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Physical Activity During Pregnancy and Age at Menarche of the Daughter

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Abstract

In utero exposures have been proposed as possible determinants of later disease risk. Given that a later age at menarche is a breast cancer risk factor, and that higher childhood physical activity has been associated with a later menarcheal age, it is possible that a pregnant mothers' activity may also influence this outcome. The purpose of this study was to determine if mothers' physical activity during pregnancy is related to their daughters' menarcheal age. Participants of the Nurse's Health Study II reported their age at menarche to the nearest year, while their mothers (n=33,016) completed surveys regarding their health and lifestyle habits during their pregnancy with their daughters. Mothers reported their home, occupational, and leisure-time physical activity, as well as the activity of their daughters at ages 5–10 years. Using multiple linear regression analysis with adjustment for specific covariates including daughters' childhood body size, neither home nor occupational activity alone were associated with age at menarche of the daughter, but there was a direct association with leisure-time physical activity ($p_{\text{trend}} < 0.001$). Compared to women inactive in their leisure-time, women who were highly active had daughters with menarche 1.1 (95% CI, 0.3 – 1.9) months later. Using a composite variable of both home and leisure-time activity, daughters of women who were highly active at home and in their leisure-time had daughters with menarche 3.1 (95% CI, 0.4 – 5.9) months later than those who were highly inactive in both. Physical activity during pregnancy may be associated with a modest delay in menarcheal age in offspring.

Keywords

exercise; menarche; pregnancy; puberty

Introduction

Age at menarche, a well-known reproductive-related risk factor for breast cancer, is associated with an approximate 10–20% reduction in risk for each year of delay in menses (1). Several studies have noted a later age at menarche in active girls when compared to their less active peers (2–4). This delay in menarche has been suggested as one possible mechanism through which physical activity may reduce the risk of breast cancer (5;6).

Chronic diseases have been associated with earlier life exposures. Birthweight is linked to the development of hypertension, insulin resistance, and cardiovascular disease in adulthood (7–10). These relationships form the basis of what has been termed “fetal programming” of chronic disease, in which it has been hypothesized that interactions of fetal exposures and genotypes in utero can alter the architecture and physiologic function of organs throughout life (11).

Although initial hypotheses focused on cardiovascular-related diseases, Trichopoulos suggested that in utero exposures might also be related to the development of breast cancer, and that this relationship might be due to alterations in estrogen exposure (12). This hypothesis has been supported by epidemiologic evidence demonstrating a higher breast cancer risk in dizygotic twins, and a lower risk in daughters born to pre-eclamptic mothers (13). There is also a fairly consistent direct association between birth weight and breast cancer risk (14;15).

Interestingly, age at menarche has been associated with potential exposures in utero. Specifically, exposure to dichlorodiphenyldichloroethylene (DDE) (16) and maternal cigarette smoking and tea drinking in pregnancy are related to an earlier age at menarche (17). Bouts of physical activity and exercise can result in numerous metabolic, hormonal, and physiologic changes in the body, dependent on the intensity, duration, and type of activity performed; therefore activity during pregnancy may change the milieu of the fetus. In particular, it is possible that the total estrogen or growth factor-related exposure of the fetus is altered with physical activity of the pregnant mother, and that these changes could be related to age at menarche in the daughter and thus, her breast cancer risk. In a cohort of nurses whose mothers reported physical activity in the index pregnancy, we therefore hypothesized that daughters of mothers who were physically active will have a delayed age at menarche compared to daughters of mothers who were less physically active while pregnant.

Materials and Methods

Study population

The study population consists of participants in the Nurse’s Health Study II (NHS II) whose mothers were enrolled in the Nurses’ Mothers’ Cohort Study. In 2001, members of the NHS and NHS II who were free of cancer (other than non-melanoma skin cancer) and who had mothers who were still alive (n=52,166), were sent surveys for their mothers to complete concerning their pregnancy with the nurse daughter. A total of 39,904 (76.5%) of the surveys were returned. The Institutional Review Board of the Brigham and Women’s Hospital approved this study. For ease of analysis, we have limited the current analytic dataset to the women from NHS II, from which 35,830 surveys were returned. The nurse daughters were born between 1946 and 1965. The mothers completed surveys regarding demographics, health, and lifestyle habits pertaining to the pregnancy with their nurse daughters, as well as early life events of the daughters. The women reported information from memory, sources such as baby books or birth certificates, or help from family members. Additionally, some information was reported by the nurse daughters on NHS II surveys (age at menarche, somatograms at ages five and ten years) and merged with the mothers’ information. Of the 35,830 women who completed the survey, 88 identified that their daughter’s were adopted, and 1807 were missing adoption information, and thus were excluded from the study. Of the remaining women, 804 were

missing physical activity information and 115 of the daughters were missing their age at menarche for a final analytic sample of 33,016.

