Age at Menarche and Type 2 Diabetes Risk

The EPIC-InterAct study

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OBJECTIVE—Younger age at menarche, a marker of pubertal timing in girls, is associated with higher risk of later type 2 diabetes. We aimed to confirm this association and to examine whether it is explained by adiposity.

RESEARCH DESIGN AND METHODS—The prospective European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct case-cohort study consists of 12,403 incident type 2 diabetes cases and a stratified subcohort of 16,154 individuals from 26 research centers across eight European countries. We tested the association between age at menarche and incident type 2 diabetes using Prentice-weighted Cox regression in 15,168 women (n = 5,995 cases). Models were adjusted in a sequential manner for potential confounding and mediating factors, including adult BMI.

RESULTS—Mean menarcheal age ranged from 12.6 to 13.6 years across InterAct countries. Each year later menarche was associated with 0.32 kg/m^2 lower adult BMI. Women in the earliest menarche quintile (8–11 years, n = 2,418) had 70% higher incidence of type 2 diabetes compared with those in the middle quintile (13 years, n = 3,634), adjusting for age at recruitment, research center, and a range of lifestyle and reproductive factors (hazard ratio [HR], 1.70; 95% CI, 1.49–1.94; $P < 0.001$). Adjustment for BMI partially attenuated this association (HR, 1.42; 95% CI, 1.18–1.71; $P < 0.001$). Later menarche beyond the median age was not protective against type 2 diabetes.

CONCLUSIONS—Women with history of early menarche have higher risk of type 2 diabetes in adulthood. Less than half of this association appears to be mediated by higher adult BMI, suggesting that early pubertal development also may directly increase type 2 diabetes risk.

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The influence of etiological factors underlying type 2 diabetes risk may begin many years before the manifestation of disturbed glycemic control. Biological processes implicated in pubertal development may be one example of early life determinants of later disease risk. Age at menarche, the age at onset of first menstruation in girls, is frequently used as a marker of puberty timing in epidemiological studies to explore the association between developmental tempo and later disease risk. Age at menarche represents a distinct event in puberty, is usually well recalled into adulthood, and therefore is a convenient noninvasive measure of pubertal timing (1). Earlier menarche has been associated with adverse outcomes, including obesity, cardiovascular disease, some types of cancer, and mortality, demonstrating potential long-lasting effects of the timing of pubertal development on health (2).

Increasing rates of type 2 diabetes in recent decades (3) have occurred in parallel with a secular decline in the average age at menarche (4). Although the marked increases in diabetes incidence are undoubtedly driven by dramatic changes in environment and lifestyle, these concurrent trends may, to some extent, reflect a biological link between puberty timing and diabetes risk. In support of a direct link between puberty timing and glucose regulation, a recent study showed that the insulin-sensitizing agent metformin delays menarche in girls with precocious pubarche (5). A number of studies have reported adverse metabolic consequences of early sexual maturation (6–9). However, some smaller studies have not found this association, possibly because of insufficient power (10,11).

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Others have reported associations between earlier menarche timing and intermediate quantitative traits such as increased blood glucose levels (11,12), impaired glucose tolerance (13), and insulin resistance (14,15), further supporting a link between early pubertal development and an adverse metabolic profile.

It is conceivable that part of the association between menarche timing and type 2 diabetes risk is explained by increased adiposity. It is well established that younger age at menarche is associated with higher BMI in later life (16), and elevated BMI itself is a major risk factor for type 2 diabetes (17). One study reported a complete attenuation of the association between age at menarche and diabetes after accounting for BMI (18); however, notably, that study relied on self-reported BMI. In the smaller cross-sectional KORA study, the association between younger age at menarche and risk of type 2 diabetes remained after adjustment for measured BMI (9). In addition to the uncertainty about the degree to which adiposity explains the relationship between menarche and diabetes risk, there is further uncertainty regarding the shape of the association. Although earlier menarche is associated with higher risk of type 2 diabetes, it is unclear whether older age at menarche beyond the average is associated with lower risk. Nonlinear associations between age at menarche and cardiovascular disease and mortality have been observed previously (19). We sought to investigate the association between age at menarche and type 2 diabetes incidence in a large European prospective study, and to explore whether observed associations were mediated by adult BMI.

RESEARCH DESIGN AND METHODS

Participants and study design

InterAct is a large, prospective, case-cohort study of 27,779 individuals from eight European countries (Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden, and U.K.) nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) (20). The objective of the study was to investigate the interplay between genetic and lifestyle factors and the effect on risk of type 2 diabetes (21). The sample was taken from a total cohort of 340,234 individuals comprising 3.99 million person-years of follow-up time; 12,403 individuals (6,238 women) with clinically incident type 2 diabetes were selected for InterAct together with a representative subcohort of 16,835 individuals (10,378 women). After exclusion of those with prevalent diabetes (n = 548), those without information regarding diabetes status (n = 129), and individuals with postcensoring diabetes (n = 4), 16,154 subcohort members were available for analysis (10,043 women), 778 of whom were also incident cases (394 women). All EPIC centers obtained written informed consent from participants and obtained approval from local ethics committees.

