although our primary aim was to estimate the total effect of red meat intake on age at menarche, we conducted additional supplemental analyses to ascertain the potential mediating effect of BMI-for-age by introducing it as a covariate into the multivariable models. These analyses assumed a lack of interaction between frequency of intake and BMI-for-age on age at menarche, and no unmeasured confounding of the association between BMI-for-age and age at menarche (27).

Finally, although our intent was to assess pre-pubertal usual intake of red meat and menarche, it is possible that some girls were pubertal at baseline. Thus, we conducted sensitivity analyses among girls <10 y at baseline (n=368) to assess whether estimates were substantially different from results including girls >10 y at baseline.

RESULTS

The mean age ± SD of girls at recruitment was 8.4 ± 1.7 years. Their mean ± SD red meat intake frequency was 1.3 ± 1.2 times per day. Mean total energy intake was 1478 ± 718 kcal/d. The median length of follow up was 5.6 years (IQR 2.6 to 6.8 years). It was shorter for girls who were censored (median 2.5 years; IQR 1.7 to 4.0 years) than for those who had menarche during follow-up (median 6.2 years; IQR 5.2 to 6.8 years) due to losses to follow up. Nevertheless, the two groups did not differ from each other with respect to frequency of red meat intake, age, socioeconomic status, or BMI-for-age.

The estimated median age at menarche was 12.4 years (IQR 12.2 to 12.5 years). Girls' baseline height-for-age *z* scores, BMI-for-age *z* scores, and socioeconomic status were inversely associated with age at menarche, whereas maternal age at menarche and parity were positively associated with age at menarche (**Table 3.1**).

Red meat intake frequency was positively related to height-for-age and BMI-for-age *z* scores, total energy intake, and socioeconomic status; and inversely associated with maternal parity (**Table 3.2**). Red meat intake frequency was also correlated with dairy ($\rho=0.45$, $P<0.0001$) and poultry ($\rho=0.44$, $P<0.0001$) frequency of intake (**Table 3.4**).

In bivariate analysis, red meat intake frequency was inversely associated with age at menarche (**Table 3.3**). Compared to girls with red meat intake <4 times per week, those with intake ≥2 times per day had a significantly earlier age at menarche (HR=1.41; 95% CI: 1.02, 1.95; *P*-trend=0.04). We also noted that intake frequency of canned tuna/sardines was positively related to age at menarche in a non-linear manner; girls with intake ≥1 time per month had a significantly later age at menarche than girls with tuna/sardine intake <1 time per month (HR=0.78; 95% CI: 0.62, 0.98; *P*=0.03).

After adjustment for total energy intake, maternal parity, and socioeconomic status red meat intake frequency remained linearly associated with age at menarche (**Table 3.3**). Compared to girls with red meat intake <4 times per week, those consuming it ≥2 times per day had a significantly earlier age at menarche (HR=1.64; 95% CI: 1.11, 2.41; *P*-trend=0.0009). On the other hand, compared to girls with tuna/sardines intake <1 time per month, those with intake >1 time per week had a later age at menarche (HR=0.62; 95% CI: 0.42, 0.90; *P*=0.01). Results remained essentially unchanged after additional adjustment for dairy and poultry intake frequencies. Similarly, using multiple imputation of missing covariate values did not change the results.

In supplemental mediation analyses, introducing BMI-for-age z-score at baseline into the multivariable imputed model resulted in an attenuation of the estimates for red meat. Compared to an intake frequency <4 times per week, the adjusted hazard ratios (95% CI) for categories 4 to 6 per week, 1 per day, and ≥2 per day were, respectively, 1.16 (0.85, 1.60), 1.17 (0.85, 1.62), and 1.33 (0.90, 1.96) (*P*-trend=0.17). The estimates for intake frequency of tuna/sardines did not change.

Intake frequency of other animal food groups including dairy, poultry, eggs, fresh water fish, or innards was not significantly associated with age at menarche in bivariate (**Table 3.5**) or multivariable adjusted (**Table 3.6**) analyses. Finally, restriction of analyses to girls <10 y at baseline did not substantially alter results (**Table 3.7**).

DISCUSSION

In this cohort study of school-aged girls, childhood intake frequency of red meat was inversely related to age at menarche in a linear fashion. This relation was independent of potential sociodemographic and dietary confounders. Unexpectedly, we also found that canned tuna/sardine intake frequency was positively associated with age at menarche.

Although earlier studies had reported associations between intake of animal foods and age at menarche (11-17), our study substantially extends previous findings by examining intake frequency of specific categories of animal food sources in mid childhood. The association of red meat intake frequency and age at menarche is generally consistent with previous studies that linked pre-pubertal consumption of animal protein and food sources to earlier puberty (11-17). Nevertheless, it is opposite to findings from an investigation of US girls in which intake of red meat at ages 9 to 14 y was not associated with age at menarche (18). One reason for the discrepancy could be related to the timing of the dietary assessment. Whereas dietary assessment in our study occurred at an average 8 y of age, girls in the US study were on average 11 y of age at baseline and much closer to the timing of menarche. Some authors have proposed that diet at younger ages may be more important for the timing of puberty than peri-pubertal intake (13). In fact, some argue that the timing of puberty is determined by environmental conditions acting as early as around the time of birth (28). This is not necessarily contrary to our findings if we assume that diet tracks during childhood. Second, reverse causation bias could have affected the results of the US study since the dietary exposures were assessed within a short period with respect to the outcome. Because menarche is a relatively late event during sexual development, girls may have initiated puberty at the time of dietary assessment, and their diet might have changed as a consequence (18).