Assessment of physical activity, age at menarche, and covariates

Physical activity during pregnancy was queried using three separate questions for household, occupational, and leisure-time activity. For both household and occupational activities, the questions began: “When you were pregnant with your nurse daughter, how would you classify your physical activity patterns...” and ended with “...at home” or “...at work (outside the home).” For household activity, possible responses were: mostly sitting, mostly walking and standing with some sitting, active housework most of the time with little sitting, or heavy manual work at home. For occupational activity, mothers chose from categories of: not applicable/not working, mostly sitting and standing, mostly walking with some sitting and standing, or mostly heavy labor with some walking and standing and little sitting. The leisure-time activity question read: “When you were pregnant with your nurse daughter, aside from housework and job-related activities, which of the following best describes your physical activity (e.g., walking and recreation).” An ordered categorical response with five options ranging from highly active to inactive, with cues (equivalent to walking about three or more miles every day, to no walking or other regular exercise, respectively) was selected. A composite activity variable was created using the home and leisure questions to categorize women into five groups ranging from highly inactive to highly active as depicted in Table 1. Additionally, the mothers reported their nurse daughter’s overall physical activity at ages three-five and five-ten years using a similar ordered categorical response in which they compared them to other girls their age.

The mothers self-reported their usual body weight prior to pregnancy, height, race, education, home ownership, dates of their own and their daughter’s birth, the sibship and birthweight of the daughter, approximate weight gain during pregnancy, and smoking status during their pregnancy. On the 1989 NHS II questionnaire, the nurses reported their age at menarche to the nearest year and their body shape at ages five and ten years using somatograms (1–9 scale). We calculated a “growth velocity” measure and categorized the nurses by change in somatogram score between ages five and ten years. Girls staying within one unit of their age five somatogram over the five year period were classified as stable, and girls who increased or decreased two or more units on the 1–9 scale were considered as increasing or decreasing body size, respectively.

Statistical analysis

Multiple linear regression was used to examine the association between physical activity of the mothers during pregnancy and age at menarche of the daughters. Since the age at menarche was reported to the nearest year and the differences by level of physical activity were small, we multiplied the beta coefficients by 12 to calculate the difference in age at menarche in months. Separate models were analyzed for each activity variable, and then one model with all three main types of activities was also analyzed. Covariates included in the models were the mothers’ race (White, non-White), home ownership (yes, no), education (< four years high school, four years high school, at least some college), smoking during pregnancy (yes, no), age at birth of the daughter (<23, 23–25, 26–29, ≥30), pre-pregnancy body mass index (BMI) (≤20, >20 to ≤25, >25 to <30, ≥30), and the birth order of the daughter (first or later birth) and the daughters’ age ten somatogram classification (1,2,3,4,5–9). To examine potential mediating variables, daughters’ activity at ages three-five and five-ten (highly active, active, mostly active, inactive), growth velocity at ages five-ten (increasing, stable, decreasing), birth weight (quartiles), birth size for age (<10%, 10–90%, >90%), and mothers’ weight gain during pregnancy (<14, 15–19, 20–29, ≥30 lbs) were considered in separate models. Missing data for each covariate was included as a separate category in each model. Models were re-run

excluding all women with any missing covariates, and results were unchanged. Age at menarche was also treated categorically with ≤ 11 , 12–13, and ≥ 14 years of age in an ordered logistic regression (i.e., proportional odds model) to estimate the odds of having the next earlier level of menarche vs. the next later level by mothers' physical activity level. For the test of trends, the levels of activity were scored with integers that increased with increasing activity level. Trends across physical activity groupings for each model were examined by testing the beta coefficient for an ordered categorical activity variable in separate models. All statistical tests were two-sided with level of significance set at $p=0.05$.

