Age at Menarche in Relation to Maternal Use of Tobacco, Alcohol, Coffee, and Tea during Pregnancy

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To investigate the potential effects of common early life exposures on age at menarche, the authors examined data collected in a follow-up study of pregnancies that occurred during the 1960s in California. Among 994 female offspring interviewed as adolescents, 98% had started their menstrual periods at a mean age of 12.96 years. After adjustment, the mean age at menarche was a few months earlier among girls whose mothers smoked a pack or more of cigarettes daily during pregnancy compared with unexposed girls (difference = –0.22 years, 95% confidence interval (CI): –0.49, 0.05) and more so among girls who were not White (difference = –0.52 years, 95% CI: –1.1, 0.08). Girls with both high prenatal and childhood passive smoke exposure had an adjusted mean age at menarche about 4 months earlier than those unexposed. The daughter’s mean age at menarche varied little by maternal prenatal alcohol consumption. Daughters of tea consumers had a later mean age (difference = 0.41 years at ≥3 cups (0.7 liter)/day, 95% CI: 0.03, 0.80) and were more likely to start menarche later (>13 years) (odds ratio = 1.7, 95% CI: 0.91, 3.2), but daughters of coffee consumers did not. These suggestive findings, which merit further investigation, may be related to hormonal effects.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

Secular trends in the mean age at menarche suggest a relatively large decline during the first half of the 1900s that may be continuing but to a lesser degree (1–3). A nationwide study (3) received much attention by suggesting that girls seen in the United States were developing pubertal characteristics at ages much younger than pediatric norms, particularly Black girls. These changes have raised the possibility that exogenous exposures may be exerting an effect on puberty and reproductive maturation (3, 4).

Relatively little is known about what triggers menstruation in adolescents; the strongest predictors are mother’s age at menarche and some aspect of larger body size (2, 5–7). Menses onset is under the control of the hypothalamic-pituitary-gonadal system (8), so exposures that affect the endocrine or central nervous system or its development might lead to alterations. Impaired reproduction and development have been reported in animals exposed to “endocrine disrupters” or compounds that appear to be hormonally active, including earlier puberty (9–12). Recent data support these findings in children exposed prenatally (13, 14).

Tobacco smoke contains numerous reproductive toxins and appears to have endocrine reactive properties (15–19). Maternal cigarette smoking and alcohol consumption during pregnancy are associated with adverse fetal health outcomes and lasting effects on children, including on the central nervous system (15, 20–26). A few small studies have reported changes in age at menarche related to passive smoke exposure (27, 28) and to maternal alcohol consumption during pregnancy (29).

Few studies have examined environmental influences on pubertal development in humans, perhaps partly because of design difficulties, as prenatal exposures are likely to be important but are hard to ascertain accurately at the time a child is approaching puberty. Conversely, following children from birth to puberty is expensive and time consuming. We explore the hypothesis that prenatal exposures may affect offspring reproductive maturation, as measured by age at menarche, using previously collected data. Our focus is on...
common exposures, such as tobacco smoke, which are thought to have potential endocrine or reproductive effects, as a model for other exogenous exposures and for designing future studies.

**MATERIALS AND METHODS**

Data were analyzed from the Child Health and Development Study, a large longitudinal study conducted among families residing in the San Francisco Bay Area of California, which has been described in over 100 reports (30). Pregnant women who were members of the Kaiser Permanente Health Plan were recruited during the early 1960s for an extensive set of interviews, biologic sampling, and medical record review. Subsets of the offspring of the 20,000 pregnancies were followed for additional interviews and developmental examinations at ages 5, 9–11, and/or 15–17 years (30).

The adolescent study was designed to investigate hypertension. About 2,000 adolescents (or 80 percent of those eligible) participated, most of whom were 16 or 17 years of age, including 1,003 girls. Eligibility criteria were based on birth date, residence in the San Francisco Bay Area, and participation in an earlier follow-up (99 percent and 87 percent had participated in the examinations for girls aged 9–11 years and 5 years, respectively). Mothers and their adolescents were seen in the clinic for anthropometric and blood pressure measurements, as well as for health interviews and completion of self-administered forms on behavior and attitudes. Mothers of participating adolescents were very similar to the initial study population by race, occupation, and parity, although slightly older and of higher socioeconomic status.