Type 2 diabetes case ascertainment

As previously described (21), cases of incident type 2 diabetes were ascertained using multiple sources of evidence, including self-report (self-reported or doctor-diagnosed history of type 2 diabetes or diabetes drug use), linkage to primary or secondary care registers, medication use reported from drug registers, hospital admissions, and mortality data. In most centers, evidence of type 2 diabetes was sought from at least two independent sources from those listed or by reviewing individual medical records to verify incident cases. The exceptions were Danish and Swedish centers where cases were ascertained through local and national diabetes and pharmaceutical registers rather than self-reported; thus, all cases were considered to be verified. Information regarding diabetes status was used from any follow-up visit or external evidence with a date later than that of baseline data collection. Follow-up was censored at the date of diagnosis, 31 December 2007, or the date of death, whichever occurred first. If a diagnosis date could not be identified from any of the sources described, then the midpoint between recruitment and censoring was used.

Ascertainment of age at menarche

Information regarding age at menarche in completed whole years was obtained by questionnaire in each of the contributing centers. The normal physiological age range at menarche was considered to be between 8 and 18 years. A total of 34 women were excluded because they reported menarche after age 18 years, which may reflect an underlying pathological cause. Another 685 women were excluded because they did not provide information about age at menarche. This left 15,168 women, of whom 5,955 were considered incident type 2 diabetes cases and 9,590 were represented in the subcohort (377 of whom became type 2 diabetes cases). Early menarche was

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defined as onset of menstruation occurring between ages 8 and 11 years.

Other measurements

Baseline information regarding reproductive factors was collected using self-administered questionnaires, which asked about age at first full-term pregnancy, number of still births and live births, menopausal status, and use of the oral contraceptives and hormone replacement therapy. Parity was derived from the number of reported live births and still births. In the Bilthoven center (the Netherlands), this information was unavailable and number of children was used. Lifestyle factors including smoking status, alcohol consumption, and educational level also were assessed at baseline by self-report. Levels of physical activity were assessed using a questionnaire previously validated against objective methods and coded as inactive, moderately inactive, moderately active, and active (22). Height, weight, and waist circumference of participants were measured by trained health professionals, except in the French centers and the U.K. Oxford center, where height and weight were self-reported. Waist circumference was unavailable in the Swedish Umeå center. BMI was calculated as weight (in kg) divided by height (in m) squared. Recalled body weight at age 20 years was available in five countries (Italy, U.K., Germany, Sweden, and Denmark) and was used to calculate estimated BMI in young adulthood (recalled body weight at age 20 [kg] divided by height [m] squared). BMI cutoffs of 25 kg/m^2 and 30 kg/m^2 were used to define overweight and obesity, respectively, in accordance with guidelines from the World Health Organization (23).

Statistical analysis

Baseline characteristics of InterAct study participants were explored by categories of age at menarche. The association between age at menarche and adult BMI was tested in the InterAct subcohort using linear regression with adjustment for age at recruitment and center in each country before using random-effects meta-analysis to obtain a pooled estimate.

To estimate the association between age at menarche and type 2 diabetes, Prentice-weighted Cox regression models, with age as the underlying time scale, were fitted within each country (24). Country-specific hazard ratios (HRs) for type 2 diabetes per year later age at menarche were subsequently combined using random-effects meta-analysis. Heterogeneity between countries was assessed using the I^2 statistic. Because girls previously have been shown to be at increased risk for later disease according to age at menarche in a nonlinear manner (6,19), we also modeled menarche as a categorical variable (8–11, 12, 13, 14, and 15–18 years, which approximately equate to quintiles) with the median age (13 years) as the reference category. A quadratic age at menarche term added to the existing linear model also was tested for significance.

Basic models were adjusted for center, age at recruitment, and date of birth to account for potential cohort effects. A structured approach then was used to adjust for additional potential confounders. First, lifestyle factors including smoking status (never, former, current), alcohol consumption (<0.5 g/day, 0.5–10 g/day, 10.5–30 g/day, ≥30.5 g/day), education level (none, primary school, technical school or professional school, secondary school, longer education), and physical activity level were included. Next, we included the following reproductive factors: age at first full-term pregnancy (modeled continuously), parity (no children, one or two children, three or more children), menopausal status (premenopausal, perimenopausal, and postmenopausal), use of the oral contraceptive pill (ever or never), and use of hormone replacement therapy (ever or never).