Results

A majority of the mothers (62.4 %) reported not working outside the home during their pregnancy, while 18.0%, 16.7%, and 2.9% reported they mostly sat or stood, mostly walked, or mostly did heavy labor at work, respectively. At home, 2.9% reported mostly sitting, 17.0% mostly walking, 77.7% active housework, and 2.4% heavy manual labor. For self-reported leisure-time activity, 9.8% of the women reported being highly active, 19.8% mostly active, 40.0% active, 20.4% mostly inactive, and 10.0% inactive. The composite physical activity classification based on home and leisure-time responses had 1.1% of the sample who were classified as highly active, 26.3% as mostly active, 42.1% as active, 29.5% as mostly inactive, and 1.0% as inactive. Most (96.7%) of the study sample was Caucasian. Characteristics of the women in relation to their leisure-time physical activity levels are reported in Table 2.

The mothers age at the time of questionnaire completion was 72.2 ± 6.5 years (mean $\pm$ standard deviation (SD)), while the birth of their nurse daughter occurred from 36–57 years earlier. The nurse daughters were 33.9 ± 4.6 years (mean $\pm$ SD) when they reported their age at menarche, which on average was 12.4 ± 1.4 years. In multiple linear regression analyses, neither occupational ($p_{\text{trend}}=0.30$) nor home ($p_{\text{trend}}=0.94$) activity was associated with age at menarche when adjusted for the mothers' race, home ownership, education, smoking during pregnancy, age at birth, pre-pregnancy BMI, the birth order of the nurse, or the nurses' somatogram at age ten (Table 3). Maternal leisure-time physical activity outside the home was significantly associated with the daughter's age at menarche ($p_{\text{trend}}=0.001$). Daughters of women who reported being mostly active or highly active had ages at menarche 0.9 (95% CI; 0.2 – 1.6) and 1.1 (95% CI; 0.3 – 1.9) months later than those whose mothers reported being inactive during their pregnancies. When occupational, home, and activity outside the home were entered in the same multiple linear regression model, the associations with age at menarche were not appreciably altered. In the association between the composite activity classification and age at menarche, women who were highly active had a daughter who experienced a 3.1 (95% CI; 0.4 – 5.9) month later age at menarche than highly inactive women. The trend across increasing levels of activity was significant ($p_{\text{trend}}=0.001$).

Variables that could potentially mediate the significant relationships between physical activity outside the home or the composite variable and age at menarche were included one at a time in separate models. Maternal weight gain of the mother, the daughter's birth weight, birth weight for gestational age, and growth velocity from ages five-ten did not influence the results. The nurse daughter's physical activity at ages five-ten was directly associated with age at menarche. In a model that adjusted for this factor, the risk estimates for maternal activity were attenuated somewhat, with the maximum delay in age at menarche for maternal activity outside the home now 0.9 (0.1 – 1.7) months ($p_{\text{trend}}=0.01$), and for the highly active composite variable now 3.0 (0.3 – 5.7) months ($p_{\text{trend}}=0.01$). The results of the proportional odds logistic regression examining categories of menarcheal age were consistent with the multiple linear regression results. There was no association between occupational ($p_{\text{trend}}=0.14$) or home activity ($p_{\text{trend}}=0.96$) and category of age at menarche (Table 4). The odds of being in the next lower level of age at menarche compared to the next higher level was lower for the daughters of

women who were mostly active (OR=0.91; 95% CI, 0.84–0.99) or highly active in their leisure-time (OR=0.91; 95% CI, 0.83–1.01) compared to the daughters of the inactive ($p_{\text{trend}}=0.01$). This relationship was attenuated with further adjustment for the daughters' activity at ages 5–10 ($p_{\text{trend}}=0.03$). The daughters of women who were considered highly active in both their home and leisure-time had a lower odds of being in the next lower level of age at menarche compared to the daughters of women who were highly inactive (OR=0.67; 95% CI, 0.48–0.92), and the trend across levels of activity was significant ($p_{\text{trend}}=0.01$).

