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Reproductive history and risk of type 2 diabetes mellitus in postmenopausal women: Findings from the Women's Health Initiative

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Abstract

Objective—To understand the association between women's reproductive history and their risk of developing type 2 diabetes. We hypothesized that characteristics signifying lower cumulative endogenous estrogen exposure would be associated with increased risk.

Methods—Prospective cohort analysis of 124,379 postmenopausal women aged 50–79 from the Women's Health Initiative. We determined age of menarche and final menstrual period, and

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Author Contributions

ESL contributed to the study conception, design, and interpretation of results, and developed the first draft of the manuscript. KK, HH, and MD contributed to the study conception and design, researched and analyzed the data, contributed to interpretation of results, and reviewed/edited the manuscript. The remaining authors contributed to the study conception and design and reviewed/edited the manuscript. The final draft for submission was approved by all authors. ESL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

history of irregular menses from questionnaires at baseline, and calculated reproductive length from age of menarche and final menstrual period. Presence of new onset type 2 diabetes was from self-report. Using multivariable Cox proportional hazards models, we assessed associations between reproductive variables and incidence of type 2 diabetes.

Results—In age-adjusted models, women with the shortest (<30 years) reproductive periods had a 37% (95% CI = 30–45%) greater risk of developing type 2 diabetes than women with medium-length reproductive periods (36 to 40 years). Women with the longest (45+ years) reproductive periods had a 23% (95% CI = 12–37%) higher risk than women with medium-length periods. These associations were attenuated after full adjustment (HR of 1.07 [1.01, 1.14] for shortest and HR of 1.09 [0.99, 1.22] for longest, compared to medium duration). Those with a final menstrual period before age 45 and after age 55 had an increased risk of diabetes (HR 1.04, 95% CI 0.99, 1.09 and HR 1.08, 95% CI 1.01, 1.14, respectively) compared to those with age of final menstrual period between 46 and 55. Timing of menarche and cycle regularity were not associated with risk after full adjustment.

Conclusions—Reproductive history may be associated with type 2 diabetes risk. Women with shorter and longer reproductive periods may benefit from lifestyle counseling to prevent type 2 diabetes.

Keywords

Diabetes; menopause; menarche; cycle regularity; reproductive risk duration

Introduction

In animal models, oophorectomy leads to visceral obesity and development of metabolic syndrome.[1] In vitro, estrogens have been shown to have metabolic actions on skeletal muscle, pancreas, adipose tissue, and the central nervous system.[1] In particular, low levels of estrogen tend to adversely affect body fat distribution and accumulation, appetite, energy expenditure, insulin secretion, and glucose homeostasis,[1,2] critical contributors to the development of type 2 diabetes. In humans, however, exogenous estrogen has been associated with reversal of these symptoms, including positive effects on body fat and energy expenditure, and prevention of diabetes,[1,3–5] although exogenous estrogen may have different effects due to the different route, dose and timing of administration.[6]

Reproductive factors such as age of menarche, age of menopause, and cycle irregularity can serve as proxies for endogenous estrogen exposure. Earlier age of menarche and later age of menopause have been associated with an increased risk of insulin resistance and type 2 diabetes in some,[7–11] but not all,[12,13] studies. A history of bilateral oophorectomy, which would result in a shortened reproductive period, and earlier menopause, have also been associated with less favorable glucose and insulin levels,[14,15] and increased risk of type 2 diabetes in some,[13,16] but not all,[12,17–20] studies. Menstrual cycle characteristics such as length and regularity of menstrual cycle have also been associated with gestational diabetes and glucose intolerance in some,[21–23] but not all,[13,24] studies.

Many of these previous studies were limited by small sample sizes and lack of rigorous, prospective ascertainment of type 2 diabetes. Because of its large size, robust characterization of participants' reproductive history, long duration of follow-up, and prospective ascertainment of diabetes, the Women's Health Initiative provides a unique setting to evaluate the association between reproductive characteristics and type 2 diabetes. In the current study, we examined the hypothesis that reproductive-factor characteristics consistent with lower lifelong endogenous estrogen (shorter reproductive period over the lifetime and history of irregular menses) would be associated with increased risk of type 2 diabetes.

Methods

Study population

The Women's Health Initiative (WHI) is a large, multicenter study evaluating effects of postmenopausal hormone therapy, diet modification, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer, as well as factors contributing to cardiovascular disease, cancer, osteoporosis (the most common causes of death, disability, and poor quality of life in this population). The study has been described in detail previously.[25,26] Briefly, postmenopausal women between 50 and 79 years of age who were accessible for follow-up, with a minimum life expectancy of 3 years, were recruited between September 1, 1993, and December 31, 1998, at 40 clinical sites. The WHI clinical trials enrolled a total of 68,132 women, and 93,676 were enrolled in an observational study. The clinical trials (CTs) were designed to test the effects of postmenopausal hormone therapy, dietary modification, and calcium and vitamin D supplements on cardiovascular disease, fractures, and breast and colorectal cancer. The observational study (OS) enrolled women who were recruited but did not meet eligibility criteria for or did not wish to participate in one of the randomized trials. All clinical centers obtained institutional review board approval, and all women provided written informed consent.

In this study, all CT and OS women were included except those who reported a history of diabetes at baseline. Women who were missing the outcome, any of the exposure variables, or the covariates included in our models were excluded from the primary analyses.

Data collection

Full details of data collection have been published previously.[25] Briefly, at baseline, participants completed questionnaires on demographics, medical and family history, and various lifestyle factors such as physical activity. Height, weight, and waist circumference were measured by trained clinic staff and used to determine body mass index (BMI). At baseline and some follow-up visits, participants were asked to bring all current, regularly taken medications (prescription and over-the-counter) to their clinic visits. After 2005, women were asked to complete the medication inventory by mail. Clinic interviewers entered each medication name and strength directly from the containers into a computer-driven medication system that assigned drug codes using Medi-Span software (First DataBank, Inc., San Bruno, CA).