Subsequent models were performed to examine potential mediation by BMI. First, adult BMI was added to the model that included all these potential confounders, and a subsequent model additionally included waist circumference. Finally, in the centers with this information available, estimated BMI at age 20 years was included in place of adult BMI and waist circumference. Because information regarding all covariates was not available in the full sample of women with menarche data, for each model we repeated the basic model including only individuals with all relevant covariate information. In addition, because information regarding reproductive and lifestyle factors was missing for many individuals in the InterAct sample, we tested the association between menarche timing and incident type 2 diabetes in a "maximum sample" basic model with and without adjustment for adult BMI.

To calculate the proportion of the association between early menarche and type 2 diabetes risk that is mediated by adult BMI, we performed mediation analyses in the InterAct subcohort using methods previously described for dichotomous outcomes (25,26). This approach allows estimation of the direct effect of early menarche on diabetes risk (i.e., that driven directly by menarche timing and independently of the mediator) and an indirect effect (i.e., via the mediator) of early menarche using logistic regression.

Tests for interaction between early (8–11 years) versus later (12–18 years) menarche and menopausal status, BMI (continuous), obesity (BMI >30 kg/m^2), overweight (BMI >25 kg/m^2), smoking status, and physical activity level and the effects on the risk of diabetes were performed in Prentice-weighted Cox regression models adjusted for center, age at recruitment, lifestyle and reproductive factors, and adult BMI. Analyses were performed separately by country and were pooled using random-effects meta-analysis.

To explore whether the association between menarche timing and type 2 diabetes differed according to the age of onset of diabetes, we defined the following two new outcomes: type 2 diabetes diagnosed before age 60 years and type 2 diabetes diagnosed at age 60 years or older. The association between age at menarche and each outcome was then estimated using the methods described, with follow-up censored at age 60 years for the analysis of younger-onset diabetes. All analyses were conducted using Stata version 11.2 (StataCorp, College Station, TX).

RESULTS

Study participant characteristics

Age at menarche was normally distributed in both the InterAct incident type 2 diabetes cases (mean, 13.08 years; SD, 1.73) and subcohort (mean, 13.14 years; SD, 1.58). Women not reporting age at menarche were slightly older at recruitment and weighed more than those included in our analyses. Characteristics of the subcohort by age at menarche are described in Table 1. Those with younger age at menarche tended to be younger at baseline (likely reflecting the secular decline in menarcheal age), heavier, shorter, less active, more educated, and more likely to have higher parity. Overall, the average age at recruitment was 52 years and the mean BMI was 25.7 kg/m^2. Age at diagnosis of type 2 diabetes ranged from 32 to 85 years.

Age at menarche and adult BMI in the InterAct subcohort

Mean ages at recruitment and ages at menarche of the InterAct subcohort stratified