One pathway to explain potential effects of animal foods, particularly dairy, on the timing of puberty has been related to a protein-mediated stimulation of insulin-like growth factor (IGF)-1 secretion (29, 30). However, meat intake has not been related to IGF-1 secretion and there could be other plausible mechanisms. Availability of micronutrients found in red meat such as iron and zinc could signal the body to initiate puberty since these nutrients are essential for sustaining pregnancy and for the offspring's survival and development. In one small randomized trial, zinc supplementation resulted in earlier age at menarche (31). Another mechanism could be through the development of adiposity. Childhood obesity is related to early menarche (25), and intake of some foods in the red meats group, including hot dogs and hamburgers, was related to child overweight in this population (32). In supplemental mediation analyses, the association of red meat intake frequency with age at menarche was attenuated after adjustment for BMI-for-age z-score at baseline, suggesting that part of the effect of red meat on age at menarche could be mediated through body size. There are also other potential mechanisms related to substances ingested with red meat, including estrogenic mycotoxins such as zearalenone (33, 34), or heterocyclic amines produced during preparation of red meat at high temperatures (34).

Previous investigations have consistently shown an association between early onset of menses and breast cancer in adulthood (1). Also, red meat intake during adolescence has been related to pre-menopausal breast cancer risk (19). Our finding suggests a potential mechanism to explain these relations, in that early age at menarche could be a mediator on the causal pathway between adolescent red meat intake during childhood and breast cancer risk.

Of note, we incidentally found that tuna/sardine intake frequency was related to a later age at menarche. Two previous studies that examined associations between fish intake and age at menarche found no relation (35, 36). While the finding in our study could have been due to chance, there are potential underlying mechanisms to explain it. Tuna and sardines are rich in long-chain polyunsaturated fatty acids (PUFAs), which are related to more favorable cardiovascular profiles in adolescents (37), including slower weight gain (38).

Our study has several strengths. First, its longitudinal design precluded bias due to reverse causation. The prospective collection of data on age at menarche prevented recall bias. Any misclassification of the outcome is unlikely to be differential with respect to exposure status. In addition, follow-up was high. Other strengths included the ability to examine different animal food groups and the possibility to adjust for important confounders. Adjusted hazard ratios for red meat intake frequency became stronger than the unadjusted estimates after controlling for negative confounding by tuna/sardines intake. The association of tuna/sardines intake frequency was strengthened in multivariable analyses after controlling for negative confounding by red meat intake and maternal parity. We assessed intake using an FFQ that measures animal food intake validly (21). Our data were internally consistent considering that the associations of age at menarche with known predictors of puberty were in the expected directions. Red meat intake was also positively associated with height, BMI, total energy intake, and socioeconomic status as expected in this population. Finally, we accounted for missing data in the analysis using state-of-the-art multiple imputation techniques.

The study also has some limitations. First, the results may not be generalizable to girls of the highest socioeconomic levels. Second, unmeasured intake of foods or nutrients that are associated with red meat intake and are independent predictors of age at menarche (e.g. fiber, isoflavones (39, 40)) could have introduced residual confounding. Third, misclassification of exposure due to measurement errors in the FFQ could have been a source of bias. Because the FFQ was administered to the girls' mothers, intake of foods eaten away from home may have been underestimated. Measurement error in the report of diet is likely not associated with the recall of age at menarche; thus, its potential consequence could be an attenuation of the true underlying effect. Fourth, some girls were lost to follow-up and this could potentially introduce selection bias. Fifth, we could not account for potential changes in diet after the childhood measurement. Sixth, we were unable to examine associations of micronutrients present in red meat with age at menarche. Finally, although the short-term recall of age at menarche is highly reliable (41), the effects of diet on earlier events of puberty may differ from those on menarche. It is uncertain whether they represent effects on the onset vs. the duration of puberty.

In summary, red meat intake frequency during childhood was inversely associated with age at menarche whereas fatty fish intake frequency was positively associated with age at onset of menses. Future studies should examine the role of particular components of red meat, including micronutrients and by-products of processing, on the timing of sexual maturation. Examining the role of fish intake and the timing of puberty in other populations is also warranted. Whether replacing red meat intake with other animal food sources influences age at menarche would need to be determined in intervention studies.

ACKNOWLEDGEMENTS

EV designed the research; MM-P and CM conducted the research; ECJ and EV analyzed the data; ECJ and EV wrote the paper and have primary responsibility for final content. All authors read and approved the final manuscript.

Table 3.1 Age at menarche in 456 Colombian schoolgirls according to sociodemographic characteristics

Baseline characteristics	n[1]	Median age at menarche[2], years	Hazard ratio (95% CI)[3]
Girl's year of birth			
1993 to 1996	165	12.4	1.00
1997 to 1998	176	12.4	1.21 (0.96, 1.54)
1999 to 2001	115	12.2	1.28 (0.94, 1.74)
P-trend[4]			0.07
Girl was born in Bogotá			
Yes	382	12.4	1.00
No	51	12.2	1.22 (0.85, 1.76)
P			0.28
Girl's height-for-age *z* score[5]			
<-2	42	13.4	0.36 (0.24, 0.55)
-2 to <-1	132	12.8	0.45 (0.33, 0.61)
-1 to <0	157	12.2	0.82 (0.62, 1.09)
0 to <1	97	12.0	1.00
≥1	21	11.7	1.34 (0.76, 2.37)
P-trend			<0.0001
Girl's BMI-for-age *z* score[5]			
<-1	64	12.9	0.72 (0.51, 1.00)
-1 to <0	150	12.6	0.91 (0.70, 1.19)
0 to <1	160	12.3	1.00
≥1	74	11.9	1.82 (1.33, 2.49)
P-trend			<0.0001
Time viewing TV/playing games, h/wk			
<10.0	129	12.6	1.00
10.0 to 19.9	112	12.3	1.08 (0.81, 1.44)
20.0 to 29.9	90	12.3	1.05 (0.77, 1.43)
≥30.0	52	12.5	0.95 (0.65, 1.38)
P-trend			0.88
Time playing outdoors, h/wk			
<1.5	104	12.5	1.00
1.5 to 4.4	112	12.2	0.97 (0.71, 1.33)
4.5 to 9.9	87	12.5	0.92 (0.66, 1.30)
≥10	72	12.3	1.03 (0.72, 1.48)
P-trend			0.99

