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 mother's activity may also influence this outcome. The purpose of this study was to determine if a mother's physical activity during pregnancy is related to their daughter's menarcheal age. Participants of the Nurses' Health Study II reported their age at menarche to the nearest year, whereas 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 activities, as well as the activity of their daughters at ages 5 to 10 years. Using multiple linear regression analysis with adjustment for specific covariates including daughter's 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_{trend} < 0.001). Compared with women inactive in their leisure-time, women who were highly active had daughters with menarche 1.1 (95% confidence interval, 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% confidence interval, 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.** (Cancer Epidemiol Biomarkers Prev 2008;17(10):2656–62)

Introduction

Age at menarche, a well-known reproductive-related risk factor for breast cancer, is associated with an ~10% to 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 with 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 preeclamptic mothers (13). There is also a fairly consistent direct association between birthweight and breast cancer risk (14, 15).

Interestingly, age at menarche has been associated with potential exposures *in utero*. Specifically, exposure to dichlorodiphenyldichloroethylene (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 done; 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

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physically active will have a delayed age at menarche compared with daughters of mothers who were less physically active while pregnant.

Materials and Methods

Study Population. The study population consists of participants in the Nurses' Health Study II (NHS II) whose mothers were enrolled in the Nurses' Mothers' Cohort Study. In 2001, members of the NHS I and NHS II who were free of cancer (other than nonmelanoma 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 data set 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 5 and 10 years) and merged with the mother's information. Of the 35,830 women who completed the survey, 88 identified that their daughters were adopted, and 1,807 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 with ''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 ~3 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 3 to 5 and 5 to 10 years using a similarly 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 5 and 10 years using somatograms (on a scale ranging from 1 to 9). We calculated a ''growth velocity'' measure and categorized the nurses by change in somatogram score between ages 5 and 10 years. Girls staying within one unit of their age 5 somatogram over the 5-year period were classified as stable, and girls who increased or decreased two or more units on the 1 to 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. Because the age at menarche was reported to the nearest year and the differences by level of physical activity were small, we multiplied the β-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 for the mother were race (White, non-White), home ownership (yes, no),

Table 1. 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	4
	Mostly active	170	5,477	850	36
	Active	157	10,439	2,476	134
	Mostly inactive	45	4,563	1,686	437
	Inactive	57	2,464	440	340

NOTE: 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)
Mother's 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 weight 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)
Prepregnancy body mass index (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 (y), mean (SD)	26.2 (5.1)	25.6 (5.0)	25.7 (4.9)	25.8 (4.9)	26.4 (4.9)
Daughter's characteristics					
Firstborn, n (%)	1,391 (42)	3,533 (52)	5,961 (45)	2,392 (37)	800 (25)
Birthweight (g), mean (SD)	3,280 (539)	3,284 (520)	3,285 (497)	3,290 (504)	3,306 (519)
Physical activity at ages 5 to 10 (%)					
Mostly inactive and 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)
2	1,003 (30)	2,031 (30)	4,139 (31)	2,096 (32)	998 (31)
3	728 (22)	1,566 (23)	3,131 (24)	1,602 (25)	786 (24)
4	513 (16)	1,122 (17)	2,117 (16)	994 (15)	521 (16)
5-9	446 (14)	813 (12)	1,470 (11)	654 (10)	323 (10)
Age at menarche (y), mean (SD)	12.4 (1.4)	12.4 (1.4)	12.4 (1.4)	12.5 (1.4)	12.5 (1.4)

NOTE: Sum of percentages do not always add to one due to exclusion of those with missing values.

education (<4 years high school, 4 years high school, at least some college), smoking during pregnancy (yes, no), age at birth of the daughter (<23, 23-25, 26-29, ≥30), prepregnancy body mass index (≤20, >20 to ≤25, >25 to <30, ≥30); and for the daughter, the birth order of the daughter (first or later birth) and the daughter's age 10 somatogram classification (1, 2, 3, 4, 5-9). To examine potential mediating variables, the daughter's activity at ages 3 to 5 and 5 to 10 (highly active, active, mostly active, inactive), growth velocity at ages 5 to 10 (increasing, stable, decreasing), birthweight (quartiles), birthweight for gestational age (<10%, 10-90%, >90%), and mother's weight gain during pregnancy (<14, 15-19, 20-29, ≥30 lbs.) were each 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 to 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 versus the next later level by mother's 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 groups for each model were examined by testing the β-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, whereas 18.0%, 16.7%, and 2.9% reported that 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 mother's age at the time of questionnaire completion was 72.2 ± 6.5 years (mean ± SD), whereas the birth of their nurse daughter occurred from 36 to 57 years earlier. The nurse daughter's were 33.9 ± 4.6 years (mean ± SD) when they reported their age at menarche, which on average was 12.4 ± 1.4 years. In multiple linear regression analyses, neither occupational ($P_{trend} = 0.30$) nor home ($P_{trend} = 0.94$) activity was associated with age at menarche when adjusted for the mother's race, home ownership, education, smoking during pregnancy, age at