Table 1—*Baseline characteristics of the InterAct subcohort by age at menarche*

Variables	Age at menarche, years						
	8–11	12	13	14	15–18		
	1,392 (14.5)	1,995 (20.8)	2,396 (25.0)	2,166 (22.6)	1,641 (17.1)	*P*	Overall subcohort
Age at recruitment, years	50.1 (8.5)	50.4 (9.1)	51.9 (9.0)	53.5 (8.9)	55.9 (8.7)	**<0.001**	9,590 52.4 (9.1)
Anthropometry							
BMI, kg/m^2	26.8 (4.8)	25.8 (4.5)	25.6 (4.5)	25.4 (4.5)	25.3 (4.2)	**<0.001**	9,526 25.7 (4.5)
BMI at age 20, kg/m^2	22.0 (2.8)	21.7 (2.7)	21.3 (2.7)	21.1 (2.5)	20.8 (2.5)	**<0.001**	3,665 21.3 (2.7)
Waist circumference, cm	82.9 (12.1)	81.1 (11.2)	81.0 (11.0)	80.9 (11.2)	81.0 (11.0)	**<0.001**	9,303 81.3 (11.3)
Height, cm	159.8 (6.5)	161.0 (6.6)	161.4 (6.7)	161.9 (6.9)	162.1 (6.6)	**<0.001**	9,558 161.3 (6.7)
Lifestyle factors, *n* (%)							
Smoking status							
Never	758 (54.5)	1,138 (57.0)	1,309 (54.6)	1,200 (55.4)	937 (57.1)		5,342 (56.0)
Former	297 (21.3)	415 (20.8)	533 (22.3)	466 (21.5)	352 (21.5)		2,063 (21.6)
Current	333 (23.9)	430 (21.6)	542 (22.6)	494 (22.8)	337 (20.5)	0.22	2,136 (22.4)
Physical activity							
Inactive	454 (32.8)	514 (26.0)	660 (27.7)	554 (25.7)	397 (24.4)		2,579 (27.1)
Moderately inactive	487 (35.2)	705 (35.7)	855 (35.9)	795 (36.9)	529 (32.5)		3,371 (35.4)
Moderately active	269 (19.4)	429 (21.7)	474 (19.9)	438 (20.3)	349 (21.4)		1,959 (20.6)
Active	174 (12.6)	327 (16.6)	394 (16.5)	368 (17.1)	355 (21.8)	**0.006**	1,618 (17.0)
Alcohol intake							
0 g/day	291 (24.3)	354 (21.5)	422 (22.5)	354 (21.2)	251 (20.1)		1,672 (21.9)
0.5–10 g/day	686 (57.3)	925 (56.3)	1,033 (55.0)	975 (58.3)	728 (58.3)		4,347 (56.9)
10.5–30 g/day	201 (16.8)	332 (20.2)	389 (20.7)	313 (18.7)	255 (20.4)		1,490 (19.5)
≥30.5 g/day	20 (1.7)	33 (2.0)	35 (1.9)	31 (1.9)	15 (1.2)	0.86	134 (1.8)
Educational level							
None	154 (11.2)	158 (8.0)	213 (8.9)	200 (9.3)	148 (9.1)		873 (9.2)
Primary school	423 (30.7)	591 (29.9)	763 (31.9)	754 (35.0)	585 (35.9)		3,116 (33.0)
Technical/ professional school	277 (20.1)	445 (22.5)	546 (22.9)	509 (23.6)	450 (27.6)		2,227 (23.6)
Secondary school	246 (17.8)	354 (17.9)	382 (16.0)	315 (14.6)	218 (13.4)		1,515 (16.0)
Longer education	262 (19.0)	415 (21.0)	463 (19.4)	362 (16.8)	219 (13.4)	**<0.001**	1,721 (18.2)
Reproductive factors							
Age at first full-term pregnancy, years	24.9 (4.5)	25.0 (4.3)	24.9 (4.3)	24.8 (4.3)	25.0 (4.2)	0.79	8,402 24.5 (4.2)
Parity, *n* (%)							
0	180 (13.1)	286 (14.6)	312 (13.3)	250 (11.7)	191 (11.8)		1,219 (12.9)
1–2	802 (58.5)	1,140 (58.2)	1,360 (57.8)	1,238 (57.9)	887 (54.8)		5,427 (57.5)
≥3	388 (28.3)	534 (27.2)	683 (29.0)	649 (30.4)	540 (33.4)	**0.01**	2,794 (29.6)
Menopausal status							
Premenopausal	575 (42.9)	792 (41.3)	773 (33.4)	615 (29.3)	289 (18.4)		3,044 (32.9)
Perimenopausal	246 (18.3)	351 (18.3)	412 (17.8)	342 (16.3)	235 (15.0)		1,586 (17.2)
Postmenopausal	521 (38.8)	776 (40.4)	1,128 (48.8)	1,139 (54.3)	1,048 (66.7)	0.54	4,612 (49.9)
Use of contraceptive pill							
Ever	803 (57.9)	1,171 (58.9)	1,358 (56.8)	961 (44.5)	772 (47.3)		5,394 (56.4)
Never	583 (42.1)	818 (41.1)	1,033 (43.2)	1,201 (55.6)	861 (52.7)	0.80	4,167 (43.6)
Use of HRT							
Ever	278 (21.5)	425 (23.3)	538 (25.6)	537 (28.1)	446 (31.0)		2,224 (26.0)
Never	1,014 (78.5)	1,398 (76.7)	1,564 (74.4)	1,376 (71.9)	992 (69.0)	0.38	6,344 (74.0)

Data presented as mean (SD) or *n* (%). Overall cohort, *N* = 9,590. *P* for trend across categories of age at menarche was calculated from linear regression analyses adjusted for age at baseline (except for analyses for age at recruitment), center, and country. Results considered statistically significant ($P < 0.05$) are presented in boldface. HRT, hormone replacement therapy.

by country are presented in Table 2. Mean menarcheal age ranged from 12.6 years in Italy to 13.6 years in Sweden and Denmark. Older age at menarche was consistently associated with decreased adult BMI across all countries in the InterAct subcohort (Table 2). Overall, menarche at each year later was associated with 0.32 kg/m^2 lower BMI in adulthood (95% CI, 0.27–0.32; $P < 0.001$). The magnitude of association with estimated BMI at age 20 years (in the five countries that had this information available, Italy, U.K., Germany, Sweden, and Denmark; overall n = 3,665) was smaller, with menarche at each year later conferring 0.21 kg/m^2 lower BMI (95% CI, 0.15–0.26; $P < 0.001$). Heterogeneity across countries was not statistically significant in either analysis.