Mother's age at girl's birth, y			
<20	58	12.3	1.00
20 to <25	120	12.3	0.98 (0.68, 1.43)
25 to <30	117	12.3	0.92 (0.64, 1.34)
30 to <35	85	12.6	0.90 (0.61, 1.33)
≥35	53	12.9	0.77 (0.50, 1.21)
P-trend			0.21
Mother's age at menarche, y			
<11.5	40	11.9	1.00
11.5 to <12.5	89	12.3	0.80 (0.52, 1.25)
12.5 to <13.5	110	12.5	0.66 (0.43, 1.00)
13.5 to <14.5	90	12.5	0.65 (0.42, 1.01)
≥14.5	82	13.0	0.48 (0.31, 0.76)
P-trend			0.0006
Mother's education, y			
Incomplete primary (1-4)	32	12.2	1.18 (0.72, 1.94)
Complete primary (5)	86	12.3	0.95 (0.70, 1.28)
Incomplete secondary (6-10)	107	12.5	0.85 (0.65, 1.11)
Complete secondary (11)	187	12.4	1.00
University (≥12)	19	13.2	0.76 (0.41, 1.40)
P-trend			0.80
Mother's parity			
1	50	11.9	1.00
2	154	12.4	0.65 (0.46, 0.93)
3	148	12.5	0.54 (0.38, 0.78)
4	41	12.1	0.59 (0.37, 0.95)
≥5	36	12.9	0.53 (0.33, 0.85)
P-trend			0.01
Mother's BMI, kg/m^2			
<18.5	17	12.2	1.29 (0.70, 2.37)
18.5-24.9	261	12.4	1.00
25.0-29.9	119	12.6	0.96 (0.75, 1.23)
≥30.0	40	12.3	1.41 (0.96, 2.06)
P-trend			0.47
Socioeconomic status[6]			
1	29	12.8	1.00
2	162	12.5	1.41 (0.86, 2.31)
3	223	12.2	1.79 (1.10, 2.93)
4	39	12.0	2.27 (1.26, 4.07)
P-trend			0.0006

[1] N ranges from 375 to 456 due to missing values.
[2] From Kaplan-Meier survival probabilities.
[3] From Cox proportional hazards models with age at menarche as the outcome and each predictor as the covariate.
[4] From a Wald test of a covariate representing ordinal categories of the predictor, introduced into the model as continuous.
[5] According to the World Health Organization reference (23).
[6] According to the city's classification of neighborhoods' public services fees.

Table 3.2 Sociodemographic characteristics of 456 Colombian schoolgirls according to frequency of red meat intake in childhood[1]

Baseline characteristics	<4 per week n=120	4 to 6 per week n=129	1 per day n=109	≥2 per day n=81[2]	*P*-trend[3]
Girls					
Age, y	8.5 ± 1.7	8.3 ± 1.6	8.2 ± 1.7	8.5 ± 1.7	0.59
Born in Bogotá, %	87.3	88.1	89.1	87.3	0.90
Height-for-age *z* score[4]	-0.84 ± 0.92	-0.71 ± 1.03	-0.76 ± 1.05	-0.49 ± 0.97	0.03
BMI-for-age *z* score[4]	-0.07 ± 0.93	0.01 ± 0.99	0.14 ± 0.94	0.24 ± 0.93	0.01
Time viewing TV/playing games, h/wk	17.5 ± 14.9	18.2 ± 14.4	16.2 ± 11.8	16.6 ± 10.5	0.44
Time playing outdoors, h/wk	7.1 ± 11.8	5.7 ± 7.9	6.0 ± 7.0	7.0 ± 7.3	0.89
Total energy intake, Kcal/d	1175 ± 524	1314 ± 470	1471 ± 590	2147 ± 984	<0.0001
Mothers					
Age at girl's birth, y	27.5 ± 6.6	26.8 ± 6.0	26.6 ± 6.0	27.8 ± 6.8	0.96
Age at menarche, y	13.3 ± 1.4	13.4 ± 1.5	13.1 ± 1.4	13.3 ± 1.5	0.54
Education, y	8.4 ± 3.3	8.9 ± 3.0	8.3 ± 3.0	8.9 ± 3.1	0.73
Parity, number of live births	2.9 ± 1.2	2.6 ± 1.0	2.6 ± 1.1	2.5 ± 1.0	0.04
BMI, kg/m^2	24.7 ± 3.8	24.1 ± 3.9	24.4 ± 4.2	24.2 ± 3.6	0.38

Socioeconomic status[5]	2.4 ± 0.8	2.8 ± 0.6	2.7 ± 0.7	2.6 ± 0.7	0.02

[1]Mean ± SD, unless noted otherwise.

[2] Totals <456 due to missing responses to specific food items in the FFQ.

[3] For continuous variables, Wald test when a variable representing ordinal categories of red meat intake was introduced in a linear regression model as a continuous predictor. Robust estimates of the variance were specified in each model. For place of birth, Cochrane-Armitage Test.

[4] According to the WHO reference (23).

[5]According to the city's classification of neighborhoods' public services fees.

Table 3.3 Multivariable-adjusted hazard ratios for age at menarche in Colombian schoolgirls according to red meat and fatty fish intake frequencies during childhood

Frequency of intake	n[1]	Median age at menarche[2]	Unadjusted hazard ratio (95% CI)[3]	Adjusted hazard ratio (95% CI)[4]	Adjusted hazard ratio (95% CI)[5]
Red meat					
<4 per week	120	12.7	1.00	1.00	1.00
4 to 6 per week	129	12.3	1.23 (0.91, 1.65)	1.16 (0.84, 1.60)	1.20 (0.87, 1.64)
1 per day	109	12.3	1.24 (0.92, 1.69)	1.32 (0.95, 1.83)	1.28 (0.93, 1.76)
≥2 per day	81	12.3	1.41 (1.02, 1.95)	1.64 (1.11, 2.41)	1.59 (1.09, 2.32)
P-trend [6]			0.04	0.009	0.02
Tuna/sardines					
<1 per month	144	12.2	1.00	1.00	1.00
1 to 3 per month	122	12.6	0.77 (0.58, 1.02)	0.70 (0.52, 0.94)	0.70 (0.53, 0.93)
1 per week	110	12.4	0.79 (0.59, 1.06)	0.67 (0.49, 0.92)	0.66 (0.48, 0.90)
>1 per week	75	12.5	0.79 (0.57, 1.10)	0.62 (0.42, 0.90)	0.69 (0.48, 0.98)
P-trend [6]			0.11	0.008	0.01