Ascertainment of reproductive exposures

Information on reproductive history was collected using a questionnaire at baseline (from 1993–1998). Participants were asked about age at menarche ("*how old were you when you had your first menstrual period [menses]?*"), age at final menstrual period ("*how old were you when you last had regular menstrual bleeding [a period]?*"), history of irregular periods ("*during most of your life, were your periods regular; that is, did they occur about once a month? [Do not include any time when you were pregnant or taking birth control pills.]*"), surgical menopause history, and number of pregnancies. Reproductive-period duration (in years) was determined by subtracting age of menarche from age at final menstrual period.

Identification of women with type 2 diabetes

The primary outcome for this study was new diagnosis of diabetes. Diabetes status was determined through medical histories and medication inventories. Participants were asked at baseline and annually, "*Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?*" In addition, they were asked, "*Since the date given on this form, has a doctor prescribed any of the following pills or treatments?*" Choices included "*pills for diabetes*" and "*insulin shots for diabetes*." Diabetes diagnosis was further identified through use of diabetes medications on the medication inventory. This definition has been validated in the WHI study and is consistent with medication inventories and fasting glucose measurements.[27]

Women in the study were followed from randomization (CT) or enrollment (OS) until the first time they responded yes to these three questions. Participants who did not develop diabetes during the period of study were censored at last study follow-up. Participants who died were censored at death.

Measurement of covariates

Considered covariates include baseline information on age (50–54, 55–59, 60–69, 70–79), race (white, Hispanic, black, other), BMI (<18.5, 18.5 to <25, 25 to <30, >=30 kg/m2), waist circumference (cm), education (less than high school, high school, college), marital status (never married, marriage-like relationship, presently married, divorced or separated, widowed), physical activity (baseline MET-min/week: <100; 100–500; 500–1200; >1200), smoking status (never/past/current smoker), alcohol use (<1 drink/week, 1–3 drinks/week, >3 drinks/week), hormone therapy (HT) intervention arm (not randomized to HT; estrogen plus progestin (E+P) intervention; E+P control; E-alone intervention; E alone control), postmenopausal HT use (never, past, now), oral contraceptive use (yes, no), metformin use (yes, no), family history of diabetes, years since final menstrual period, and number of full-term pregnancies (none, 1–2, >3).

Incidence of diabetes outcome

The primary outcome of this study was a new diagnosis of diabetes; women with a previous diagnosis of diabetes were excluded from analyses.

Exposure variables

The primary exposure was reproductive-period duration over a lifetime (age of final menstrual period minus age at menarche in years). This was examined both as a continuous variable and categorical variable categorized by length in years (<30, 30–35, 36–40, 41–45, 45+). These categories were chosen to be clinically meaningful and equally spaced. Secondary exposures included history of irregular periods (not regular, sometimes regular, regular), menarche timing by age (<12, 12, >12),[28,29] and timing of final menstrual period by age (<45, 45–55, and >55).[28,30]

Statistical analysis

Means and standard deviations or frequency distributions were calculated for baseline variables by categories of the reproductive-period duration categories. We examined Kaplan-Meier curves displayed by categories of the reproductive-period duration for time-to-event outcomes with censoring.

Cox proportional hazards techniques were used to estimate unadjusted and age-adjusted associations between the reproductive-period duration and incidence of type 2 diabetes. We also fit multivariable models to obtain effects adjusted for important covariates: age, race, baseline BMI, HT intervention arm membership, baseline physical activity, baseline alcohol consumption, baseline smoking history, education, baseline marital status, number of term pregnancies, family history of diabetes, years since final menstrual period at baseline, baseline waist circumference, ever use of oral contraceptives at baseline, and baseline metformin use. We also conducted analyses to separately assess the association of the age of menarche, age at final menstrual period, and cycle irregularity with risk of type 2 diabetes. Kaplan-Meier curves were used to check the assumption of proportional hazards. All tests were two-sided and conducted at the alpha=0.05 level of significance.

Because of their potential to modify the association between reproductive history and diabetes risk, we evaluated whether the following variables were effect modifiers: number of pregnancies (0, 1–2, 3+), baseline BMI category (0–18.5, 18.5– 25, 25–<30, ≥30 kg/m^2), postmenopausal HT use (ever vs. never), randomization to hormone therapy arm (yes or no), type of menopause (surgical [hysterectomy and/or oophorectomy] vs. natural), family history of diabetes (yes or no), randomization to dietary modification arm (yes or no), and randomization to calcium and vitamin D arm (yes or no). The variables considered as potential effect modifiers were specified *a priori*. We added a statistical interaction term between each potential effect modifier and the exposure of interest to the models. We did not adjust for multiple comparisons, as these analyses were exploratory in nature and need careful interpretation and subsequent follow-up.

In a sensitivity analysis, we included women who had missing exposure or confounder variables and refit the primary models using multiple imputations via the predictive mean matching method. All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Description of cohort

Of the 161,808 participants in the OS and CT cohorts, 9,728 were excluded because of a history of diabetes at baseline, 21,479 were missing confounding covariates, and 6,224 were missing outcome or exposure data. This left an analytic cohort of 124,379 participants for the primary analysis (Figure 1). Also, data from 152,080 women were used to fit the models using multiple imputations in the sensitivity analysis, where we included women missing exposure or confounder variables. Women were followed for a mean (SD) of 12.2 (4.2) years. The unadjusted incidence of diabetes was 7.4/1,000 person-years.

Baseline characteristics

Baseline characteristics by reproductive duration category are shown in Table 1. Compared to women with shorter reproductive durations, women with the longest reproductive-period duration were older at the baseline visit and less likely to be Black. They had achieved a higher education level, were less likely to be past or current smokers, were more physically active, and drank more alcoholic beverages per week. The association between reproductive period and BMI and waist circumference was U-shaped, with those with the shortest and longest reproductive period having higher BMIs and waist circumference compared to those with mid-range reproductive lengths. Women with shorter reproductive-period duration were more likely to have undergone surgical menopause and more likely to be current or past users of HT. Women with longer reproductive-period duration were less likely to have ever used oral contraceptives. Very few had used metformin as it was not approved by the FDA for diabetes until 1994. About one-third had a family history of diabetes. Women with longer reproductive-period durations had more term pregnancies. Those with shorter reproductive duration had more irregular cycles. As expected, women with longer reproductive-period duration were more likely to have had an early menarche and a late menopause. Women with longer reproductive-period duration had been menopausal for a shorter amount of time before study entry.