Age at menarche and type 2 diabetes

The incidence of type 2 diabetes in women with history of early menarche in the InterAct subcohort was 4.3 cases per 1,000 person-years, compared with 2.9 cases per 1,000 person-years in those with the median age at menarche. Menarche at each year later was associated with a 9% lower risk of development of type 2 diabetes in a linear model adjusting for age at recruitment, date of birth, and center (HR, 0.91; 95% CI, 0.88–0.93; $P < 0.001$) (Table 3, model 1). This association was largely unchanged after adjusting for lifestyle and reproductive factors (Table 3, models 2 and 3). Quadratic age at menarche terms were significant ($P < 0.001$). In models using categorical age at menarche, compared with women in the middle category of age at menarche (13 years), the risk of development of diabetes in women in the earliest category (8–11 years) was 70% higher (HR, 1.70; 95% CI, 1.48–1.94; $P < 0.001$) after accounting for potential confounding factors. There also was a less pronounced association with diabetes in women who had menarche at age 12 years compared with the median age (HR, 1.26; 95% CI, 1.10–1.44; $P = 0.001$). In contrast, there did not appear to be a protective effect of older age at menarche in women with menarche between 15 and 18 years (HR, 0.97; 95% CI, 0.84–1.11 in women; $P = 0.63$), suggesting a nonlinear association between menarche timing and diabetes (Fig. 1).

Mediation of the early menarche and type 2 diabetes association by BMI

Adjusting for adult BMI partially reduced the HR for type 2 diabetes in girls with early menarche (8–11 years) compared with a median menarcheal age from 1.70 to 1.42 (95% CI, 1.18–1.71; $P < 0.001$) in models adjusted for all measured potential confounders (Table 3, model 4). Additional inclusion of waist circumference into the model had a negligible effect on these results (model 5). Adjusting for BMI at the age of 20 years, rather than later adult BMI, only modestly attenuated the association between early menarche and diabetes from 1.63 (95% CI, 1.30–2.04) to 1.58 (95% CI, 1.25–2.01) (model 6). In a maximum sample analysis, the addition of adult BMI to the basic model resulted in a similar attenuation in the HR (Table 3, model 7). By country, the association between early menarche (8–11 years compared with all others) and type 2 diabetes was directionally consistent both before and after adjustment for adult BMI, with no detectable heterogeneity (Supplementary Fig. 1).

In mediation analyses in the InterAct subcohort, the estimated HR for type 2 diabetes in girls with early menarche (8–11 years) compared with menarche at older ages (total effect, 1.68; 95% CI, 1.27–2.22) comprised a direct effect of early menarche (HR, 1.33; 95% CI, 1.00–1.78) and an indirect effect mediated by adult BMI (HR, 1.23; 95% CI, 1.18–1.30). Overall, 41% (95% CI, 31–50%) of the higher risk of type 2 diabetes related to early menarche in the InterAct subcohort was attributable to higher adult BMI (Supplementary Table 1).

Interactions with age at menarche

There was no statistically significant interaction between menarcheal age and menopausal status, BMI, obesity status, smoking status, or physical activity level and the effect on the risk of development of type 2 diabetes (data not shown).

Age at menarche association with type 2 diabetes diagnosed before or after age 60 years

The association between early menarche and type 2 diabetes diagnosed at age 60 years or older (HR, 1.67; 95% CI, 1.43–1.95; $P < 0.001$) was comparable with the association with type 2 diabetes diagnosed before age 60 years (HR, 1.64; 95% CI, 1.43–1.89; $P < 0.001$) in a model adjusting for potential confounding factors. For both end points, the association between early menarche and incident diabetes was partially attenuated by adjustment for adult BMI (Supplementary Table 2).

CONCLUSIONS—In a large case-cohort study nested with a large pan-European cohort study, we have demonstrated an association between early menarche and increased risk of type 2 diabetes that was highly consistent across eight European countries. Girls in the youngest category of age at menarche had the highest risk, with women who were between 8 and 11 years at the time of menarche having a 70% higher incidence of future diabetes than women who had menarche at the average age of 13 years. Although these findings are generally consistent with previous reports (6–9,18), the large size of our study allowed us to demonstrate the nonlinear nature of the association and to formally quantify the extent of mediation by higher adult BMI, which explained less than half of the increased diabetes risk associated with early menarche. These findings suggest that early puberty has an effect on metabolic disease risk, which is partly mediated by increased BMI, but also has some direct effect through other biological pathways that act independently of adiposity.