Discussion

While previous studies have demonstrated that a girl's physical activity is related to her age at menarche (2–4), to our knowledge, we are the first to report that the mother's activity while pregnant may also be related to the daughter's age at menarche. A direct association was observed between leisure-time activity, but not occupational or housework-related activity, in the index pregnancy and age at menarche of the daughter. Women who reported the most activity, equivalent to walking about three or more miles per day, had daughters who began menstruating 1.1 months later than the daughters of women who reported no regular walking or other form of exercise in their leisure-time. The relationship was even stronger when looking at combined home and leisure-time activity, with a 3.1 month delay in age at menarche for the daughters of women who were highly active vs. highly inactive in both types of activity during their pregnancies.

Other fetal exposures that have been associated with the daughters' age at menarche include: organochlorine exposure (15ug/l serum concentrations) and a one year earlier age at menarche ($p=0.04$)(16); smoking a pack or more of cigarettes/day during pregnancy and a 2.6 month-earlier age at menarche (17); and drinking three or more cups/day of tea with a 4.9 month later age at menarche (17). In comparison, the difference in age at menarche associated with maternal physical activity in our study was similar to that for these behavioral factors. Though the difference is reasonably small, it is similar to the small differences in the mean age at menarche of African American and White US girls (18). Whether or not pregnancy physical activity relates to future breast cancer risk, and whether or not it is mediated by an alteration of age at menarche remains to be determined. Age at menarche is only one of several reproductive-related breast cancer risk factors, and the evidence suggests that a one-year delay in menarche can reduce breast cancer risk by 10–20%(1). Therefore, although interesting, if pregnancy physical activity has this small an impact on menarcheal age, the concomitant impact on breast cancer risk may be quite small.

When looking at specific activity types, there was no association between occupational activity and menarcheal age in our study. The majority of the women (62%) reported not working outside of the home. It is probable that among those who were working outside the home, the true range of physical activity volumes and intensities would be reasonably small among pregnant women of that era. Very few of the women (3%) reported heavy physical labor, with the remaining women reporting either mostly standing or sitting, and mostly walking. We also saw no significant association with housework alone. It is likely that the true range in housework activity was also rather small, and in fact a large majority of the women (78%) fell into the active housework category. This relatively homogeneous distribution in housework activities may also be indicative of women of the era, with the majority of women responsible for the household work and with fewer women receiving either hired help or help from their spouses. We did, however, find a significant association with leisure-time activity, and there was more variability in reports of this type of activity. Additionally, when we further classified women by both their home and leisure-time activity, there was a larger delay in menarche for daughters of the most active women compared to daughters of those who were the most inactive.

We found that adjustment for the daughters' activity during childhood attenuated the relationship between their age at menarche and their mothers' activity while pregnant, but only minimally. Intense levels of pre-pubertal physical activity have been related to age at menarche in prior studies, with trained athletes having as much as a two year delay in age at menarche compared to the least active (2–4). The attenuation we noted could be explained by the strong relationship between the maternal-reported pregnancy activity and their daughters' childhood activity. It is possible that mothers who recalled their activity as greater than others similarly recalled their daughter's activity as greater than others. However, it is just as likely that the daughters of active mothers were active themselves. Indeed, a strong predictor of childhood physical activity is parental activity and parental support of their children's activity (19–21). Given that the mothers reported both observations, it is difficult to disentangle these relationships.

We adjusted for as many potential confounders of the association as possible, while trying not to enter variables in the models that could be in the causal pathway. We did, however, assess several variables that could fall into the latter category, such as maternal weight gain during pregnancy, daughter's birthweight, and birth size for gestational age, none of which affected our estimates of association. Variables that assessed daughter characteristics closer in time to their age at menarche did attenuate relationships somewhat; although adjustment for daughters' activity at ages five-ten years did influence the estimates, they were still significant despite the inclusion of somatograms at age ten.