Reproductive-period duration and type 2 diabetes risk

Over 974,714 person-years of follow-up, 11,262 women reported new diagnoses of type 2 diabetes mellitus. In Cox-proportional hazards models, there was a statistically significant association between reproductive-period duration and type 2 diabetes risk (fully adjusted $p=0.04$). The relationship was U-shaped in that women with both the shortest (<30 years), and longest (more than 45 years) reproductive-period durations were at higher risk of developing type 2 diabetes during the study period than those with reproductive-period durations in the middle (36–40 years) (Figure 2A). In age adjusted models, women with the shortest reproductive-period durations (<30 years) had a 37% (HR 1.37, 95% CI 1.30, 1.45) increased risk of developing type 2 diabetes relative to women whose reproductive-period durations were in the middle (36–40 years) (Table 2). After adjustment for multiple covariates, women with the shortest reproductive-period durations still had a significantly greater risk of developing type 2 diabetes than those with reproductive-period durations in the middle, although the risk estimates were somewhat attenuated (HR 1.07; 95% CI 1.01, 1.14).

Compared to women whose reproductive-period durations were in the middle (36–40 years), women with the longest reproductive-period durations (more than 45 years) had a 23% (HR 1.23; 95% CI 1.12, 1.37) increased risk of type 2 diabetes in age-adjusted models. After full adjustment, women with the longest reproductive-period durations had a 9% (HR 1.09 95% CI 0.99, 1.21) greater risk of type 2 diabetes than those with reproductive durations in the middle.

As with reproductive-period duration, the association between menopausal timing and risk of type 2 diabetes was U-shaped (Table 2; fully adjusted p=0.02). Women who experienced their final menstrual period before 46 years of age as well as those who experienced their final menstrual period after age 55 were at higher risk of developing type 2 diabetes during the study period compared to those who had a final menstrual period between ages 46 and 55. In age-adjusted models, those who experienced their final menstrual period before age 46 were 25% (HR 1.25, 95% CI 1.20, 1.30) more likely to develop type 2 diabetes than those experiencing their final menstrual period between the ages of 46 and 55. Those who had their final menstrual period after age 55 were 12% (HR 1.12, 95%CI 1.06, 1.18) more likely to develop type 2 diabetes than those with a final menstrual period occurring between ages 46 and 55. After full adjustment for additional covariates, the risk estimates for the development of type 2 diabetes remained elevated for both those with a final menstrual period before age 45 (HR 1.04, 95% CI 0.99, 1.09) and those with a final menstrual period after age 55 (HR 1.08, 95% CI 1.01, 1.14) compared to those with final menstrual periods between ages 46 and 55.

Lower age at menarche was associated with an increased risk of developing type 2 diabetes in age adjusted models (Table 2). Women who experienced menarche before age 12 had an increased risk of type 2 diabetes in age-adjusted models (HR 1.14 95% CI 1.08, 1.20) compared to those who experienced menarche at age 12. On the other hand, women with menarche after 12 years of age had a decreased risk of type 2 diabetes in age-adjusted (HR 0.93 95% CI 0.89, 0.97) models compared to those who experienced menarche at 12 years of age. However, the associations were no longer significant after full adjustment (HR 1.01 95% CI 0.95, 1.06 and HR 0.99 95% CI 0.95, 1.04 for menarche at <12 years and >12 years, respectively).

History of irregular cycles was associated with risk of developing type 2 diabetes (Figure 2B). In age-adjusted models, women with irregular cycles had an 11% increased risk of type 2 diabetes compared to women with regular cycles (Table 2; HR 1.11 95% CI = 1.04, 1.19). However, cycle regularity was no longer associated with type 2 diabetes risk after full adjustment (fully adjusted p=0.46). After full adjustment, women with irregular cycles no longer had a significantly increased risk of developing diabetes (HR 1.04 95% CI = 0.97, 1.11) compared to women with regular cycles.

In a sensitivity analysis, we found that the results did not change when we used multiple imputed data instead of excluding women who were missing data. We examined several effect modifiers including number of previous pregnancies, age at first birth, menopause type (surgical vs. natural), BMI, postmenopausal HT use, randomization to HT arm, family history of diabetes, randomization to diet modification trial arm, and randomization to

calcium/vitamin D trial arm (data not shown). No effect modifiers were found to be statistically significant.

Discussion

As hypothesized, we found that women with short reproductive-period durations (<30 years) had an increased risk of type 2 diabetes compared to women whose reproductive durations were in the middle (36–40 years). Surprisingly, women with long (>45 years) reproductive-period durations were also more likely to develop type 2 diabetes. When the components of reproductive-period duration were examined separately, age at final menstrual period, not age at menarche, was associated with type 2 diabetes risk, in a U-shaped pattern similar to the association with reproductive-period duration. Women with irregular cycles were not at greater risk of developing diabetes.

These findings have important implications given the high prevalence of type 2 diabetes in postmenopausal women. Among adults in the United States, the estimated overall prevalence of diabetes ranges from 5.8% to 12.9% (median 8.4%).[31] Therefore, the increased risk associated with reproductive characteristics noted in this study (4%–9% for the fully adjusted models and 14%–37% for the age-adjusted models) could have significant clinical impact. Indeed, the absolute risk increase for women with a long reproductive period (>45 years) was 1.6 events per 1000 person-years, and the absolute risk increase for those with a short reproductive period (<30 years) was 2.5 events per 1000 person-years. This suggests important public health benefits to targeting modifiable risk factor reduction advice to women whose reproductive history suggests they may be at greater risk for developing type 2 diabetes.