Overall, early menarche conferred a 42% increase in the risk of development of diabetes independently of adult BMI. In contrast to our findings, results from the Nurses' Health Study (NHS) showed that accounting for self-reported BMI collected during follow-up in adulthood completely attenuated the association between early menarche and diabetes risk (18). However, among younger women in NHS-II, the increased risk of type 2 diabetes persisted after adjustment for BMI (18). In the Atherosclerosis Risk in Communities (ARIC) study, adulthood adiposity partially attenuated the association between early menarche and prevalent diabetes and completely attenuated the association with incident diabetes (6). In EPIC-Norfolk, the effect of later menarche on diabetes risk appeared to be completely attenuated after adjustment for adult BMI (7). Such contrasting findings may be attributable to the lower power of these studies to detect the more modest direct association between age at menarche and type 2 diabetes (7), or because of error introduced by using self-reported rather than measured BMI in some of the studies (18). Consistent with our findings, in the KORA F4 study of 1,503 German women, the association between older age at menarche and lower diabetes risk remained significant after adjustment for BMI (9).

The causality of the association between menarche timing and diabetes is

Table 2—*Mean age at menarche by country and its association with adult BMI in the InterAct subcohort*

				Subcohort characteristics			Association between age at menarche and adult BMI		
	N	Mean age at recruitment	SD	Mean age at menarche	SD	Adjusted age at menarche*	Beta (kg/m^2 per +1 year of age at menarche)†	95% CI	*P*
Sweden	1,372	56.2	8.2	13.6	1.4	13.5	−0.31	(−0.47 to −0.14)	<0.001
Denmark	946	56.5	4.3	13.6	1.6	13.5	−0.37	(−0.54 to −0.20)	<0.001
Germany	1,194	48.9	8.9	13.2	1.6	13.1	−0.42	(−0.58 to −0.26)	<0.001
UK	747	55.8	11.2	12.9	1.6	13.3	−0.34	(−0.52 to −0.16)	<0.001
Netherlands	1,199	54.0	9.9	13.4	1.6	13.3	−0.34	(−0.47 to −0.20)	<0.001
France	585	56.3	6.5	12.9	1.4	13.2	−0.30	(−0.51 to −0.09)	0.006
Italy	1,339	50.4	8.0	12.6	1.5	12.9	−0.25	(−0.41 to −0.09)	0.003
Spain	2,218	48.2	8.2	12.9	1.6	12.7	−0.27	(−0.39 to −0.15)	<0.001
Total subcohort	9,590	52.4	9.1	13.1	1.6	13.1	−0.32‡	(−0.38 to −0.27)	<0.001

*Mean age at menarche adjusted for age at recruitment. †Results are from linear regression with adjustment for age at recruitment and center. ‡From a meta-analysis of country-specific results.

unclear. The association between menarche and diabetes may exist because early menarche may be a marker of higher prepubertal BMI, with prolonged effects of increased adiposity being the main risk factor for diabetes. However, girls with earlier puberty have higher weight, height, BMI, and waist circumference measurements in young childhood, and it is highly unlikely that early maturation is associated with adiposity or lean mass alone (27,28). Our results suggest an association between menarche and diabetes risk independent of adult BMI. However, the true nature of this relationship is difficult to determine without information about body size during childhood, which was unavailable in our study. BMI at age 20 years was available in a subset of InterAct participants, which is likely to be a better marker of prepubertal BMI than when assessed in later adulthood. Consistent with some previous reports (8,18), the association between age at menarche and diabetes risk was attenuated to a larger extent when accounting for later adult BMI compared with BMI measured in childhood, adolescence, or early adulthood. This suggests that excess adiposity in later adulthood, a more likely indicator of long-term exposure to being overweight, is more important in the mediation of increased diabetes risk associated with early menarche than BMI earlier in life. In further support of this, one study has shown that the association between menarche and increased adult BMI is not explained by higher prepubertal BMI (29).

Using genetic variation at *LIN28B*, which is associated with age at menarche but not prepubertal BMI, we previously provided evidence for a possible direct effect of puberty timing on adiposity in young adult life in women (30). Our findings of a consistent association between early menarche and diabetes in women diagnosed at ages older than and younger than 60 years support the finding that puberty timing has a long-lasting effect on metabolic health. Findings from the NHS showed that there was a stronger association between early menarche and diabetes in younger women (younger than 45 years) compared with older women (45 years or older). Because our participants were older at recruitment, we did not have sufficient cases to explore the association between menarche timing and diabetes diagnosed at this particularly young age.

The strengths of this study lie in the large scale and the prospective nature of InterAct, together with the heterogeneity in age at menarche across eight European countries, the accurate assessment of BMI, and comprehensive consideration of a range of confounding factors. The high number of verified incident diabetes cases incorporated using the case-cohort design make this study a powerful resource to address questions relating to diabetes etiology. Our prospective analysis of incident cases of type 2 diabetes avoids the problem of reverse causality, whereby insulin resistance during early life may increase the tempo of development (31).