**Definition of endpoints**

During the interview of adolescents, girls were asked whether their menstrual periods had started and, if so, at what age (year and months). The 994 girls who responded comprise the “subjects” of this analysis, of whom 13 had not yet started their periods. There was some digit preference for additional months of age; about 45 percent of the girls supplied only the year of age (or months = 0), and 16 percent said 6 months. We calculated the mean age at menarche using the information reported but tried different analytical techniques (see below) to account for this potential error in exact age. We also categorized age at menarche as “early” (<12 years) and “late” (>13 years), using 12–13 years as the “average age” referent group. Girls who had not started menses were included in the late menarche group, but they were not included in the analysis of mean age.

**Definition of exposure**

Most exposures were based on data from the prospective interview conducted with the mother during pregnancy. In addition to demographics and health history, women were asked a series of questions about smoking and consumption of various beverages (including coffee, tea, wine, cocktails, and beer).

Prenatal smoke exposure was ascertained from the smoking status of the gravida, and the amount smoked per day was recorded in categories, which we combined into four categories. Environmental tobacco smoke exposure during the subject’s childhood was estimated from the mother’s report of parental smoking at the follow-up when her daughter was aged 9–11 years. We calculated pack-years of smoking for each parent by multiplying the years smoked during the child’s lifetime by the number of packs smoked per day. The sum of these was categorized into an ordinal environmental tobacco smoke variable as none, medium (>0–8 pack-years), and high (>8 pack-years). Childhood environmental tobacco smoke exposure was combined with maternal prenatal smoking into a categorical variable: 1) no exposure (referent group), 2) some prenatal exposure (any amount) but no childhood environmental tobacco smoke exposure, 3) no prenatal but some childhood exposure, 4) high prenatal (>20 cigarettes/day) and high childhood environmental tobacco smoke exposure (>8 pack-years), and 5) some of each (any remaining smoke exposure). Rather than exclude about 200 girls missing smoking information from one parent (primarily the father), we attempted to classify their exposure with data available from the other parent.

As adolescents, 26 percent of the girls reported having smoked regularly for at least 1 year. Of these, only 20 girls started smoking before and 39 girls started smoking during the same year of age that menarche occurred, which we considered the risk period of interest.

For alcohol, consumption of less than one glass or bottle per week was recoded to 0.5 drink/week, and lower amounts were recoded to none. The three types of alcoholic beverages were summed to calculate the total number of drinks per week and then examined as a categorical variable. As there was little variation with age at menarche, alcohol was usually included in models as a dichotomous variable (<1 drink/week vs. more).

Coffee and tea consumption were analyzed separately as categorized cups/day (with <1/day recoded to no consumption). Coffee and tea were assumed to be caffeinated at the time, so they were also converted into milligrams of caffeine consumed daily (107 mg/cup of coffee and 34 mg/cup of tea (31); 1 cup = 0.24 liter). Coffee and tea are presented separately, rather than the caffeine level, because of the different effects observed.

The beverage variables reflect the usual amount consumed around the time pregnancy started, with the assumption that this would represent early pregnancy consumption. There were substantial missing data on these variables; 274 were missing alcohol and 253 were missing tea or coffee consumption, most of whom were missing all three (n = 242).

**Covariates**

We examined numerous covariates from the prenatal and two childhood examinations for their potential association with the subjects’ age at menarche. However, we focused on prenatal data because that is when the exposures of interest occurred, and later factors might reflect stage of development, including earlier onset of the pubertal transition.
Prenatal records. Reproductive history, maternal age at delivery, age at menarche, race, education, employment status, prepregnancy weight and height (converted to body mass index), and household income were obtained from the interview. Maternal age at menarche was missing from nearly 400 records, so we used the prenatal clinic record to supplement information, ascertaining this variable for 924 mothers. In a comparison of the mean age at menarche calculated from each data source among women who had both, the correlation was high (\(r = 0.84, p < 0.0001\)). Infant birth weight and race were obtained from delivery and newborn records. Race was categorized as White, Black, and “others,” which included mostly Asians (Japanese and Chinese) or mixed-race codes. Hispanic ethnicity was not coded for children and was rare among mothers (\(n = 24\)).

Childhood examinations. The variables examined included family structure (number and gender of siblings, parents in the home, and so on); behavior inventory including thumb sucking, bed-wetting, and nightmares; hospitalizations; and general health. Weight and height measurements were used to calculate child body mass index and were also available standardized to race and sex. We selected size at age 5 years, before puberty onset, and analyzed these variables as the lowest or highest quartile, compared with the middle two. As nearly all girls had reached menarche by the adolescent interview, no independent variables besides smoking were used from this time (beverage consumption was not available).