An association between mothers' physical activity during pregnancy and daughters' menarcheal age is biologically plausible. One potential mechanism may be through alterations in birth size or weight as a result of the mother's pregnancy physical activity. Both prenatal and postnatal growth trajectories appear to be predictive of age at menarche with a somewhat complicated interaction (22–24). Pregnancy physical activity may affect prenatal growth and subsequent birth weight and size; however, published studies have not been consistent (25), perhaps due to the measurement error associated with epidemiologic studies and the likely small association to be detected (26), as well as what may be a complex interaction between the type, intensity, and timing of activity in relation to trimester of pregnancy as well as a significant effect of the composition of the pregnancy diet (27;28). A recent study that assessed pregnancy physical activity using objective accelerometer measures found a strong inverse association between activity and fetal growth ratio, an indicator of birth size that accounts for gestational age (29). Perhaps unrelated to birth weight or size, exercise may alter the fetal milieu in ways that could impact pubertal development. In a well-controlled animal study, a high fat diet in pregnant rats has been found to increase their estrogen levels as well as to result in earlier pubertal development and an increased susceptibility to carcinogen-induced mammary tumors of the offspring (30). Although there is little evidence in pregnant women, physical activity has been shown to decrease estrogens in women of reproductive age (31). It has been suggested that even transient changes in estrogen exposure in utero may affect the development of reproductive-related organs (32). Finally, indirect evidence suggests that exercise during pregnancy alters the blood flow to and growth of the placenta (28), and additionally, is related to enhanced glucose tolerance and lower risks of gestational diabetes and preeclampsia (27;33). These alterations in glucose tolerance and thus insulin levels may be responsible for subsequent changes in development. Clearly more research into the potential biological mechanisms is warranted.

In interpreting the results, the strengths and limitations of our study must be considered. Our primary measures of age at menarche and activity while pregnant are self-reported with lengthy recall periods. Since the recall is long, there is likely to be measurement error. The measurement error could be unrelated to our outcome of age at menarche, i.e., non-differential, which would attenuate our associations. However, more of a concern would be if the measurement error was

related the outcome, i.e., differential error. For example, women who were less active tended to over report their activity compared to those who were more active. With differential error, our associations could be biased in either direction, i.e., toward a larger or smaller association. Unfortunately, the nature of the measurement error cannot be determined from our study. Therefore the reader should be cautious in the interpretation of the results. We also asked about physical activity across the whole pregnancy rather than specific to trimesters; however, only 8% of the women reported changing their activity levels from the first to second half of their pregnancy. Childhood body size was also self-reported with a lengthy recall. We have previously found, however, that women's recall of their childhood body size 55 years later is moderately correlated with measured BMI at ages 5–10 ($r=0.57-0.70$) and has decent sensitivity (40%) and excellent specificity (100%)(34). We have tried to account for many potentially confounding variables, but we cannot rule out residual confounding as a possible explanation for our findings. Finally, it is possible the activity women reported during pregnancy is reflective of their pre-pregnancy levels of activity, and therefore, that it is their usual activity levels that are associated with the outcome examined here. We do not have any reporting of pre-pregnancy physical activity to try and examine this. The strengths of our study are the large numbers of mothers and daughters; the internal validity of the data with, for example, mothers who smoked in pregnancy reporting less activity than non-smokers; and different information sources for the endpoint than for the exposures.

To our knowledge, this is the first study to examine the relationship between mothers' physical activity in the index pregnancy and their daughters' age at menarche. There are few datasets available that can examine fetal exposures and offspring outcomes in such a large sample. Our results suggest that greater levels of physical activity during pregnancy are associated with later ages at menarche in daughters. These associations were of a small magnitude, and may have limited clinical significance, but are worthy of note. While interesting, the findings should be interpreted with caution until additional studies address this topic of interest.

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References

1. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. *J Mammary Gland Biol Neoplasia* 2002;7:3–15. [PubMed: 12160084]
2. Frisch R, Gotz-Welbergen A, McArthur J, et al. Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. *JAMA* 1981;246:1559–63. [PubMed: 7277629]
3. Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. *Am J Epidemiol* 1993;138:217–24. [PubMed: 8356963]
4. Bale P, Doust J, Dawson D. Gymnasts, distance runners, anorexics body composition and menstrual status. *J Sport Med Phys Fitness* 1996;36:49–53.
5. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. *Cancer Causes Control* 1998;9:487–509. [PubMed: 9934715]
6. Friedenreich C, Orenstein M. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr* 2002;132:345S–64S. [PubMed: 12421870]
7. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Soc Med* 1977;31:91–5. [PubMed: 884401]
8. Barker D, Winter P, Osmond C, Margetts B, Simmonds S. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;2:577–80. [PubMed: 2570282]
9. Phipps K, Barker D, Hales C, Fall C, Osmond C, Clark P. Fetal growth and impaired glucose tolerance in men and women. *Diabetologia* 1993;36:225–8. [PubMed: 8462770]