Limitations of this study include the fact that age at menarche was recalled in adulthood and was only recorded to the nearest year. However, age at menarche assessed by recall during adulthood has shown high correlations with prospectively assessed childhood data (1,32). Furthermore, any misclassification would be expected to be nondifferential with respect to type 2 diabetes status and therefore cause an underestimation of the true association. It is likely that BMI may not adequately account for adiposity, because it does not differentiate between fat and fat-free mass. However, accounting for waist circumference, which is a better indicator of central adiposity, made little difference in our findings. Furthermore, results from the Framingham Heart Study have shown that BMI appears to be a good marker of differences in body composition (33). Body weight at age 20 years was assessed by recall and is likely to introduce error rather than bias, therefore leading to an underestimation of the true association. However, in the NHS recalled body weight at age 18 years was highly correlated with measured weight (Pearson coefficient r = 0.96) (34), so the degree of error may be small. Finally, although we considered a wide range of potential confounders, it is possible that imprecision in measurement could lead to residual confounding, and there remains the possibility of confounding by other unconsidered factors.

Mechanisms explaining the direct relationship between pubertal timing and later metabolic risk are not well understood. We and others identified *LIN28B* as the first genetic locus to be robustly associated with age at menarche (35). Mice that overexpress *Lin28*, a homolog of this gene, exhibit both later pubertal maturation and increased glucose uptake (36). In addition, they are resistant to obesity and type 2 diabetes when placed on a high-fat diet (36). This shows a direct link between genes controlling puberty timing

Table 3—*Age at menarche and HRs for type 2 diabetes in the InterAct study*

		Age at menarche															
		8–11 years			12 years			13 years	14 years			15–18 years			Per +1 year age at menarche		
Model	*n* (cases)	HR	95% CI	*P*	HR	95% CI	*P*	Ref.	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Model 1	15,168																
Basic*	(5,955)	1.64	(1.51–1.78)	<0.001	1.20	(1.1–1.31)	<0.001	1.00	0.97	(0.88–1.07)	0.52	0.97	(0.89–1.05)	0.47	0.91	(0.88–0.93)	<0.001
Model 2 (model 1 + lifestyle factors)																	
Basic*	14,731	1.65	(1.47–1.85)	<0.001	1.23	(1.11–1.36)	<0.001	1.00	0.99	(0.89–1.09)	0.78	1.00	(0.89–1.12)	0.98	0.91	(0.88–0.94)	<0.001
Adjusted†	(5,762)	1.64	(1.46–1.85)	<0.001	1.25	(1.12–1.39)	<0.001	1.00	0.97	(0.87–1.08)	0.58	0.97	(0.87–1.09)	0.63	0.90	(0.88–0.93)	<0.001
Model 3 (model 2 + reproductive factors)																	
Basic*	10,903	1.70	(1.49–1.94)	<0.001	1.25	(1.10–1.42)	0.001	1.00	0.96	(0.85–1.09)	0.53	1.00	(0.87–1.14)	0.94	0.90	(0.88–0.93)	<0.001
Adjusted‡	(4,242)	1.70	(1.48–1.94)	<0.001	1.26	(1.10–1.44)	0.001	1.00	0.95	(0.83–1.07)	0.37	0.97	(0.84–1.11)	0.63	0.89	(0.86–0.93)	<0.001
Model 4 (model 3 + adult BMI)																	
Basic*	10,832	1.70	(1.49–1.94)	<0.001	1.24	(1.08–1.42)	0.002	1.00	0.96	(0.84–1.09)	0.54	1.01	(0.88–1.15)	0.94	0.90	(0.88–0.93)	<0.001
Adjusted§	(4,215)	1.42	(1.18–1.71)	<0.001	1.23	(1.02–1.47)	0.03	1.00	1.03	(0.88–1.21)	0.70	1.18	(1.01–1.38)	0.04	0.96	(0.91–1.01)	0.11
Model 5 (model 4 + waist circumference)																	
Basic*	10,542	1.71	(1.50–1.96)	<0.001	1.28	(1.13–1.45)	<0.001	1.00	1.00	(0.88–1.12)	0.94	1.02	(0.89–1.16)	0.80	0.90	(0.88–0.93)	<0.001
Adjusted¶	(4,070)	1.43	(1.21–1.68)	<0.001	1.27	(1.08–1.48)	0.003	1.00	1.03	(0.88–1.21)	0.69	1.15	(0.97–1.36)	0.10	0.95	(0.91–1.00)	0.056
Model 6 (model 3 + BMI at age 20)																	
Basic*	4,065	1.63	(1.30–2.04)	<0.001	1.10	(0.85–1.42)	0.46	1.00	0.89	(0.73–1.07)	0.22	0.98	(0.80–1.20)	0.84	0.92	(0.88–0.96)	<0.001
Adjusted‖	(1,669)	1.58	(1.25–2.01)	<0.001	1.06	(0.81–1.39)	0.96	1.00	0.87	(0.71–1.07)	0.18	0.99	(0.80–1.22)	0.91	0.92	(0.86–0.98)	0.007
Model 7 (model 1 + adult BMI)																	
Basic*	15,066	1.64	(1.46–1.83)	<0.001	1.20	(1.08–1.33)	<0.001	1.00	0.98	(0.89–1.09)	0.70	0.99	(0.88–1.10)	0.79	0.91	(0.88–0.94)	<0.001
Adjusted**	(5,913)	1.35	(1.15–1.58)	<0.001	1.18	(1.01–1.38)	0.04	1.00	1.03	(0.91–1.17)	0.64	1.14	(1.00–1.30)	0.05	0.97	(0.93–1.01)	0.09