Statistical analysis

The distribution of age at menarche was confirmed to be approximately normally distributed, with some deviations at yearly and half-yearly intervals due to the digit preferences noted above. Univariate analyses were conducted to examine mean age by category of independent variables using an \(F\)
test, and the distribution of early and late menarche was examined in contingency tables with a chi-square test (table 1). The variables considered potential confounders from the univariate analyses were included in multiple regression models and then removed individually to examine the change in the estimate for each exposure (32). Variables that changed the estimate by more than 10 percent were retained. Because of substantial loss of data, we tried to maximize sample size by considering potential confounders unique to each exposure, but we also ran a model including all exposures and the important confounders. These later coefficients are presented in the table of adjusted differences in mean age, for ease of interpretation and because results were basically similar, but they do not represent the most parsimonious model.

To accommodate the potential misclassification of reported age at menarche in months, we developed a model based on interval censoring (33). Girls who did not report any months were assumed to have started menses in the interval from 3 months before to 9 months after the year of age provided. For girls who reported 6 months, the interval selected was 3 months on either side. All other girls were assumed to have reported their age accurately. Probability models were fit using the SAS (SAS Institute, Inc., Cary, North Carolina) LIFEREG procedure (34), assuming that age at menarche was normally distributed. We also ran ordinary least-squares models (SAS PROC GLM) for comparison, treating reported age at menarche as exact for every subject. For simplicity and because they tended to be more conservative, the least-squares model estimates are presented in tables. For additional comparison, some general linear models were run using only the reported year of age at menarche for all subjects, with little difference in results. These models provide adjusted estimates of the difference in mean age at menarche by the exposure variable levels. Adjusted odds ratios and 95 percent confidence intervals for

**TABLE 1. Continued**

<table>
<thead>
<tr>
<th>Variables by level</th>
<th>Distribution</th>
<th>% with early menarche (&lt;12 years)</th>
<th>% with late menarche (&gt;13 years)</th>
<th>Mean age (years)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous pregnancies (no.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>206</td>
<td>20.7</td>
<td>21.8</td>
<td>18.9</td>
<td>12.83</td>
</tr>
<tr>
<td>1–2</td>
<td>444</td>
<td>44.7</td>
<td>14.2</td>
<td>26.6</td>
<td>13.03</td>
</tr>
<tr>
<td>&gt;2</td>
<td>344</td>
<td>34.6</td>
<td>13.7</td>
<td>23.3</td>
<td>12.95</td>
</tr>
<tr>
<td>Total</td>
<td>994</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Overall, n = 994; however, numbers do not add to 994 because of missing data. In addition, over 200 subjects did not participate in an examination for girls 5 years of age, so the total is less for body mass index and number of siblings. The number for mean age excludes 13 who had not started menarche by the interview.

† Overall, early menarche: n = 155 (15.6%); late menarche: n = 236 (23.7%); mean age: 12.96 years.
early and late menarche, compared with “average” age, were calculated in separate logistic regression models, adjusting for the exposure-specific confounders. We explored whether results differed by race category by running separate models. As girls in the Black and other race groups had very similar mean ages at menarche and earlier onset than White girls (table 1), they were merged into a “non-White” category to increase power for these analyses.

RESULTS

The mean age at menarche of the subjects was 12.96 (standard deviation, 1.21) years, with 16 percent of the girls experiencing onset early and 24 percent late, as shown by the demographic characteristics in table 1. The mean age at menarche was younger in girls who were non-White, first-born or an only child, and of larger size at age 5 years (body mass index reported, but all measures indicated this association) and whose mothers were not college educated, were employed during pregnancy, or had a younger age at menarche (table 1). Most of these associations were consistent for early menarche as well. Factors not related to age at menarche included low birth weight status, gender of prior livebirth, and mother’s prepregnancy body mass index, as well as health status, family income during childhood, living with only one biologic parent, or most behavioral indicators during childhood.