[1] N ranges from 439 to 451 due to missing values.
[2] From Kaplan-Meier survival probabilities.
[3] From Cox proportional hazards models with age at menarche as the outcome and indicator variables for intake frequency of each food as predictors.
[4] Complete-case analysis (n=407). Estimates are from Cox proportional hazards models with age at menarche as the outcome and predictors that included indicator variables for red meat and tuna/sardines intake frequencies, total energy intake, maternal parity, and socioeconomic status.
[5] Multiple imputation analysis (n=456). Estimates are from multivariable Cox proportional hazards models including imputed data for missing values.
[6] From a Wald test when a variable representing ordinal categories of each food group was introduced in the Cox model as a continuous covariate.

Table 3.4 Spearman correlations between intake frequencies of animal food groups[1]

	Red meat	Dairy	Poultry	Freshwater fish	Tuna/sardines	Eggs
Dairy	0.45	-	-	-	-	-
Poultry	0.44	0.26	-	-	-	-
Freshwater Fish	0.34	0.29	0.26	-	-	-
Tuna/sardines	0.23	0.31	0.16	0.29	-	-
Eggs	0.21	0.25	0.24	0.13	0.19	-
Innards	0.21	0.12	0.21	0.26	0.14	0.08

[1] Red meat includes beef, cold cuts, and hamburger or hot dog; dairy incudes milk, cheese, and yogurt; and innards include cow's liver, spleen, lung, and tripe. *P*<0.001 for all correlations except innards-dairy (*P*=0.01), innards-tuna/sardines (*P*=0.005) and innards-eggs (*P*=0.10).

Table 3.5 Unadjusted analyses of age at menarche according to frequency of intake of animal food groups in 456 Colombian school age girls

Frequency of intake[1]	n[2]	Median age at menarche[3]	Hazard ratio (95% CI)[4]
Red meat			
<4 per week	120	12.7	1.00
4 to 6 per week	129	12.3	1.23 (0.91, 1.65)
1 per day	109	12.3	1.24 (0.92, 1.69)
≥2 per day	81	12.3	1.41 (1.02, 1.95)
P-trend[5]			0.04
Dairy			
<1 per day	45	12.9	1.00
1 per day	140	12.4	1.17 (0.79, 1.76)
2 per day	89	12.2	1.24 (0.81, 1.90)
≥3 per day	154	12.3	1.32 (0.89, 1.97)
P-trend			0.16
Poultry			
≤1 per week	127	12.2	1.00
2 to 4 per week	179	12.5	0.92 (0.70, 1.20)
5 to 6 per week	59	12.6	0.96 (0.67, 1.37)
≥1 per day	90	12.2	1.01 (0.74, 1.38)
P-trend			0.87
Freshwater fish			
Never	78	12.3	1.00
<1 per month	152	12.5	1.17 (0.85, 1.60)
1 to 3 per month	114	12.4	1.09 (0.78, 1.53)
≥1 per week	105	12.2	1.16 (0.82, 1.63)
P-trend			0.57
Tuna/sardines			
<1 per month	144	12.2	1.00
1 to 3 per month	122	12.6	0.77 (0.58, 1.02)
1 per week	110	12.4	0.79 (0.59, 1.06)
>1 per week	75	12.5	0.79 (0.57, 1.10)
P-trend			0.11
Eggs			
≤1 per week	63	12.4	1.00
2 to 4 per week	131	12.3	0.97 (0.69, 1.36)
5 to 6 per week	54	12.5	0.80 (0.53, 1.21)
≥1 per day	202	12.3	1.00 (0.72, 1.38)
P-trend			0.95

Frequency of intake[1]	n[2]	Median age at menarche[3]	Hazard ratio (95% CI)[4]
Innards			
<1 per month	122	12.3	1.00
1 to 2 per month	83	12.5	0.81 (0.59, 1.11)
3 per month to 1 per week	89	12.0	0.98 (0.71, 1.35)
>1 per week	145	12.4	0.77 (0.58, 1.03)
P-trend			0.15
Total energy intake, per 100 Kcal/day	456		1.00 (0.98, 1.01)
P			0.52

[1] Frequency of intake refers to the following average portion sizes: meat including beef (30 g), cold cuts (20 g), and hamburger or hot dog (30 g); dairy including milk (200 g), cheese (20 g), and yogurt (200 g); poultry (30 g); fresh water fish (25 g); canned tuna or sardines (20 g); eggs (1 unit); and innards including cow's liver, spleen, and lung (30 g) and cow's tripe (1 tablespoon).
[2] Totals may be <456 due to missing responses to specific food items in the FFQ.
[3] From Kaplan-Meier survival probabilities.
[4] From Cox proportional hazards models with age at menarche as the outcome and each food item as the predictor.
[5] From a Wald test when a variable representing ordinal categories of each food group frequency of intake was introduced into a linear regression model as a continuous predictor.

Table 3.6 Adjusted hazard ratios for menarche according to frequency of intake of animal food groups in 456 Colombian school-aged girls