Our finding that a shorter reproductive duration and earlier menopause were associated with increased type 2 diabetes risk is consistent with a previous report from Europe. In that nested, prospective case-cohort study of more than 8,000 postmenopausal women followed for 11 years, there was a 6% increased risk of type 2 diabetes per standard deviation of lower reproductive lifespan in years.[16] Shorter reproductive period is a marker for decreased exposure to endogenous estrogens over the lifetime. Estrogens help long term to preserve insulin secretion and glucose homeostasis.[1,2] Low estrogen negatively affects body fat distribution and fat accumulation,[1,2] important contributors to type 2 diabetes risk. Adipokines could also be contributing to the association. Adiponectin has been inversely associated with estradiol levels.[32] Adiponectin, an adipocyte-derived cytokine, has been associated with better glycemic control and reduced inflammation in persons with diabetes.[33] Low adiponectin levels have been associated with the development of insulin resistance and development of type 2 diabetes.[34]

On the other hand, later age of menopause, which leads to longer reproductive-period durations, has not previously been associated with an increased risk of type 2 diabetes.[12,13] We found that having more pregnancies, which would be associated with higher lifetime estrogen exposure, further increased risk of type 2 diabetes in those with long reproductive-period durations. Exogenous estrogen has been associated with unfavorable effects on carbohydrate metabolism.[2] Previous prospective cohorts of both men and postmenopausal

women have found that high endogenous estrogen levels are associated with increased type 2 diabetes risk.[35] Low sex hormone-binding globulin (SHBG), which leads to increases in free estradiol, has also been associated with increased diabetes risk.[6] Postmenopausal estrogen therapy has been associated with a deterioration of glucose tolerance.[36,37] Therefore, we are expanding our original hypothesis to be that not only lower, but also higher, cumulative endogenous estrogen exposure leads to adverse effects on insulin and glucose levels and the development of type 2 diabetes. Such "U" shaped associations have been seen with other cardiovascular disease risk factors such as blood pressure and alcohol use.[38,39]

Unlike other studies,[7–11] we did not find that earlier age at menarche was associated with an increased risk of type 2 diabetes. Our cutoffs for age of menarche differed slightly from other studies, which could have influenced our null findings. Earlier age of menarche has been previously associated with earlier age of final menstrual period, which is why we controlled for years since final menstrual period.[40] While some previous studies included menopausal status, none took into account age of final menstrual period and, as a result, their results may have been confounded by age of final menstrual period.

We also did not find that cycle irregularity was associated with type 2 diabetes risk in fully adjusted models. This was surprising given that women with polycystic ovarian syndrome (PCOS), which is characterized by irregular cycles, have been shown to have an increased risk of type 2 diabetes. We hypothesize that since women with polycystic ovary syndrome have a substantially earlier age of type 2 diabetes onset (third to fourth decades) than in the general population (sixth to seventh decades),[41] many women with PCOS may have developed type 2 diabetes prior to the start of the observation period (and thus were ineligible for the study).

Our study had several strengths. We prospectively followed women for the diagnosis of diabetes, which was based on medical history and medication inventory. We had a large sample size, which gave us sufficient power to detect important associations. Although we excluded women who were missing confounder data in the primary analysis, we included all women in a sensitivity analysis using multiple imputations to avoid potential bias due to missing data.

Our study also had several limitations. In particular, women were asked to recall age of menarche and cycle irregularity, which occurred in what they may have considered the distant past and could have resulted in measurement error. However, we would not expect differential recall between groups. Because medically diagnosed diabetes was not available for all WHI women and we did not have data on glucose measurements at baseline or follow-up, we used self-reported diabetes; however, self-reports of "treated diabetes" in WHI have been shown to be sufficiently accurate to allow use in epidemiologic studies such as this one.[27] We used the date that a woman reported diabetes instead of the date of diabetes diagnosis, which was not available. We did not evaluate the effects of several other factors that could be associated with diabetes risk, including PCOS, infertility, lactation, or gestational diabetes.

Conclusion

Our study found that both shorter and longer reproductive-duration lengths are associated with increased risk of type 2 diabetes. This suggests that lifetime estrogen exposure may play a role in the development of type 2 diabetes—there may be an “optimal” amount of estrogen exposure for metabolic functioning, although exogenous estrogen may have different effects due to different route, dose and timing of administration.[6] If other prospective studies confirm these findings, future research should focus on possible mechanisms in order to determine ways to prevent type 2 diabetes as women age. Understanding who is at risk for type 2 diabetes is important because preventive measures such as weight loss, improved dietary quality and increased exercise can decrease risk. Endogenous sex hormones had previously been thought to be markers of adiposity. However, this study adds to the growing literature suggesting that endogenous sex hormone biomarkers could potentially add predictive risk information above and beyond obesity. Reproductive period length and age of final menstrual period may be important factors to add to the risk pool when counseling women about their risk of diabetes and the need to make lifestyle changes.

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References

1. Cignarella A, Bolego C. Mechanisms of Estrogen Protection in Diabetes and Metabolic Disease. Hormone Molecular Biology and CLinical Investigation. 2011; 4(2):575–580.
2. Godsland IF. Oestrogens and insulin secretion. Diabetologia. 2005; 48(11):2213–2220. [PubMed: 16193292]
3. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia. 2004; 47(7):1175–1187. [PubMed: 15252707]
4. Pentti K, Tuppurainen MT, Honkanen R, et al. Hormone therapy protects from diabetes: the Kuopio osteoporosis risk factor and prevention study. Eur J Endocrinol. 2009; 160(6):979–983. [PubMed: 19321660]
5. Rossi R, Origliani G, Modena MG. Transdermal 17-beta-estradiol and risk of developing type 2 diabetes in a population of healthy, nonobese postmenopausal women. Diabetes Care. 2004; 27(3): 645–649. [PubMed: 14988279]
6. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006; 295(11):1288–1299. [PubMed: 16537739]
7. He C, Zhang C, Hunter DJ, et al. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. Am J Epidemiol. 2010; 171(3):334–344. [PubMed: 20026580]