Tobacco smoke exposure

Over half the girls had prenatal smoke exposure, with a tendency toward earlier mean age at menarche at the highest exposures (table 2). Mothers who smoked were more likely to be White, younger, and with earlier menarche, higher household income, and greater coffee and alcohol consumption. After adjustment, the mean age at menarche was a few months earlier among daughters whose mothers smoked a pack or more of cigarettes per day (table 3). The decrement in age at menarche among the girls who were not White was about 6 months (–0.52 years) (table 3) and may also occur at lower smoking levels. The interval model yielded an estimate that was about 20 percent earlier for non-Whites than the exact model.

The mean age at menarche was slightly lower (–0.15 years) among girls with more than 8 pack-years of environmental tobacco smoke exposure. The girls with high exposure to both prenatal smoking and environmental tobacco smoke had a mean age at menarche 4 months earlier than the unexposed girls did (table 2), which was little affected by adjustment (table 3). Overall, there was no evidence for a dose-response effect (table 3). The interval model again produced a slightly stronger estimate in non-Whites, by about 2 months.

Among offspring of heavily smoking mothers, the odds ratio for early menarche was not elevated, but the odds of late menarche were reduced slightly (adjusted odds ratio (AOR) = 0.69, 95 percent confidence interval (CI): 0.38, 1.23). These measures did not vary much by race (data not shown), but there were no non-White girls with late menarche and heavy prenatal exposure. Girls highly exposed to smoke pre- and postnatally were half as likely to start menarche late (AOR = 0.49, 95 percent CI: 0.23, 1.0), but there was little association with risk of early menarche after adjustment.

The 59 girls who reported smoking by the time menarche occurred tended to have a later mean age (13.7 years) than the entire sample, perhaps because of more opportunity to start smoking if menarche occurred later. Thus, they are unlikely to account for the finding of earlier age with parental smoking.

Alcohol

About 56 percent of the subjects’ mothers drank some alcohol during pregnancy (table 2); they were more likely to be White; of higher income, education, and age; to drink coffee; or to smoke. After adjustment, there was little variation in mean age at menarche by alcohol as a dichotomous (table 3) or continuous variable. The adjusted odds ratio for late menarche and alcohol consumption among Whites was 1.3 (95 percent CI: 0.84, 2.1).

Coffee and tea

A majority of the mothers drank some coffee, but only one third consumed tea, and the two were inversely related. There was a tendency toward delayed age at menarche with increasing maternal caffeine consumption that was, however, stronger for tea than coffee (table 2). Coffee and tea consumption were associated with maternal age and income; coffee consumption was also associated with employment, White race, and smoking, whereas tea consumption was associated with being Asian and not smoking. After adjustment, there was little variation in mean age at menarche by coffee consumption overall (table 3). Among non-White girls, the mean age appeared to be earlier (table 3), and the rate of late menarche was reduced with high maternal coffee consumption (AOR = 0.28, 95 percent CI: 0.07, 1.1).

The few month delay in mean age at menarche observed with high maternal tea consumption persisted after adjustment and was also apparent at moderate consumption among non-White girls (table 3). The delay did not appear to be related to an inverse association with smoking status, as it was even greater among nonsmokers’ daughters (β = 0.72 years at ≥3 cups/day, 95 percent CI: 0.23, 1.2). There was no association of high maternal tea consumption with early menarche. The rate of late menarche was elevated 72 percent overall, primarily among Whites (AOR = 1.9, 95 percent CI: 0.95, 3.9).

DISCUSSION

This is one of the first reports examining the influence of common, early exposures on reproductive maturation in humans. There is growing interest in the effects of prenatal exposures on later sexual development and other health endpoints. Prenatal exposure to potential endocrine disrupters has been associated with earlier sexual maturation in animals (9–12) and with earlier age at menarche and pubic hair development in girls exposed in utero or lactationally to polybrominated biphenyls (13). Thus, the mechanism may
be an effect on the maternal endocrine system that controls fetal development or the offspring’s endocrine system that controls later sexual maturation. Chemicals that affect the central nervous system, such as lead (35, 36), might also disturb hypothalamic-pituitary control of puberty onset.

We observed consistently that daughters of heavy smokers had a reduced mean age at menarche and odds of late menarche. A few preliminary findings support these results, although they do not specifically address prenatal exposure. Polish studies (27, 28) reported a lower age at menarche among daughters of smoking compared with nonsmoking mothers, and colleagues found that women whose parents reportedly smoked in the home had a slightly higher risk of early menarche (37). A recent Canadian longitudinal study showed an association of maternal prenatal smoking with earlier pubertal milestones in male adolescents, suggesting a potentially similar mechanism (38). The authors reported no association with age at menarche, but the study had extremely small numbers (n = 69), and numerical results were not presented.