10. Huxley R, Shiell A, Law C. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hyperten* 2000;18:831.
11. Barker D. Fetal programming of coronary heart disease. *Trends Endocrinol Metab* 2002;13:364–8. [PubMed: 12367816]
12. Trichopoulos D. Hypothesis: does breast cancer originate in utero? *Lancet* 1990;335:939–40. [PubMed: 1970028]
13. Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. *Cancer Causes Control* 1999;10:561–73. [PubMed: 10616825]
14. Forman M, Cantwell M, Ronckers C, Zhang Y. Through the looking glass at early-life exposures and breast cancer risk. *Cancer Investigation* 2005;23:609–24. [PubMed: 16305989]
15. Michels K, Xue F. Role of birthweight in the etiology of breast cancer. *Int J Cancer* 2006;119:2007–25. [PubMed: 16823839]
16. Vasiliu O, Muttineni J, Karmaus W. *In utero* exposure to organochlorines and age at menarche. *Human Reproduction* 2004;19:1506–12. [PubMed: 15131079]
17. Windham G, Bottomley C, Birner C, Fenster L. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea. *Am J Epidemiol* 2004;159:862–71. [PubMed: 15105179]
18. Bernstein L, Teal C, Joslyn S, Wilson J. Ethnicity-related variation in breast cancer risk factors. *Cancer* 2003;97:222–9. [PubMed: 12491485]
19. Moore L, Lombardi D, White M, Campbell J, Oliveria S, Ellison R. Influence of parents' physical activity levels on activity levels of young children. *J Pediatr* 1991;118:215–9. [PubMed: 1993947]
20. Fogelholm M, Nuutinen O, Pasanen M, Myohanen E, Saatela T. Parent-child relationship of physical activity patterns and obesity. *Int J Obes Relat Metab Disord* 1999;23:1262–8. [PubMed: 10643682]
21. Davison K, Cutting T, Birch L. Parents' activity-related parenting practices predict girls' physical activity. *Med Sci Sports Exerc* 2003;35:1589–95. [PubMed: 12972881]
22. dos Santos Silva I, de Stavola B, Mann V, Kuh D, Hardy R, Wadsworth M. Prenatal factors, childhood growth trajectories and age at menarche. *Int J Epidemiol* 2002;31:405–12. [PubMed: 11980804]
23. Tam C, de Zegher F, Garnett S, Baur L, Cowell C. Opposing influences of prenatal and postnatal growth on the timing of menarche. *J Clin Endocrinol Metab* 2006;91:4369–73. [PubMed: 16926251]
24. Sloboda D, Hart R, Doherty D, Pennell C, Hickey M. Age at menarche: influences of prenatal and postnatal growth. *J Clin Endocrinol Metab* 2007;92:46–50. [PubMed: 17062767]
25. Gavard J, Artal R. Effect of exercise on pregnancy outcome. *Clin Obstetrics Gynecol* 2008;51:467–80.
26. Chasan-Taber L, Evenson K, Sternfeld B, Kengeri S. Assessment of recreational physical activity during pregnancy in epidemiologic studies of birthweight and length of gestation: methodologic aspects. *Women Health* 2007;45:85–107. [PubMed: 18032169]
27. Pivarnik J, Chambliss H, Clapp J, et al. Impact of physical activity during pregnancy and postpartum on chronic disease risk. *Med Sci Sports Exerc* 2006;38:989–1006. [PubMed: 16672855]
28. Clapp J. Influence of endurance exercise and diet on human placental development and fetal growth. *Placenta* 2006;27:527–34. [PubMed: 16165206]
29. Perkins C, Pivarnik J, Paneth N, Stein A. Physical activity and fetal growth during pregnancy. *Obstet Gynecol* 2007;109:81–7. [PubMed: 17197591]
30. Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman M. A maternal diet high in n-6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. *Proc Natl Acad Sci* 1997;94:9377.
31. Jasienska G, Ziolkiewicz A, Thune I, Lipson S, Ellison P. Habitual physical activity and estradiol levels in women of reproductive age. *Eur J Cancer Prev* 2006;15:439–45. [PubMed: 16912573]
32. Hilakivi-Clarke L, de Assis S. Fetal origins of breast cancer. *Trends Endocrinol Metab* 2006;17:340–8. [PubMed: 16997567]
33. Oken E, Ning Y, Rifas-Shiman S, Radesky J, Rich-Edwards J, Gillman M. Associations of physical activity and inactivity before and during pregnancy with glucose tolerance. *Obstet Gynecol* 2006;108:1200–7. [PubMed: 17077243]
34. Must A, Willett W, Dietz W. Remote recall of childhood height, weight, and body build by elderly subjects. *Am J Epidemiol* 1993;138:56–64. [PubMed: 8333427]

Distribution of combined home and leisure activity categories for creation of composite physical activity variable among 33,016 mothers*.