8. Lakshman R, Forouhi N, Luben R, et al. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. Diabetologia. 2008; 51(5):781–786. [PubMed: 18320165]
9. Stockl D, Doring A, Peters A, et al. Age at menarche is associated with prediabetes and diabetes in women (aged 32–81 years) from the general population: the KORA F4 Study. Diabetologia. 2012; 55(3):681–688. [PubMed: 22170465]
10. Dreyfus JG, Lutsey PL, Huxley R, et al. Age at menarche and risk of type 2 diabetes among African-American and white women in the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2012; 55(9):2371–2380. [PubMed: 22760786]
11. Elks CE, Ong KK, Scott RA, et al. Age at menarche and type 2 diabetes risk: the EPIC-InterAct study. Diabetes Care. 2013; 36(11):3526–3534. [PubMed: 24159179]
12. Qiu C, Chen H, Wen J, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. J Clin Endocrinol Metab. 2013; 98(4):1612–1621. [PubMed: 23471979]
13. Heianza Y, Arase Y, Kodama S, et al. Effect of postmenopausal status and age at menopause on type 2 diabetes and prediabetes in Japanese individuals: Toranomon Hospital Health Management Center Study 17 (TOPICS 17). Diabetes Care. 2013; 36(12):4007–4014. [PubMed: 24170752]
14. Kritz-Silverstein D, Barrett-Connor E, Wingard DL. Hysterectomy, oophorectomy, and heart disease risk factors in older women. Am J Public Health. 1997; 87(4):676–680. [PubMed: 9146454]
15. Pirimoglu ZM, Arslan C, Buyukbayrak EE, et al. Glucose tolerance of premenopausal women after menopause due to surgical removal of ovaries. Climacteric. 2011; 14(4):453–457. [PubMed: 21271939]
16. Brand JS, van der Schouw YT, Onland-Moret NC, et al. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. Diabetes Care. 2013; 36(4):1012–1019. [PubMed: 23230098]
17. Monterrosa-Castro A, Blumel JE, Portela-Buelvas K, et al. Type II diabetes mellitus and menopause: a multinational study. Climacteric. 2013; 16(6):663–672. [PubMed: 23617887]
18. Di Donato P, Giulini NA, Bacchi Modena A, et al. Risk factors for type 2 diabetes in women attending menopause clinics in Italy: a cross-sectional study. Climacteric. 2005; 8(3):287–293. [PubMed: 16397927]
19. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod. 2003; 18(1):199–206. [PubMed: 12525467]
20. Kim C, Edelstein SL, Crandall JP, et al. Menopause and risk of diabetes in the Diabetes Prevention Program. Menopause. 2011; 18(8):857–868. [PubMed: 21709591]
21. Dishi M, Enquobahrie DA, Abetew DF, Qiu C, Rudra CB, Williams MA. Age at menarche, menstrual cycle characteristics and risk of gestational diabetes. Diabetes Res Clin Pract. 2011; 93(3):437–442. [PubMed: 21816498]
22. Brower M, Brennan K, Pall M, Azziz R. The severity of menstrual dysfunction as a predictor of insulin resistance in PCOS. J Clin Endocrinol Metab. 2013; 98(12):E1967–E1971. [PubMed: 24092831]
23. Morrison JA, Glueck CJ, Daniels S, Wang P, Stroop D. Ramifications of adolescent menstrual cycles >/=42 days in young adults. Fertil Steril. 2011; 96(1):236–240. [PubMed: 21550045]
24. Solomon CG, Hu FB, Dunaif A, et al. Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. JAMA. 2001; 286(19):2421–2426. [PubMed: 11712937]
25. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. Ann Epidemiol. 2003; 13(9 Suppl):S5–S17. [PubMed: 14575938]
26. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol. 2003; 13(9 Suppl):S18–S77. [PubMed: 14575939]
27. Margolis KL, Lihong Q, Brzyski R, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials. 2008; 5(3):240–247. [PubMed: 18559413]

28. Weinstein M, Gorrindo T, Riley A, et al. Timing of menopause and patterns of menstrual bleeding. Am J Epidemiol. 2003; 158(8):782–791. [PubMed: 14561668]
29. Yermachenko A, Dvornyk V. Nongenetic determinants of age at menarche: a systematic review. Biomed Res Int. 2014; 2014:371583. [PubMed: 25050345]
30. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas. 1992; 14(2):103–115. [PubMed: 1565019]
31. Beckles GL, Chou CF. Diabetes - United States, 2006 and 2010. MMWR Surveill Summ. 2013; 62(Suppl 3):99–104.
32. Karim R, Stanczyk FZ, Brinton RD, Rettberg J, Hodis HN, Mack WJ. Association of endogenous sex hormones with adipokines and ghrelin in postmenopausal women. J Clin Endocrinol Metab. 2015; 100(2):508–515. [PubMed: 25405497]
33. Mantzoros CS, Li T, Manson JE, Meigs JB, Hu FB. Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. J Clin Endocrinol Metab. 2005; 90(8):4542–4548. [PubMed: 15914524]
34. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. Jama. 2009; 302(2):179–188. [PubMed: 19584347]
35. Kalyani RR, Franco M, Dobs AS, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. J Clin Endocrinol Metab. 2009; 94(11):4127–4135. [PubMed: 19789205]
36. Zhang Y, Howard BV, Cowan LD, et al. The effect of estrogen use on levels of glucose and insulin and the risk of type 2 diabetes in american Indian postmenopausal women : the strong heart study. Diabetes Care. 2002; 25(3):500–504. [PubMed: 11874937]
37. Espeland MA, Hogan PE, Fineberg SE, et al. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. Diabetes Care. 1998; 21(10):1589–1595. [PubMed: 9773716]
38. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? Jama. 1991; 265(4):489–495. [PubMed: 1824642]
39. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. J Am Coll Cardiol. 2007; 50(11):1009–1014. [PubMed: 17825708]
40. Dasgupta D, Pal B, Ray S. Factors that discriminate age at menopause: A study of Bengali Hindu women of West Bengal. Am J Hum Biol. 2015; 27(5):710–715. [PubMed: 25754515]
41. Dunaif A. Hyperandrogenic Anovulation (PCOS): A Unique Disorder of Insulin Action Associated With an Increased Risk of Non-Insulin-Dependent Diabetes Mellitus. The American Journal of Medicine. 1995; 98(1):S33–S39.