	Complete-case analysis		Multiple imputation analysis	
	Adjusted HR (95% CI)[1]	*P*-trend[2]	Adjusted HR (95% CI)[3]	*P*-trend[2]
Dairy		0.47		0.35
<1 per day	1.00		1.00	
1 per day	1.08 (0.70, 1.66)		1.17 (0.78, 1.74)	
2 per day	1.11 (0.70, 1.78)		1.22 (0.79, 1.90)	
≥3 per day	1.19 (0.73, 1.94)		1.27 (0.80, 2.00)	
Poultry		0.81		0.81
≤1 per week	1.00		1.00	
2 to 4 per week	0.97 (0.73, 1.29)		0.90 (0.69, 1.19)	
5 to 6 per week	1.13 (0.77, 1.66)		1.01 (0.70, 1.47)	
≥1 per day	0.91 (0.63, 1.31)		0.93 (0.66, 1.32)	
Freshwater fish		0.64		0.49
Never	1.00		1.00	
<1 per month	1.07 (0.77, 1.50)		1.13 (0.82, 1.55)	
1 to 3 per month	1.07 (0.75, 1.53)		1.08 (0.77, 1.53)	
≥1 per week	1.10 (0.75, 1.64)		1.14 (0.79, 1.65)	
Eggs		0.85		0.73
≤1 per week	1.00		1.00	
2 to 4 per week	1.03 (0.71, 1.49)		1.04 (0.73, 1.48)	
5 to 6 per week	0.77 (0.49, 1.22)		0.84 (0.55, 1.30)	
≥1 per day	1.05 (0.74, 1.48)		1.08 (0.77, 1.50)	
Innards		0.19		0.34
<1 per month	1.00		1.00	
1 to 2 per month	0.74 (0.52, 1.04)		0.76 (0.55, 1.05)	
3 per month to 1 per week	1.03 (0.73, 1.47)		1.08 (0.77, 1.52)	
>1 per week	0.74 (0.54, 1.02)		0.79 (0.57, 1.08)	

[1] From Cox proportional hazards models with age at menarche as the outcome and predictors that included indicator variables for the food group plus red meat intake frequency, tuna/sardines intake frequency, total energy intake, maternal parity, and socioeconomic status.
[2] From a Wald test when a variable representing ordinal categories of each food group was introduced in the Cox model as a continuous covariate.
[3] From Cox proportional hazards models including imputed data for missing values.

Table 3.7 Multivariable-adjusted hazard ratios for age at menarche in Colombian schoolgirls <10 y at baseline according to red meat and fatty fish intake frequencies during childhood

Frequency of intake	n[1]	Median age at menarche[2]	Unadjusted hazard ratio (95% CI)[3]	Adjusted hazard ratio (95% CI)[4]	Adjusted hazard ratio (95% CI)[5]
Red meat					
<4 per week	92	12.5	1.00	1.00	1.00
4 to 6 per week	105	12.2	1.18 (0.84, 1.65)	1.27 (0.86, 1.85)	1.24 (0.86, 1.78)
1 per day	92	12.3	1.04 (0.73, 1.47)	1.21 (0.82, 1.79)	1.14 (0.79, 1.65)
≥2 per day	65	12.0	1.38 (0.96, 2.00)	1.54 (0.96, 2.47)	1.50 (0.95, 2.35)
P-trend[6]			0.14	0.12	0.16
Tuna/sardines					
<1 per month	115	12.2	1.00	1.00	1.00
1 to 3 per month	97	12.5	0.92 (0.67, 1.25)	0.86 (0.61, 1.21)	0.84 (0.59, 1.17)
1 per week	90	12.4	0.79 (0.57, 1.10)	0.69 (0.47, 1.00)	0.68 (0.47, 0.97)
>1 per week	61	12.3	0.94 (0.65, 1.37)	0.84 (0.54, 1.33)	0.90 (0.59, 1.37)
P-trend[6]			0.42	0.13	0.19

[1] N ranges from 354 to 363 due to missing values.
[2] From Kaplan-Meier survival probabilities.
[3] From Cox proportional hazards models with age at menarche as the outcome and indicator variables for intake frequency of each food as predictors.
[4] Complete-case analysis (n=325). Estimates are from Cox proportional hazards models with age at menarche as the outcome and predictors that included indicator variables for red meat and tuna/sardines intake frequencies, total energy intake, maternal parity, and socioeconomic status.
[5] Multiple imputation analysis (n=368). Estimates are from multivariable Cox proportional hazards models including imputed data for missing values.
[6] From a Wald test when a variable representing ordinal categories of each food group was introduced in the Cox model as a continuous covariate.

REFERENCES

1. Horn J, Opdahl S, Engstrom MJ, Romundstad PR, Tretli S, Haugen OA, Bofin AM, Vatten LJ, Asvold BO. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. Cancer Causes & Control: CCC 2014;25(7):881-9. doi: 10.1007/s10552-014-0388-0.
2. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Fournier A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;127(2):442-51. doi: 10.1002/ijc.25050.
3. Peters SA, Huxley RR, Woodward M. Women's reproductive health factors and body adiposity: Findings from the UK Biobank. Int J Obes (Lond) 2015. doi: 10.1038/ijo.2015.254.
4. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, Hu FB. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. American Journal of Epidemiology 2010;171(3):334-44. doi: 10.1093/aje/kwp372.
5. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. American Journal of Epidemiology 2014;180(1):29-40. doi: 10.1093/aje/kwu113.
6. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. Pediatrics 2005;116(6):1451-6. doi: 10.1542/peds.2005-0542.
7. Vaughan EB, Van Hulle CA, Beasley WH, Rodgers JL, D'Onofrio BM. Clarifying the associations between age at menarche and adolescent emotional and behavioral problems. Journal of Youth and Adolescence 2015;44(4):922-39. doi: 10.1007/s10964-015-0255-7.
8. Jansen EC, Herran OF, Villamor E. Trends and correlates of age at menarche in Colombia: Results from a nationally representative survey. Econ Hum Biol 2015;19:138-44. doi: 10.1016/j.ehb.2015.09.001.
9. Jaruratanasirikul S, Chanpong A, Tassanakijpanich N, Sriplung H. Declining age of puberty of school girls in southern Thailand. World J Pediatr 2014;10(3):256-61. doi: 10.1007/s12519-014-0472-2.
10. Song Y, Ma J, Wang HJ, Wang Z, Hu P, Zhang B, Agardh A. Trends of age at menarche and association with body mass index in Chinese school-aged girls, 1985-2010. Journal of Pediatrics 2014;165(6):1172-7 e1. doi: 10.1016/j.jpeds.2014.08.013.
11. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiol 2000;152(5):446-52.
12. Gunther AL, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. J Nutr 2010;140(3):565-71. doi: 10.3945/jn.109.114934.
13. Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, Emmett PM. Diet throughout childhood and age at menarche in a contemporary cohort of British girls. Public Health Nutr 2010;13(12):2052-63. doi: 10.1017/S1368980010001461.
14. Li SJ, Paik HY, Joung H. Dietary patterns are associated with sexual maturation in Korean children. Br J Nutr 2006;95(4):817-23.