Results are presented for both categorized age at menarche (with age 13 years as the reference group) and linear models (per +1 year age at menarche). Results are from Prentice-weighted Cox regression models stratified by country and combined using random-effects meta-analysis. For each model, the basic model represented only those individuals with nonmissing data for all covariates in the model. *Basic models were adjusted for age at recruitment, date of birth, and center. †Additionally adjusted for lifestyle factors (smoking status, physical activity level, alcohol intake, and educational level). ‡Additionally adjusted for reproductive factors (age at first full-term pregnancy, parity, menopausal status, use of oral contraceptive pill, use of hormone replacement therapy). §Additionally adjusted for lifestyle factors, reproductive factors, and adult BMI. ¶Additionally adjusted for lifestyle factors, reproductive factors, adult BMI, and waist circumference. ‖Additionally adjusted for lifestyle factors, reproductive factors, and estimated BMI at age 20 years. **Additionally adjusted for adult BMI only. Ref, reference.

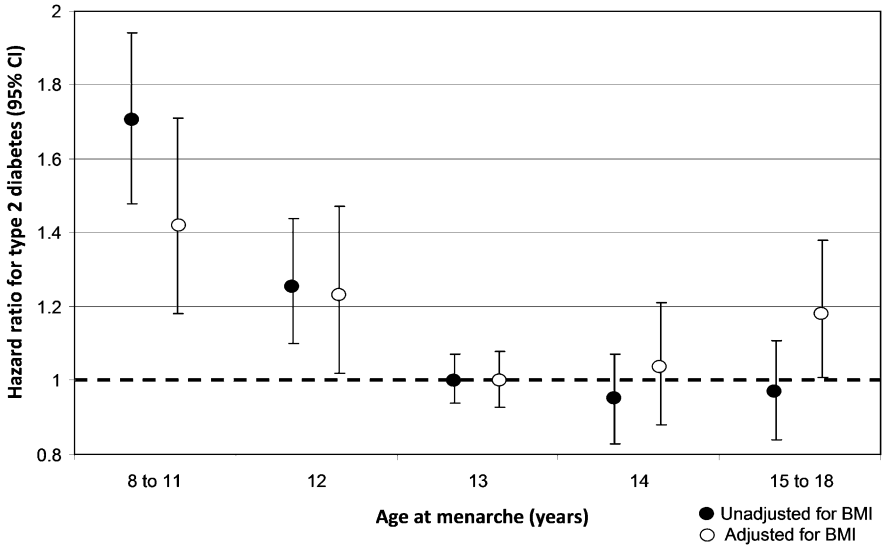

Figure 1—*HRs for type 2 diabetes by category of age at menarche in the EPIC-InterAct study. Results presented are HRs for diabetes in each group compared with the reference category (13 years, representing the median age at menarche). Results are from Prentice-weighted Cox regression models performed within each country participating in InterAct and pooled using the random-effects meta-analysis. Models are adjusted for age at recruitment, date of birth, center, and lifestyle and reproductive factors (●), and with additional adjustment for adult BMI (○).*

and glucose homeostasis and provides a possible mechanistic link between puberty and diabetes risk. Metabolic disease may be linked to differential exposure to sex hormones; early menarche is associated with higher level of sex hormones (37) and decreased levels of sex hormone–binding globulin (38), which may have a role in the pathogenesis of type 2 diabetes (39).

In conclusion, women with younger than average age at menarche are more likely to develop type 2 diabetes, and this association is only partially explained by higher adult BMI. In contrast, women with older than average age at menarche have no reduction in diabetes risk. Although avoidance of adult overweight and obesity may attenuate the risk of type 2 diabetes in women with early menarche, our findings suggest that strategies to prevent early menarche may be important in their own right.

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