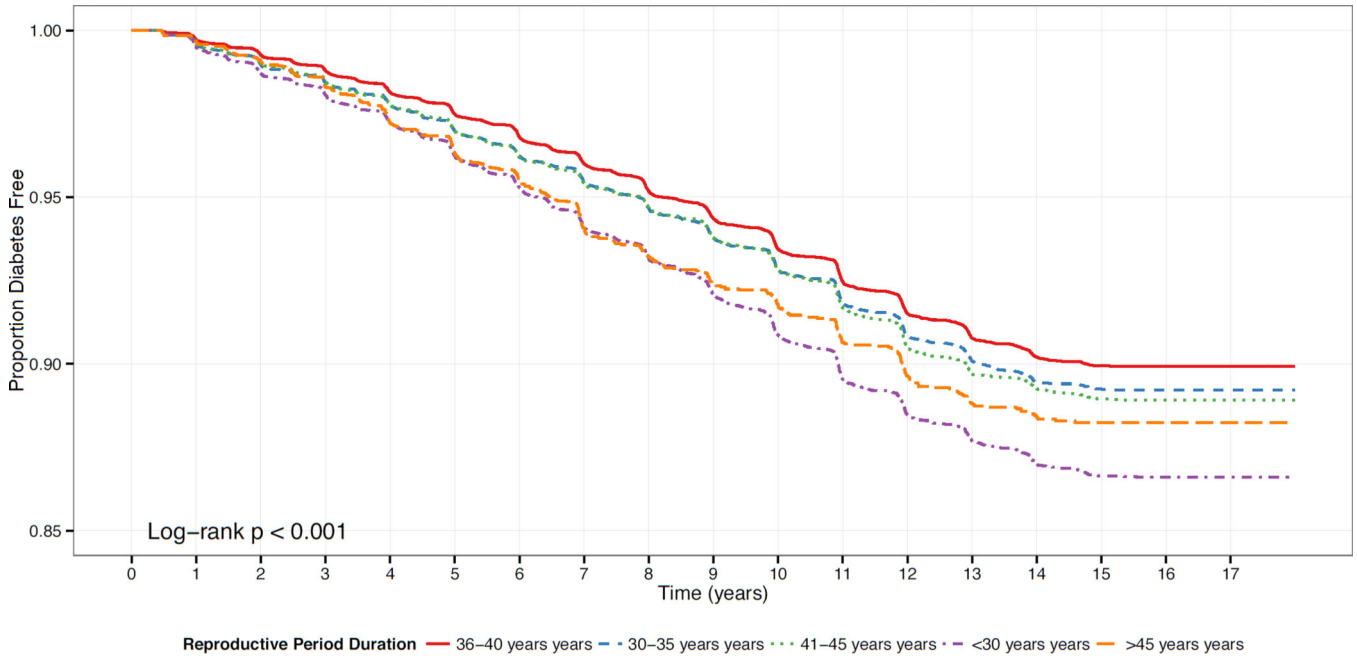

Figure 1.

The cohort diagram shows how we began with 161,808 participants, excluded participants for various reasons, and arrived at our analytic cohort of 124,379 participants.