15. Ramezani Tehrani F, Mirmiran P, Gholami R, Moslehi N, Azizi F. Factors influencing menarcheal age: results from the cohort of tehran lipid and glucose study. Int J Endocrinol Metab 2014;12(3):e16130. doi: 10.5812/ijem.16130.
16. Wiley AS. Milk intake and total dairy consumption: associations with early menarche in NHANES 1999-2004. PLoS One 2011;6(2):e14685. doi: 10.1371/journal.pone.0014685.
17. Kissinger D, Sanchez A. The association of dietary factors with age at menarche. Nutrition Research 1987;7:471-9.
18. Carwile JL, Willett WC, Wang M, Rich-Edwards J, Frazier AL, Michels KB. Milk Consumption after Age 9 Years Does Not Predict Age at Menarche. J Nutr 2015;145(8):1900-8. doi: 10.3945/jn.115.214270.
19. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Adolescent meat intake and breast cancer risk. Int J Cancer 2015;136(8):1909-20. doi: 10.1002/ijc.29218.
20. Arsenault JE, Mora-Plazas M, Forero Y, Lopez-Arana S, Marin C, Baylin A, Villamor E. Provision of a school snack is associated with vitamin B-12 status, linear growth, and morbidity in children from Bogota, Colombia. J Nutr 2009;139(9):1744-50. doi: 10.3945/jn.109.108662.
21. Villamor E, Mora-Plazas M, Forero Y, Lopez-Arana S, Baylin A. Vitamin B-12 status is associated with socioeconomic level and adherence to an animal food dietary pattern in Colombian school children. J Nutr 2008;138(7):1391-8.
22. Instituto Colombiano de Bienestar Familiar. Tabla de Composicion de Alimentos Colombianos. Bogota´: ICBF, 2005.
23. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World Health Organization 2007;85(9):660-7.
24. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica 1980;48:817-30.
25. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. Pediatrics 2007;119(3):e624-30. doi: 10.1542/peds.2006-2188.
26. Schafer JL. Analysis of incomplete multivariate data. New York: Chapman and Hall, 1997.
27. Vanderweele T. Explanation in Causal Inference: Methods for Mediation and Interaction. 1st ed. New York, NY: Oxford University Press, 2015.
28. Cole TJ. Secular trends in growth. Proceedings of the Nutrition Society 2000;59(2):317-24.
29. Kerver JM, Gardiner JC, Dorgan JF, Rosen CJ, Velie EM. Dietary predictors of the insulin-like growth factor system in adolescent females: results from the Dietary Intervention Study in Children (DISC). Am J Clin Nutr 2010;91(3):643-50. doi: 10.3945/ajcn.2009.28205.
30. Thankamony A, Ong KK, Ahmed ML, Ness AR, Holly JM, Dunger DB. Higher levels of IGF-I and adrenal androgens at age 8 years are associated with earlier age at menarche in girls. J Clin Endocrinol Metab 2012;97(5):E786-90. doi: 10.1210/jc.2011-3261.
31. Halsted JA, Ronaghy HA, Abadi P, Haghshenass M, Amirhakemi GH, Barakat RM, Reinhold JG. Zinc deficiency in man. The Shiraz experiment. Am J Med 1972;53(3):277-84.

32. McDonald CM, Baylin A, Arsenault JE, Mora-Plazas M, Villamor E. Overweight is more prevalent than stunting and is associated with socioeconomic status, maternal obesity, and a snacking dietary pattern in school children from Bogota, Colombia. J Nutr 2009;139(2):370-6. doi: 10.3945/jn.108.098111.
33. Massart F, Saggese G. Oestrogenic mycotoxin exposures and precocious pubertal development. Int J Androl 2010;33(2):369-76. doi: 10.1111/j.1365-2605.2009.01009.x.
34. Pussa T. Toxicological issues associated with production and processing of meat. Meat Sci 2013;95(4):844-53. doi: 10.1016/j.meatsci.2013.04.032.
35. Khopkar S, Kulathinal S, Virtanen SM, Saavala M. Age at menarche and diet among adolescents in slums of Nashik, India. Int J Adolesc Med Health 2015. doi: 10.1515/ijamh-2014-0056.
36. Atay Z, Turan S, Guran T, Furman A, Bereket A. Puberty and influencing factors in schoolgirls living in Istanbul: end of the secular trend? Pediatrics 2011;128(1):e40-5. doi: 10.1542/peds.2010-2267.
37. Bonafini S, Antoniazzi F, Maffeis C, Minuz P, Fava C. Beneficial effects of omega-3 PUFA in children on cardiovascular risk factors during childhood and adolescence. Prostaglandins Other Lipid Mediat 2015. doi: 10.1016/j.prostaglandins.2015.03.006.
38. Perng W, Villamor E, Mora-Plazas M, Marin C, Baylin A. Alpha-linolenic acid (ALA) is inversely related to development of adiposity in school-age children. Eur J Clin Nutr 2015;69(2):167-72. doi: 10.1038/ejcn.2014.210.
39. Cheng G, Remer T, Prinz-Langenohl R, Blaszkewicz M, Degen GH, Buyken AE. Relation of isoflavones and fiber intake in childhood to the timing of puberty. Am J Clin Nutr 2010;92(3):556-64. doi: 10.3945/ajcn.2010.29394.
40. Koo MM, Rohan TE, Jain M, McLaughlin JR, Corey PN. A cohort study of dietary fibre intake and menarche. Public Health Nutr 2002;5(2):353-60. doi: 10.1079/PHN2002261.
41. Castilho SD, Pinheiro CD, Bento CA, Barros-Filho Ade A, Cocetti M. [Secular trends in age at menarche in relation to body mass index]. Arquivos Brasileiros de Endocrinologia e Metabologia 2012;56(3):195-200.