Maternal cigarette smoking during pregnancy is well recognized to have adverse effects on fetal and infant health.

**TABLE 2. Age at menarche by prenatal (and childhood) exposure variables, Child Health and Development Study, California, pregnancy years 1959–1966.†**

<table>
<thead>
<tr>
<th>Variables by level</th>
<th>Distribution</th>
<th>% with early menarche (&lt;12 years)</th>
<th>% with late menarche (&gt;13 years)</th>
<th>Mean age (years)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (cigarettes/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>462</td>
<td>47.3</td>
<td>15.5</td>
<td>24.2</td>
<td>13.00</td>
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<tr>
<td>1–9</td>
<td>247</td>
<td>25.3</td>
<td>15.4</td>
<td>23.9</td>
<td>12.92</td>
</tr>
<tr>
<td>10–19</td>
<td>88</td>
<td>9.0</td>
<td>13.6</td>
<td>25.0</td>
<td>13.07</td>
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<tr>
<td>≥20</td>
<td>179</td>
<td>18.3</td>
<td>18.4</td>
<td>23.5</td>
<td>12.86</td>
</tr>
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<td>Total</td>
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<td></td>
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</tr>
<tr>
<td>Pre- and postnatal smoke exposure</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>219</td>
<td>24.9</td>
<td>13.7</td>
<td>26.9</td>
<td>13.08</td>
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<tr>
<td>No pre-/some postnatal exposure</td>
<td>163</td>
<td>18.6</td>
<td>14.7</td>
<td>25.2</td>
<td>13.04</td>
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<tr>
<td>Prenatal/no postnatal</td>
<td>78</td>
<td>8.9</td>
<td>14.1</td>
<td>25.6</td>
<td>13.03</td>
</tr>
<tr>
<td>Some of each</td>
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<td>32.1</td>
<td>15.3</td>
<td>25.5</td>
<td>13.00</td>
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<tr>
<td>High of both</td>
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<td>19.1</td>
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<td>Total</td>
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<td>Alcohol (no. of drinks)</td>
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<tr>
<td>&lt;1/month</td>
<td>317</td>
<td>44.1</td>
<td>16.7</td>
<td>22.4</td>
<td>12.93</td>
</tr>
<tr>
<td>&lt;1/week</td>
<td>112</td>
<td>15.6</td>
<td>17.9</td>
<td>22.3</td>
<td>12.95</td>
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<td>1–2/week</td>
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<td>13.4</td>
<td>24.8</td>
<td>13.06</td>
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<tr>
<td>3–6/week</td>
<td>65</td>
<td>9.0</td>
<td>15.4</td>
<td>36.9</td>
<td>13.17</td>
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<tr>
<td>&gt;6/week</td>
<td>76</td>
<td>10.6</td>
<td>13.2</td>
<td>25.0</td>
<td>12.93</td>
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<tr>
<td>Total</td>
<td>719</td>
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<td></td>
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<tr>
<td>Coffee (cups/day)‡</td>
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<tr>
<td>0</td>
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<td>18.1</td>
<td>25.0</td>
<td>12.90</td>
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<tr>
<td>1–2</td>
<td>232</td>
<td>31.3</td>
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<td>≥5</td>
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<td>15.7</td>
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<tr>
<td>Total</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Tea§ (cups/day)</td>
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<td>0</td>
<td>503</td>
<td>68.3</td>
<td>16.1</td>
<td>23.3</td>
<td>12.92</td>
</tr>
<tr>
<td>1–2</td>
<td>175</td>
<td>23.6</td>
<td>14.3</td>
<td>24.0</td>
<td>13.07</td>
</tr>
<tr>
<td>≥3</td>
<td>63</td>
<td>8.5</td>
<td>12.7</td>
<td>36.5</td>
<td>13.30</td>
</tr>
<tr>
<td>Total</td>
<td>741</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Overall, n = 994; however, numbers do not add to 994 because of missing data.
† Overall, early menarche: n = 155 (15.6%); late menarche: n = 236 (23.7%); mean age: 12.96 years.
‡ Metric equivalent: 1 cup = 0.24 liter.
§ p < 0.05 for mean age by F test. For all other variables, p > 0.1.
and may be associated with shorter height in offspring as well as neurobehavioral problems (21, 22). There has also been some suggestion that maternal prenatal smoking is related to obesity in children (39, 40), despite lower weight at birth. Thus, maternal prenatal smoking might lead to earlier age at menarche via the mechanism of larger child size, but controlling for body mass index at age 5 years did not change our results. Furthermore, the age at menarche did not vary by low birth weight status in this study.