	Home Activity			
	Heavy manual work	Active housework	Mostly walking/standing	Mostly sitting
Leisure Activity	Highly active	377	2,708	156
	Mostly active	170	5,477	850
	Active	157	10,439	2,476
	Mostly inactive	45	4,563	1,686
	Inactive	57	2,464	440

* Composite physical activity variables indicated by shading: Highly active, white box (n=377); Mostly active, very light gray (n=8,668); Active, light gray (n=13,907); Mostly Inactive, medium gray (n=9,724); Highly Inactive, dark gray (n=340).

Table 2

Characteristics* of mothers and their daughters by level of leisure-time activity of the mothers while pregnant.

	Leisure-time physical activity level				
	Inactive (n=3,301)	Mostly inactive (n=6,731)	Active (n=13,206)	Mostly active (n=6,533)	Highly active (n=3,245)
Mothers' Characteristics					
Education, n (%)					
< High school	576 (17)	832 (12)	1,581 (12)	872 (13)	533 (16)
High school	1,760 (53)	3,453 (51)	6,503 (49)	3,185 (49)	1,520 (47)
> High school	952 (29)	2,429 (36)	5,072 (38)	2,450 (38)	1,184 (36)
Home ownership, n (%)	1,613 (49)	2,916 (43)	6,066 (46)	3,125 (48)	1,785 (55)
Race, n (%)					
White	3,192 (97)	6,520 (97)	12,777 (97)	6,326 (97)	3,107 (96)
Non-white	104 (3)	199 (3)	394 (3)	194 (3)	130 (4)
Smoked while pregnant, n (%)	890 (27)	1,800 (27)	3,390 (26)	1,694 (26)	826 (25)
Pregnancy wgt gain, kg (%)					
<9.07	984 (30)	2,032 (30)	4,324 (33)	2,272 (35)	1,173 (36)
9.07–13.15	1,167 (35)	2,518 (37)	5,200 (39)	2,620 (40)	1,282 (40)
>13.15	790 (24)	1,615 (24)	2,751 (21)	1,204 (18)	543 (17)
Pre-pregnancy BMI (kg/m ²), mean (SD)	21.4 (2.8)	21.3 (2.7)	21.3 (2.6)	21.2 (2.5)	21.2 (2.5)
Age at daughter's birth (years), mean (SD)	26.2 (5.1)	25.6 (5.0)	25.7 (4.9)	25.8 (4.9)	26.4 (4.9)
Daughters' Characteristics					
Firstborn, n (%)	1,391 (42)	3,533 (52)	5,961 (45)	2,392 (37)	800 (25)
Birth weight (gm), mean (SD)	3,280 (539)	3,284 (520)	3,285 (497)	3,290 (504)	3,306 (519)
Physical activity at ages 5–10 (%)					
Mostly inactive & inactive	216 (7)	429 (6)	450 (3)	186 (3)	79 (2)
Active	2,234 (68)	4,784 (71)	8,977 (68)	4,166 (64)	1,672 (52)
Highly active	831 (25)	1,480 (22)	3,703 (28)	2,153 (33)	1,479 (46)
Somatogram at age 10 (%)					
1	572 (17)	1,119 (17)	2,201 (17)	1,107 (17)	580 (18)

	Leisure-time physical activity level			
	Inactive (n=3,301)	Mostly inactive (n=6,731)	Active (n=13,206)	Mostly active (n=6,533)
				Highly active (n=3,245)
2	1,003 (30)	2,031 (30)	4,139 (31)	2,096 (32)
3	728 (22)	1,566 (23)	3,131 (24)	1,602 (25)
4	513 (16)	1,122 (17)	2,117 (16)	994 (15)
5-9	446 (14)	813 (12)	1,470 (11)	654 (10)
Age at menarche (years), mean (SD)	12.4 (1.4)	12.4 (1.4)	12.4 (1.4)	12.5 (1.4)

* Sum of percentages does not always add to one due to exclusion of those with missing values.