Chapter 5

Conclusions

Summary of Main Findings

This work extends current knowledge on early life determinants of the age at menarche, including sociodemographic characteristics, perinatal climate and geographic factors, and childhood diet.

In Chapter 2, we examined correlates and recent trends of menarche in Colombia, using nationally representative data available for the first time since the initiation of the National Nutrition Surveys. We found that the current median age at menarche in Colombia was 12.6 y, which is similar to other estimates from South American countries (1, 2), but older than the US (3) and several European countries (4). We also observed that the age at menarche was related to important contextual sociodemographic characteristics; after adjustment for other sociodemographic covariates, higher wealth index and Mestizo-Caucasian ethnicity were each associated with earlier ages at menarche compared to lower wealth index and Afro-Colombian or Indigenous ethnicity, respectively. We also observed recent declines in the age at menarche among girls born 1992- 2000, and these trends were more marked among girls from urban areas, whose families had higher wealth index, and who were of Caucasian-Mestizo ethnicity. Taken together, these findings corroborate the notion that the age at menarche is a sensitive indicator of socioeconomic and sanitary conditions in the context of a middle income setting (5). The finding that the trends were more pronounced in certain groups also sheds light on the presence of the nutrition transition in this population. At the beginning of nutrition transitions, those from urban areas and of higher socioeconomic status are the first to benefit from improvements in socioeconomic conditions and higher access to foods typically ascribed to the “Western-style” diet (6). Thus, our findings on menarche trends are consistent with a population still relatively early on in the nutrition transition.

In Chapters 3 and 4, we focused on a few specific environmental predictors of the age at menarche. In Chapter 3 we examined the relation of menarche with prenatal rainy season exposure in addition to altitude of residence. We found that girls with higher gestation days exposed to the rainy season had an earlier age at menarche compared to girls with less rainy season exposure during gestation. Although a few studies have reported an association between season of birth and age at menarche (7, 8), this finding is novel within the context of a tropical climate. Mechanisms are highly speculative but could have to do with seasonal differences in intrauterine light availability, respiratory infections, or nutrition that could lead to programmed differences in the timing of menarche. We also observed that girls from higher altitudes had later ages at menarche compared to girls from lower altitudes, although this was only evident after adjusting for socioeconomic status, maternal education, and race/ethnicity. This finding adds to the body of evidence suggesting that there is a high altitude effect on timing of puberty that could have to do with oxygen deprivation during development (9, 10). Finally, we reported that there was an interaction between gestation days exposed to the rainy season and altitude in relation to menarche. Specifically, the inverse relation between number of gestation days exposed to the rainy season and age at menarche was only apparent at altitudes $\geq$2000 m, whereas there was no association between gestation days exposed to the rainy season and menarche at lower altitudes. It is possible that this could be explained through higher seasonal variation at the higher altitudes compared to the lower altitudes in Colombia.

Finally, in chapter 4 we described a longitudinal examination of the relation between childhood red meat intake frequency and age at menarche among 456 Colombian school-aged girls. We found that higher childhood red meat intake frequency was related to an earlier age at menarche. We also consequently noted that higher tuna/sardine intake frequency was related to a later age at menarche. Although our findings are consistent with studies reporting associations between animal foods and/or animal protein sources and menarche (11-13), our study substantially extends previous findings by reporting on very specific food groups. It is also of note that both of the observed relations were subject to negative confounding by other animal source food intake, a finding that underscores the importance of carefully considering confounding by other foods in analyses of childhood diet on age at menarche.

This dissertation has a number of strengths. One is the use of nationally representative data for the first two aims, which enabled us to make inference at the national level and also provided ample power to explore the research questions. Furthermore, the survey contained a wealth of information on the girls and their households, which allowed us to conduct analyses adjusted for other sociodemographic characteristics. This was perhaps most important in the examination of altitude and menarche because there was strong negative confounding by socioeconomic status. The use of a longitudinal dataset for the last aim was also a strength, as it allowed us to establish temporality between childhood diet and menarche. There are also limitations to consider in this dissertation. One was the cross-sectional nature of the ENSIN survey, which limits causal inference because the exposures were measured at the same time that menarcheal age was ascertained. Nevertheless, this should not have affected certain sociodemographic characteristics such as birthdate (used to determine gestation days exposed to the rainy season) and race/ethnicity. Another limitation was the reliance on recall of menarche, which would most likely mainly affect girls in the cross-sectional survey who had experienced their menarche several years prior to the administration of the survey. Other limitations to highlight are issues related to the dietary measurement in the third aim. First, there was potential for misclassification of food intake due to measurement errors in the FFQ. This would be most problematic if measurement error was differential with respect to age at menarche, although this was not likely to be the case. Another dietary measurement limitation was the lack of repeated FFQs administered throughout childhood. Future studies should include multiple measurements of diet in order to assess whether childhood diet remains relatively constant over time and/or if time-varying confounding of the red meat/menarche relation is present.

Public Health Implications

This work has implications for public health on a few different levels. In the first aim, we found differences in age at menarche and the recent trends according to sociodemographic characteristics related to the nutrition transition. Our findings imply that Colombian girls living in urban areas, from families of higher socioeconomic status and of Mestizo-Caucasian race could be at highest risk of having earlier menarche, a predictor of health outcomes including teenage pregnancy and breast cancer. These groups may likely benefit from public health intervention aimed at reversing accompanying characteristics of the nutrition transition, such as sedentary behavior, snacking patterns, and diets high in saturated fats and refined carbohydrates (14). In contrast, the age at menarche among girls living in rural areas and from families with the lowest wealth index had not changed in recent years. It is possible that these child populations suffer from nutrient deficiencies; certain micronutrient deficiencies should be assessed using blood samples collected in a sub-sample of ENSIN 2010 participants. Further monitoring of the age at menarche in the next wave of the ENSIN is warranted to determine whether the age at menarche continues to decline and if this decline remains heterogeneous with respect to sociodemographic characteristics. Findings from this aim could be transportable to other regions also in the early stages of the nutrition transition, but may not be generalizable to higher income settings.