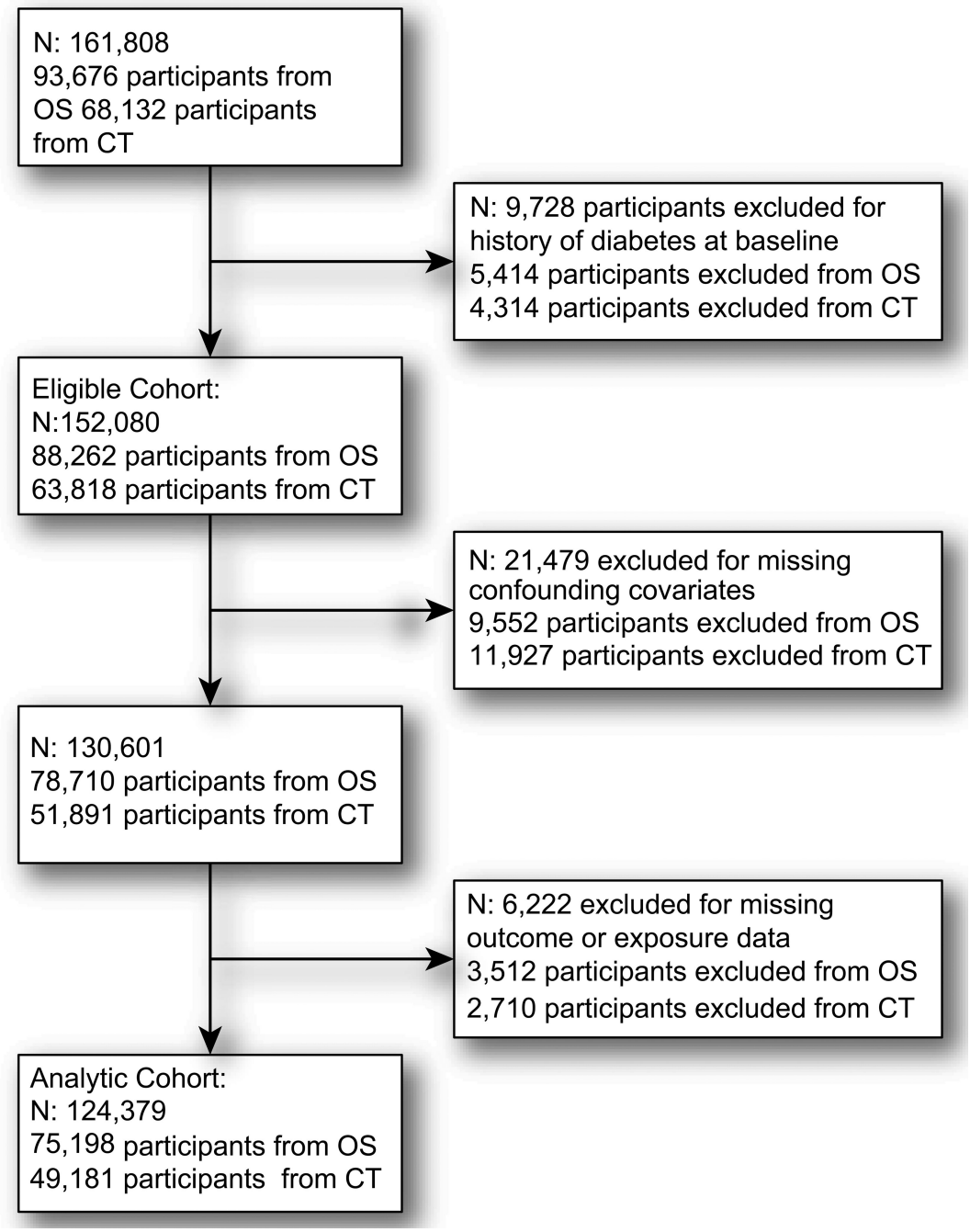

Figure 2.
Kaplan-Meier plots for development of diabetes according to reproductive period duration (A) and menstrual regularity (B) reported by post-menopausal women in the Women's Health Initiative

Table 1

Baseline characteristics by reproduction-period duration among postmenopausal women in the Women's Health Initiative

Reproductive-Period Duration (years)	<30 years	30–35 years	36–40 years	41–45 years	45+ years
Sample Size	20063	31803	47044	21003	4466
Age, n (%)					
50 to 54	2589 (12.9)	5414 (17.0)	7688 (16.3)	928 (4.4)	1 (0.0)
55 to 59	3738 (18.6)	6207 (19.5)	10335 (22)	4833 (23)	186 (4.2)
60 to 69	9341 (46.6)	13335 (41.9)	19837 (42.2)	10903 (51.9)	2581 (57.8)
70 to 79	4395 (21.9)	6847 (21.5)	9184 (19.5)	4339 (20.7)	1698 (38.0)
Years since menopause, n (%)					
<5 years	0 (0.0)	1623 (5.1)	9102 (19.3)	5414 (25.8)	984 (22.0)
5–10 years	248 (1.2)	4857 (15.3)	10411 (22.1)	5688 (27.1)	1599 (35.8)
>10 years	19815 (98.8)	25323 (79.6)	27531 (58.5)	9901 (47.1)	1883 (42.2)
Race, n (%)					
White	16245 (81.0)	27040 (85.0)	40783 (86.7)	18385 (87.5)	3859 (86.4)
Hispanic	822 (4.1)	1167 (3.7)	1510 (3.2)	601 (2.9)	140 (3.1)
Black	2276 (11.3)	2266 (7.1)	2803 (6.0)	1233 (5.9)	283 (6.3)
Other	720 (3.6)	1330 (4.2)	1948 (4.1)	784 (3.7)	184 (4.1)
BMI (kg/m2), n (%)					
Underweight (<18.5 kg/m2)	164 (0.8)	308 (1.0)	443 (0.9)	197 (0.9)	38 (0.9)
Normal (18.5 to <25 kg/m2)	6556 (32.7)	12015 (37.8)	18220 (38.7)	7309 (34.8)	1492 (33.4)
Overweight (25 to <30 kg/m2)	7160 (35.7)	11168 (35.1)	16301 (34.7)	7323 (34.9)	1570 (35.2)
Obese (>=30 kg/m2)	6183 (30.8)	8312 (26.1)	12080 (25.7)	6174 (29.4)	1366 (30.6)
Waist circumference (cm) Median (IQR)	85 (18)	83 (17.5)	83 (17.5)	84 (18)	85 (18)
Education, n (%)					
Less than high school	1328 (6.6)	1401 (4.4)	1631 (3.5)	671 (3.2)	211 (4.7)

Reproductive-Period Duration (years)	<30 years	30–35 years	36–40 years	41–45 years	45+ years
High School	3866 (19.3)	5557 (17.5)	7256 (15.4)	3271 (15.6)	688 (15.4)
College	14869 (74.1)	24845 (78.1)	38157 (81.1)	17061 (81.2)	3567 (79.9)
Marital Status, n (%)					
Never married	743 (3.7)	1496 (4.7)	2228 (4.7)	844 (4.0)	157 (3.5)
Marriage-like relationship	337 (1.7)	530 (1.7)	839 (1.8)	301 (1.4)	52 (1.2)
Presently married	11842 (59.0)	19437 (61.1)	29791 (63.3)	13602 (64.8)	2622 (58.7)
Divorced or separated	3553 (17.7)	5076 (16.0)	7137 (15.2)	2884 (13.7)	615 (13.8)
Widowed	3588 (17.9)	5264 (16.6)	7049 (15.0)	3372 (16.1)	1020 (22.8)
Baseline MET-min/wk, n (%)					
<100 MET-min/wk	5005 (24.9)	6877 (21.6)	9295 (19.8)	4026 (19.2)	881 (19.7)
100 to <500 MET-min/wk	5883 (29.3)	9013 (28.3)	12900 (27.4)	5682 (27.1)	1243 (27.8)
500 to <1200 MET-min/wk	5239 (26.1)	8933 (28.1)	13756 (29.2)	6178 (29.4)	1296 (29.0)
>=1200 MET-min/wk	3936 (19.6)	6980 (21.9)	11093 (23.6)	5117 (24.4)	1046 (23.4)
Ever Smoked, n (%)					
Never Smoked	9744 (48.6)	15661 (49.2)	23918 (50.8)	11344 (54)	2435 (54.5)
Past Smoker	8465 (42.2)	13706 (43.1)	20138 (42.8)	8733 (41.6)	1851 (41.4)
Current Smoker	1854 (9.2)	2436 (7.7)	2988 (6.4)	926 (4.4)	180 (4.0)
Alcohol Use, n (%)					
<1 drink/wk	13342 (66.5)	19369 (60.9)	27343 (58.1)	12363 (58.9)	2754 (61.7)
1–3 drinks/wk	2562 (12.8)	4675 (14.7)	7273 (15.5)	3274 (15.6)	642 (14.4)
>3 drinks/wk	4159 (20.7)	7759 (24.4)	12428 (26.4)	5366 (25.5)	1070 (24.0)
HT Intervention Arm, n (%)					
OS cohort (Not randomized)	16916 (84.3)	26960 (84.8)	39820 (84.6)	17640 (84.0)	3903 (87.4)
E+P intervention	431 (2.1)	1505 (4.7)	2891 (6.1)	1420 (6.8)	188 (4.2)
E+P control	415 (2.1)	1446 (4.5)	2837 (6)	1419 (6.8)	170 (3.8)
E-alone control	1178 (5.9)	941 (3)	751 (1.6)	253 (1.2)	109 (2.4)
E-alone intervention	1123 (5.6)	951 (3)	745 (1.6)	271 (1.3)	96 (2.1)