Active smoking is also associated with decreased fertility and menstrual disorders (15, 41–47), perhaps via an “antiestrogenic” or other endocrine mechanism (16–18). During pregnancy, smokers appear to have lower circulating levels of estriol and estradiol (17, 48). In addition, smoking is associated with elevated levels of follicle-stimulating hormone (49, 50). Thus, cigarette smoke may alter crucial endocrine pathways during fetal development.

We have previously seen greater effects of tobacco smoke exposure on pregnancy outcome among races other than White, as have some other studies (51–53). There is evidence that Blacks may metabolize cotinine differently from Whites and may have a higher frequency of genetic polymorphisms that increase susceptibility to the adverse effects of cigarette smoke (53–55). Thus, our suggestion of greater effects among non-Whites, who were primarily Blacks in this study, should be investigated further.

Our finding that tea consumption was associated with a few month delay in mean age at menarche, as well as an increased tendency toward late menarche, has not been examined previously and thus must be interpreted cautiously. Results were not consistent with coffee consumption, suggesting that caffeine may not be the sole or primary constituent of interest. Alternatively, maternal tea consumption may be associated with potential confounders, such as dietary factors or other behaviors, about which we had no data. Furthermore, we had no information on the

| TABLE 3. Adjusted* differences and their 95% confidence intervals of mean age at menarche by smoke exposure, by coffee, tea, and alcohol consumption, and by race, Child Health and Development Study, California, pregnancy years 1959–1966 |
|---------------------------------------------|-------------------|-------------------|-------------------|
|                                           | Adjusted          | Adjusted          | Adjusted          |
|                                           | differences        | 95% confidence interval | differences        | 95% confidence interval | differences        | 95% confidence interval |
| Maternal prenatal smoking (cigarettes/day)† |                   |                   |                   |
| None                                       | Referent           |                   |                   |
| 1–9                                        | –0.05, –0.29, 0.18 | –0.01, –0.30, 0.27 | –0.09, –0.50, 0.32 |
| 10–19                                       | –0.02, –0.35, 0.32 | 0.05, –0.34, 0.44 | –0.43, –1.19, 0.34 |
| ≥20                                         | –0.22, –0.49, 0.05 | –0.17, –0.48, 0.14 | –0.52, –1.12, 0.08 |
| Pre- and postnatal smoke exposure†         |                   |                   |                   |
| No exposure                                 | Referent           |                   |                   |
| No pre-/some postnatal exposure             | 0.08, –0.23, 0.39  | 0.04, –0.35, 0.43  | 0.09, –0.42, 0.61  |
| Prenatal/no postnatal                       | 0.0, –0.40, 0.41   | 0.02, –0.44, 0.48  | –0.07, –1.01, 0.87 |
| Some of each                                | –0.04, –0.31, 0.23 | –0.01, –0.34, 0.32 | –0.19, –0.70, 0.31 |
| High of both                                | –0.31, –0.65, 0.03 | –0.30, –0.69, 0.09 | –0.44, –1.2, 0.33  |
| Alcohol (drinks/week)                       |                   |                   |                   |
| None (<1)                                   | Referent           |                   |                   |
| ≥1                                          | 0.09, –0.13, 0.30  | 0.13, –0.11, 0.38  | –0.23, –0.72, 0.26 |
| Coffee (cups/day)‡                          |                   |                   |                   |
| <1                                          | Referent           |                   |                   |
| 1–2                                         | –0.07, –0.36, 0.21 | –0.04, –0.41, 0.33 | –0.26, –0.73, 0.21 |
| ≥3                                          | 0.09, –0.19, 0.36  | 0.19, –0.15, 0.53  | –0.36, –0.85, 0.13 |
| Tea (cups/day)                              |                   |                   |                   |
| <1                                          | Referent           |                   |                   |
| 1–2                                         | 0.19, –0.06, 0.43  | 0.07, –0.22, 0.36  | 0.60, 0.15, 1.0    |
| ≥3                                          | 0.41, 0.03, 0.80   | 0.43, –0.03, 0.90  | 0.34, –0.33, 1.0   |

* Adjusted for all other exposures, although the two smoking variables were run in different models, as well as for mother’s age at menarche, parity, child’s race (three categories for total, two among non-Whites, namely, Black and other), education, and income. Beverage results are from the model with pre- and postnatal smoking variables, so the sample size remains the same.