This work also illuminates the potential for public health intervention targeted towards several specific early life factors that be related to the timing of sexual maturation. In the second aim, we found that higher rainy season exposure during gestation was related to age at menarche. This reinforces the notion of the prenatal period as a critical time period when environmental exposures might affect later child health (15). The findings on gestation days exposed to the rainy season and menarche could be generalizable to other tropical climate settings, although the socioeconomic context may be an important effect modifier; for example, there may be stronger associations between gestation days exposed to the rainy season and menarche in lower-income settings where families may be less able to cope with seasonal food shortages. Future work should seek to elucidate the specific mechanisms that could play a role and might be amenable to intervention. Seasonal factors that may vary more drastically at higher altitudes, such as vitamin D levels or respiratory virus transmission, should be among the first considered.

We also found that altitude was related to delays in the timing of menarche after adjustment for socioeconomic status, which may be explained by lower oxygen concentration at higher altitudes (16). This observation is likely transportable to other Andean populations, but it is unclear whether it would apply to other high altitude populations such as the Himalayans or Rocky Mountains in the US, which are comprised of different genetic and environmental factors than Andean populations. An important next step in this area of research is to better understand the potential health consequences of a later menarche possibly induced by growing up in high altitudes. Nonetheless, the fact that developmental delays in the timing of menarche could be due to energy trade-offs suggests that certain pediatric populations growing up in high altitudes may lack adequate total energy intake and/or specific micronutrients necessary for growth and development. Whether Colombian girls residing in high altitudes have higher probability of certain micronutrient deficiencies than those from lower altitudes should be examined using available ENSIN data.

Our findings on red meat and fatty fish in relation to age at menarche further emphasize the role of childhood diet, especially animal food sources, in sexual maturation. These findings may be transportable to regions with comparable intake frequencies of these specific food items and of Hispanic origin. For example, this could include certain populations in the US and Mexico. The next steps in this area of research should be to elucidate the specific components of red meat sources that could be linked to pubertal timing, which would help guide public health action. For example, a closer examination on how hormonal substances in red meat may be related to menarche could provide evidence to inform policies on cattle feeding practices. Similarly, the findings on fatty fish should be interpreted with caution until particular components of the fish sources are systematically examined. For example, the implications of the findings would be different if the observed associations are due to polyunsaturated fatty acids present in these fish sources versus lead or mercury content in these fish. Nevertheless, these findings provide impetus for further work, such as intervention studies, to evaluate whether replacement of red meat with other protein sources, for example fatty fish, would be a viable childhood dietary intervention. Findings from intervention studies could potentially be implemented as a part of school feeding programs.

In summation, this dissertation research shows that the age at menarche is responsive to early life environmental correlates including changing socioeconomic conditions, perinatal climate and geographic factors, and diet during childhood. As research on menarche continues to grow and develop, we anticipate that monitoring the age at menarche will become a public health priority for understanding child health on a national scale, particularly in lower-income countries. Furthermore, studies evaluating the specific mechanisms underlying associations between early life factors and age at menarche will expand our knowledge on public health interventions that may be most effective for promoting optimal pubertal development.

REFERENCES

1. Orden AB, Vericat A, Apezteguia MC. Age at menarche in urban Argentinian girls: association with biological and socioeconomic factors. Anthropologischer Anzeiger 2011;68(3):309-22.
2. Ossa XM, Munoz S, Amigo H, Bangdiwala SI. Secular trend in age at menarche in indigenous and nonindigenous women in Chile. American Journal of Human Biology 2010;22(5):688-94. doi: 10.1002/ajhb.21068.
3. Vaughan EB, Van Hulle CA, Beasley WH, Rodgers JL, D'Onofrio BM. Clarifying the associations between age at menarche and adolescent emotional and behavioral problems. Journal of Youth and Adolescence 2015;44(4):922-39. doi: 10.1007/s10964-015-0255-7.
4. Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the Health Behaviour in School-aged Children Study. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 2012;50(6):621-6. doi: 10.1016/j.jadohealth.2011.10.254.
5. Tanner JM. Growth as a mirror of the condition of society: secular trends and class distinctions. Edtion ed. In: Demirjian A, ed. Human Growth: A Multidisciplinary Review. London: Taylor and Francis, 1986:3-34.
6. The Nutrition Transition: Diet and Disease in the Developing World. San Diego, California: Academic Press, 2002.
7. Klis K, Jarzebak K, Borowska-Struginska B, Mulawa A, Zurawiecka M, Wronka I. Season of birth influences the timing of first menstruation. Am J Hum Biol 2015. doi: 10.1002/ajhb.22783.
8. Matchock RL, Susman EJ, Brown FM. Seasonal rhythms of menarche in the United States: correlates to menarcheal age, birth age, and birth month. Womens Health Iss 2004;14(6):184-92. doi: 10.1016/j.whi.2004.07.007.
9. Gonzales GF, Villena A. Body mass index and age at menarche in Peruvian children living at high altitude and at sea level. Hum Biol 1996;68(2):265-75.
10. Greksa LP. Age of menarche in Bolivian girls of European and Aymara ancestry. Ann Hum Biol 1990;17(1):49-53.
11. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiol 2000;152(5):446-52.
12. Gunther AL, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. J Nutr 2010;140(3):565-71. doi: 10.3945/jn.109.114934.
13. Wiley AS. Milk intake and total dairy consumption: associations with early menarche in NHANES 1999-2004. PLoS One 2011;6(2):e14685. doi: 10.1371/journal.pone.0014685.
14. Popkin BM. Contemporary nutritional transition: determinants of diet and its impact on body composition. Proc Nutr Soc 2011;70(1):82-91. doi: 10.1017/S0029665110003903.
15. Gluckman PD, Beedle AS, Hanson MA, Low FM. Human growth: evolutionary and life history perspectives. Nestle Nutr Inst Workshop Ser 2013;71:89-102. doi: 10.1159/000342572.
16. Frisancho AR. Developmental functional adaptation to high altitude: review. Am J Hum Biol 2013;25(2):151-68. doi: 10.1002/ajhb.22367.