birth, prepregnancy body mass index, the birth order of the nurse, or the nurse's somatogram at age 10 (Table 3). Maternal leisure-time physical activity outside the home was significantly associated with the daughter's age at menarche (P_{trend} = 0.001). Daughters of women who reported being mostly active or highly active had ages at menarche 0.9 [95% confidence interval (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 menarche 3.1 (95% CI, 0.4-5.9) months later than daughters of highly inactive women. The trend across increasing levels of activity was significant (P_{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 birthweight, birthweight for gestational age, and growth velocity from ages 5 to 10 did not influence the results. The nurse daughter's physical activity at ages 5 to 10 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_{trend} = 0.01), and for the highly active composite variable now 3.0 (0.3-5.7) months (P_{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_{trend} = 0.14) or home activity (P_{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 with the next higher level was lower for the daughters of women who were mostly active [odds ratio (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 with the daughters of the inactive (P_{trend} = 0.01). This relationship was attenuated with further adjustment for the daughter's activity at ages 5 to 10 (P_{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 with 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_{trend} = 0.01).

Discussion

Although previous studies have shown 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

Table 3. Adjusted difference in daughter's age at menarche (mo) by type and level of physical activity during the mother's pregnancy

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

*Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, prepregnancy BMI, and 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 to 10.

Table 4. ORs for an earlier level of age at menarche (≤11, 12-13, ≥14) compared with the next later level by mother's physical activity

	n	OR (95% CI)*	OR (95% CI)†
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)	
P_{trend}		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)	
P_{trend}		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)
P_{trend}		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)
P_{trend}		0.01	0.02

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

† Adjusted for race, home ownership, education, smoking during pregnancy, birth order, maternal age at birth, prepregnancy BMI, daughter's somatogram at age 10, and daughter's activity at ages 5 to 10.

~3 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 compared with daughters of mothers who were highly inactive in both types of activity during their pregnancies.

Other fetal exposures that have been associated with the daughter's age at menarche include organochlorine exposure (15 μg/L serum concentrations) and a 1-year earlier age at menarche (P = 0.04; ref. 16); smoking a pack or more of cigarettes per day during pregnancy and a 2.6-month earlier age at menarche (17); and drinking three or more cups per day of tea with a 4.9-month later age at menarche (17). The difference in age at menarche associated with maternal physical activity in our study was similar to the magnitude for the abovementioned behavioral factors. Although the difference is reasonably small, it is similar to the differences in the mean age at menarche of African American and White girls from the United States (18). Whether physical activity in pregnancy relates to future breast cancer risk of the daughter, and is mediated by age at menarche, remains to be determined. Age at menarche is one of several reproductive breast cancer risk factors, and the evidence suggests that a 1-year delay in menarche can reduce breast cancer risk by 10% to 20% (1). Therefore, although interesting, if physical activity in pregnancy has an effect on menarcheal age, the concomitant effect 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 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 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 household work with a limited number receiving either hired help or help from their spouses. We did, however, find a significant association with leisure-time activity, which had 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 longer delay in menarche for daughters of the most active women compared with daughters of those who were the most inactive.

We found that adjustment for the daughter's activity during childhood attenuated the relationship between their age at menarche and their mother's activity while pregnant, but only minimally. Intense levels of prep-

ubertal physical activity have been related to age at menarche in prior studies, with trained athletes having as much as a 2-year delay in age at menarche compared with the least active (2-4). The attenuation we noted could be explained by the strong relationship between the maternal-reported pregnancy activity and their daughter's 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 daughter's activity at ages 5 to 10 years did influence the estimates, they were still significant despite the inclusion of somatograms at age 10.

An association between mother's physical activity during pregnancy and daughter's menarcheal age is biologically plausible. One potential mechanism may be through variability in birthweight for gestational age/size or weight as a result of the mother's pregnancy physical activity, although birthweight for gestational age and birthweight in quartiles did not modify the association. Earlier reports, however, indicate that both prenatal and postnatal growth trajectories seem to be predictive of age at menarche with a somewhat complicated interaction (22-24). Pregnancy physical activity may affect prenatal growth and subsequent birthweight 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 birthweight or size, exercise may alter the fetal milieu in ways that could affect pubertal development. In a well-controlled animal study, a high-fat diet in pregnant rats increased estrogen levels in pregnancy and led to an 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 the 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. Because 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., nondifferential, which would attenuate our associations. However, more of a concern would be if the measurement error was related to the outcome, i.e., differential error. For example, perhaps women who were less active tended to overreport their activity compared with those who were more active. With differential error, our associations could be biased in either direction, i.e., toward a larger or smaller association; however, the nature of the measurement error cannot be determined from our study. 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 the 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 body mass index at ages 5 to 10 (r = 0.57-0.70) and has decent sensitivity (40%) and excellent specificity (100%; ref. 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 that the activity women reported during pregnancy is reflective of their prepregnancy levels of activity, and therefore, more likely to be their usual activity levels that are associated with the outcome examined here. We do not have any reporting of prepregnancy physical activity to 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 nonsmokers; and different information sources for the end point than for the exposures.

To our knowledge, this is the first study to examine the relationship between mother's physical activity in the index pregnancy and their daughter's age at menarche. There are few data sets 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. Although interesting, the findings should be interpreted with caution until additional studies address this topic of interest.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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