† For maternal prenatal smoking, total: n = 624; Whites: n = 470; non-Whites: n = 154; for pre- and postnatal smoke exposure, total: n = 564; Whites: n = 435; non-Whites: n = 129.

‡ Metric equivalent: 1 cup = 0.24 liter.
girls’ beverage consumption. Coffee extract shows weak estrogenic activity in test systems (56, 57). However, coffee or caffeine intake was found to be inversely correlated with estradiol or its metabolite levels in pregnant and menstruating women and monkeys (56, 58, 59), while other studies of nonpregnant women found no correlation (60) or an increase in baseline levels (61). Tea contains beneficial antioxidants, such as catechins and flavonoids, which show varied estrogenic potential, depending on the levels (62–64). These constituents may contribute to different effects compared with those of coffee.

In contrast to our finding of little association with prenatal alcohol exposure, a few prior studies indicate later sexual development (29, 65, 66). The small study of girls (29) included mothers who were drinking at the level of alcoholics. Thus, our consumption levels may have been generally too low to detect effects. However, these investigators did not consider confounding factors. When we examined type of alcohol, crude results for beer consumption suggested a delay in the mean age at menarche. Our results for alcohol generally varied more by the subgroup and covariates examined than for the other exposures, indicating some instability of effect estimates that makes interpretation difficult. There is some biologic evidence to suggest effects of alcohol on reproductive maturation. Heavy drinking during pregnancy can lead to growth retardation and neurologic deficits in the offspring (24). Animal studies indicate a variety of effects on the hypothalamic-pituitary-gonadotropin system of offspring (26). Studies of healthy adult women found that estrogen levels were increased with alcohol intake (58, 67, 68), so we might expect an effect in the opposite direction of smoking.

This analysis has other limitations in addition to the problems noted previously with missing data. The sample size for non-Whites was small, so results are presented for descriptive purposes only. As exposure was based on questionnaire data, there is possible misclassification. Yet, due to the prospective nature of data collection, it should not be biased in relation to the endpoint. Furthermore, these habits were not actively discouraged among pregnant women in the early 1960s, so underreporting should be limited. Self-report of these common habits appears to have reasonable validity, and a previous analysis of these data based on a biomarker indicated that less than 2 percent of nonsmokers may have actually smoked (69). Another source of exposure misclassification is lack of information later in pregnancy, as these habits may change. We also lacked detailed data on all changes in parental smoking habits during the subjects’ childhoods and on other sources of environmental tobacco smoke exposure.

There was an indication that recall of age at menarche involved a digit preference, indicating possible misclassification. Random misclassification would tend to bias results toward the null. We compared different models to examine the impact of this misclassification but found no important variation in results. The interval models tended to produce slightly stronger estimates, further suggesting that the results presented may be underestimates. The age at menarche was ascertained retrospectively, but the time span between onset and age at reporting it was relatively short in this study. Other studies have indicated that age at menarche is moderately well reported even by adults (70, 71). As little is known about predictors of menarche, some potential confounders may have been excluded. We did examine a number of potential covariates in our models, most importantly, maternal age at menarche.

This study has other strengths, including extensive collection of longitudinal data on prenatal exposures and lifestyle factors that would be difficult to repeat. Furthermore, the frequency of exposure was greater in the 1960s than would be expected currently.

The trend toward earlier maturation in girls (1–3) may have adverse effects, including higher levels of psychological distress, experimentation with risky behaviors, and earlier age at first pregnancy (72–76). Girls with early or late menarche may be at higher risk of infertility or adverse pregnancy outcome, as well as alterations in their adult hormone excretion patterns and menstrual cycles (77–79). Early age at menarche is a well-established risk factor for breast cancer (80, 81). Thus, it is important to determine to what extent prenatal exposures are influencing sexual development in offspring, as measured by multiple markers of puberty. Our results are suggestive but should be confirmed and expanded in other studies, including those with sizable ethnic minorities to explore possible differences by race. New cohort studies designed to examine effects of environmental exposures will be important.

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REFERENCES

contaminant_table.htm).