Reproductive-Period Duration (years)	<30 years	30–35 years	36–40 years	41–45 years	45+ years
Postmenopausal HT Use, n (%)					
Never	4923 (24.5)	11119 (35)	21468 (45.6)	10926 (52)	1810 (40.5)
Past	4896 (24.4)	5890 (18.5)	6509 (13.8)	2470 (11.8)	580 (13)
Now	10244 (51.1)	14794 (46.5)	19067 (40.5)	7607 (36.2)	2076 (46.5)
Oral Contraceptive Use					
Ever	7670 (38.3)	14051 (44.3)	21418 (45.7)	8435 (40.3)	1324 (29.7)
Never	12343 (61.7)	17672 (55.7)	25489 (54.3)	12515 (59.7)	3127 (70.3)
Baseline Metformin Use					
Yes	9 (0)	15 (0)	13 (0)	9 (0)	2 (0)
No	20004 (100)	31708 (100)	46894 (100)	20941 (100)	4449 (100)
Family History of Diabetes, n (%)	7042 (35.1)	9954 (31.3)	14286 (30.4)	6687 (31.8)	1448 (32.4)
Surgical Menopause, n (%)	9458 (47.1)	8402 (26.4)	5825 (12.4)	1584 (7.5)	239 (5.4)
Number of Term Pregnancies, n (%)					
None	2793 (13.9)	4082 (12.8)	5615 (11.9)	1999 (9.5)	402 (9)
1–2	7068 (35.2)	11260 (35.4)	16361 (34.8)	6743 (32.1)	1300 (29.1)
3+	10202 (50.8)	16461 (51.8)	25068 (53.3)	12261 (58.4)	2764 (61.9)
Cycle Regularity, n (%)					
Regular	15841 (79)	26524 (83.4)	39689 (84.4)	17411 (82.9)	3745 (83.9)
Sometimes regular	2117 (10.6)	2976 (9.4)	4294 (9.1)	2075 (9.9)	389 (8.7)
Not regular	2105 (10.5)	2303 (7.2)	3061 (6.5)	1517 (7.2)	332 (7.4)
Menarche Timing, n (%)					
<12 years	3565 (17.8)	5376 (16.9)	9545 (20.3)	6968 (33.2)	1538 (34.4)
12 years	4395 (21.9)	8025 (25.2)	12978 (27.6)	5926 (28.2)	1257 (28.1)
>12 years	12103 (60.3)	18402 (57.9)	24521 (52.1)	8109 (38.6)	1671 (37.4)
Menopause Timing, n (%)					
<45 years	20033 (99.9)	14783 (46.5)	106 (0.2)	0 (0)	0 (0)
45–55 years	30 (0.1)	17020 (53.5)	45993 (97.8)	9677 (46.1)	0 (0)
>55 years	0 (0)	0 (0)	945 (2)	11326 (53.9)	4466 (100)

Table 2

Incident type 2 diabetes in relation to reproductive-period duration, timing of menopause and menarche, and period regularity among postmenopausal women in the Women's Health Initiative

Exposure	Factor Level	# Diabetes Events (Person Years Follow-up)	Age Adjusted[a] HR (95% CI)	Age Adjusted p	Fully[b] Adjusted HR (95% CI)	p[c]
Reproductive Period Duration	<30	2142 (232,670)	1.37 (1.30, 1.45)	<0.0001	1.07 (1.01, 1.14)	0.04
	30–35	2815 (386,257)	1.09 (1.03, 1.14)		1.02 (0.97, 1.07)	
	36–40	3934 (585,514)	1.00 (Ref.)		1.00 (Ref.)	
	41–45	1939 (259,544)	1.11 (1.05, 1.17)		1.06 (1.00, 1.12)	
	45+	432 (52,070)	1.23 (1.12, 1.37)		1.09 (0.99, 1.21)	
Menopause Timing	< 46 years	3523 (411,286)	1.25 (1.20, 1.30)	<0.0001	1.04 (0.99, 1.09)	0.02
	46 to 55 years	6189 (90,3007)	1.00 (Ref.)		1.00 (Ref.)	
	> 55 years	1550 (201,762)	1.12 (1.06, 1.19)		1.08 (1.01, 1.14)	
Menarche Timing	< 12 years	2,796 (328,602)	1.14 (1.08, 1.20)	<0.0001	1.01 (0.95, 1.06)	0.89
	12 years	2966 (397,946)	1.00 (Ref.)		1.00 (Ref.)	
	> 12 years	5,500 (789,507)	0.93 (0.89, 0.97)		0.99 (0.95, 1.04)	
Cycle Regularity	Not Regular	935 (113707)	1.11 (1.04, 1.19)	0.008	1.04 (0.97, 1.11)	0.46
	Sometimes Regular	1074 (146085)	1.00 (0.94, 1.06)		1.02 (0.96, 1.08)	
	Regular	9253 (1,256,262)	1.00 (Ref.)		1.00 (Ref.)	

[a] Cox proportional hazards techniques were used to estimate associations.

[b] Fully adjusted model includes age, race, baseline BMI, hormone therapy (HT) intervention arm membership, baseline physical activity, baseline alcohol consumption, baseline smoking history, education, baseline marital status, number of term pregnancies, family history of diabetes, years since menopause at baseline, baseline waist circumference, history of oral contraceptive use at baseline, and baseline metformin use.

[c] p values correspond to the fully adjusted models and reflect likelihood ratio tests of significance for the indicated exposure variable.