Table 3

Adjusted difference in daughters' age at menarche (months) by type and level of physical activity during the mothers' pregnancy.

	n	Adjusted differences* (months)	95% confidence interval	Adjusted differences† (months)	95% confidence interval
Home Activity					
Mostly sitting	951	Referent			
Mostly walking/standing	5,608	0.4	-0.8, 1.5		
Active housework	25,651	0.2	-0.9, 1.3		
Heavy manual work	806	1.0	-0.6, 2.5		
<i>P_{trend}</i>		0.94			
Occupational					
NA/Not working	20,616	-0.1	-0.6, 0.4		
Mostly sitting/standing	5,926	Referent			
Mostly walking	5,512	0.0	-0.6, 0.7		
Mostly heavy labor	962	0.6	-0.6, 1.8		
<i>P_{trend}</i>		0.30			
Leisure Activity					
Inactive	3,301	Referent		Referent	
Mostly inactive	6,731	0.3	-0.4, 1.0	0.3	-0.4, 1.0
Active	13,206	0.5	-0.2, 1.1	0.4	-0.2, 1.0
Mostly active	6,533	0.9	0.2, 1.6	0.8	0.1, 1.5
Highly active	3,245	1.1	0.3, 1.9	0.9	0.1, 1.7
<i>P_{trend}</i>		0.001		0.01	
Combined Home and Leisure Activity					
Inactive	340	Referent		Referent	
Mostly inactive	9,724	0.8	-1.2, 2.7	0.7	-1.2, 2.6
Active	13,907	1.2	-0.8, 3.1	1.0	-0.9, 3.0
Mostly Active	8,668	1.5	-0.5, 3.5	1.3	-0.7, 3.3
Highly Active	377	3.1	0.4, 5.9	3.0	0.3, 5.7
<i>P_{trend}</i>		0.001		0.01	

* Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, pre-pregnancy BMI, daughter's somatogram at age 10.

[†] Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, pre-pregnancy BMI, daughter's somatogram at age 10, and daughter's activity at ages 5–10.

Table 4

Odds ratio for an earlier level of age at menarche (≤ 11 , 12–13, ≥ 14) compared to the next later level by mothers' physical activity.

	n	Odds Ratio [*]	95% confidence interval	Odds Ratio [†]	95% confidence interval
Home Activity					
Mostly sitting	951	Referent			
Mostly walking/standing	5,608	0.98	0.86, 1.12		
Active housework	25,651	1.00	0.88, 1.13		
Heavy manual work	806	0.92	0.77, 1.11		
<i>P_{trend}</i>		0.96			
Occupational					
NA/Not working	20,616	1.03	0.97, 1.10		
Mostly sitting/standing	5,926	Referent			
Mostly walking	5,512	1.00	0.93, 1.08		
Mostly heavy labor	962	0.95	0.83, 1.08		
<i>P_{trend}</i>		0.14			
Leisure Activity					
Inactive	3,301	Referent		Referent	
Mostly inactive	6,731	0.98	0.90, 1.06	0.98	0.90, 1.06
Active	13,206	0.95	0.88, 1.03	0.96	0.89, 1.03
Mostly active	6,533	0.91	0.84, 0.99	0.92	0.85, 1.00
Highly active	3,245	0.91	0.83, 1.01	0.93	0.84, 1.02
<i>P_{trend}</i>		0.01		0.03	
Combined Home and Leisure Activity					
Inactive	340	Referent			
Mostly inactive	9,724	0.92	0.73, 1.15	0.92	0.73, 1.16
Active	13,907	0.87	0.70, 1.10	0.88	0.70, 1.11
Mostly Active	8,668	0.86	0.68, 1.09	0.87	0.69, 1.10
Highly Active	377	0.67	0.48, 0.92	0.68	0.49, 0.93
<i>P_{trend}</i>		0.01		0.02	

* Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, pre-pregnancy BMI, daughter's somatogram at age 10.

[†] Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, pre-pregnancy BMI, daughter's somatogram at age 10, and daughter's activity at ages 5–10.