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ORIGINAL ARTICLE *Reproductive epidemiology*

Diabetes and onset of natural menopause: results from the European Prospective Investigation into Cancer and Nutrition

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STUDY QUESTION: Do women who have diabetes before menopause have their menopause at an earlier age compared with women without diabetes?

SUMMARY ANSWER: Although there was no overall association between diabetes and age at menopause, our study suggests that early-onset diabetes may accelerate menopause.

WHAT IS KNOWN ALREADY: Today, more women of childbearing age are being diagnosed with diabetes, but little is known about the impact of diabetes on reproductive health.

STUDY DESIGN, SIZE, DURATION: We investigated the impact of diabetes on age at natural menopause (ANM) in 258 898 women from the European Prospective Investigation into Cancer and Nutrition (EPIC), enrolled between 1992 and 2000.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Determinant and outcome information was obtained through questionnaires. Time-dependent Cox regression analyses were used to estimate the associations of diabetes and age at diabetes diagnosis with ANM, stratified by center and adjusted for age, smoking, reproductive and diabetes risk factors and with age from birth to menopause or censoring as the underlying time scale.

MAIN RESULTS AND THE ROLE OF CHANCE: Overall, no association between diabetes and ANM was found (hazard ratio (HR) = 0.94; 95% confidence interval (CI) 0.89–1.01). However, women with diabetes before the age of 20 years had an earlier menopause (10–20 years: HR = 1.43; 95% CI 1.02–2.01, <10 years: HR = 1.59; 95% CI 1.03–2.43) compared with non-diabetic women, whereas women with diabetes at age 50 years and older had a later menopause (HR = 0.81; 95% CI 0.70–0.95). None of the other age groups were associated with ANM.

LIMITATIONS, REASONS FOR CAUTION: Strengths of the study include the large sample size and the broad set of potential confounders measured. However, results may have been underestimated due to survival bias. We cannot be sure about the sequence of the events in women with a late age at diabetes, as both events then occur in a short period. We could not distinguish between type 1 and type 2 diabetes.

WIDER IMPLICATIONS OF THE FINDINGS: Based on the literature, an accelerating effect of early-onset diabetes on ANM might be plausible. A delaying effect of late-onset diabetes on ANM has not been reported before, and is not in agreement with recent studies suggesting the opposite association.

STUDY FUNDING/COMPETING INTEREST(S): The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ) and Federal Ministry of Education and Research (BMMF) (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS), Regional Governments of Andalucía, Asturias, Basque Country, Murcia (no. 6236) and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and Wellcome Trust (UK). None of the authors reported a conflict of interest.

Key words: age at natural menopause / diabetes / time-dependent modeling / cox proportional hazards analyses

Introduction

Menopause is a universal event in women's reproductive life, but the timing of onset varies widely. In the Western world, age at natural menopause (ANM) typically ranges between 40 and 60 years, with an average age of onset of 51 years (te Velde and Pearson, 2002). Although the exact underlying mechanisms are not completely understood, timing of menopause is considered to be a complex trait, being influenced by both genetic and environmental factors. Smoking is the best-established environmental factor affecting ANM, with menopause occurring 1–2 years earlier in smokers (Gold, 2011). Other factors that have been linked to an earlier menopause are nulliparity and low socioeconomic status, while use of oral contraceptives (OCs) tends to delay menopause (Gold, 2011). Several studies have investigated the association of physical activity and dietary factors with ANM, but their impact seems to be small and not always consistent (Gold, 2011).

Next to genetic and environmental factors, chronic metabolic diseases may also influence ANM. There is some evidence suggesting that diabetes may accelerate menopausal onset. Women with type 1 diabetes (T1D) have an earlier decline of inhibin B and anti-Müllerian hormone (AMH) levels, which is indicative of premature ovarian ageing (Soto *et al.*, 2009). Furthermore, women with T1D have been reported to enter menopause 5 years earlier than non-diabetic women (Dorman *et al.*, 2001), although a later study did not confirm this (Sjoberg *et al.*, 2011). In addition, we have previously shown that women with an adverse metabolic risk factor profile enter menopause earlier (Kok *et al.*, 2006), and recently a smaller ovarian reserve has been observed in premenopausal women with type 2 diabetes (T2D) (Isik *et al.*, 2012).

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Given the increasing prevalence of diabetes in women of childbearing age (Lawrence *et al.*, 2008; Patterson *et al.*, 2009), more women could be exposed to potential adverse effects of diabetes on reproductive health. In the present study, we therefore examined the impact of diabetes on ANM in a large European cohort.

Materials and Methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a multicenter prospective cohort study aimed at investigating the relations between diet, lifestyle, and genetic factors and the incidence of cancer and other chronic diseases. The cohort was initiated in the early 1990s in 23 centers from 10 European countries (France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark and Norway). Details of EPIC, in particular on design, study population and procedures for baseline data collection have been described previously (Riboli, 1992; Riboli and Kaaks, 1997). In brief, 519 978 men and women, mostly aged 27–70 years, were mainly recruited from the general population between 1992 and 2000. Exceptions were the Oxford cohort, UK (vegetarian volunteers and healthy eaters); the Utrecht cohort, the Netherlands and the Florence, Italy, cohort (women attending breast cancer screening); the French cohort (female members of the health insurance for state school employees); and components of the Italian and Spanish cohorts (members of local blood donor associations). Baseline questionnaires included questions on diet, lifestyle, reproductive and medical factors. All participants provided written informed consent and the study was approved by the local ethics committees of the participating centers and the Internal Review Board of the International Agency for Research on Cancer.

Follow-up differed largely by country, but participants were regularly followed for the occurrence of various diseases. However, for the current analyses we only use the baseline data from EPIC.

In total, 367 331 women participated in the EPIC study. For the present study, we excluded women from the Norwegian cohorts ($N = 37\,200$) and the Swedish cohorts ($N = 30\,329$), because of lack of data on hysterectomy and/or oophorectomy status. We further excluded women with missing data on diabetes status ($N = 5891$) and post-menopausal women with missing data on menopausal age ($N = 35\,013$), leaving 258 898 women for the analyses.

Exposure assessment

Diabetes status, defined as being diagnosed with diabetes, at baseline was based on self-report and obtained through a questionnaire in which participants were asked if they had ever been diagnosed with diabetes and if so at what age. In the questionnaire, no distinction was made between T1D and T2D. In part of the cohort self-reported diabetes was medically verified (Sluik *et al.*, 2011): 119 613 women from 13 centers in five EPIC countries (Italy: Florence, Milan, Naples, Ragusa, Turin; Spain: Pamplona, San Sebastian; Netherlands: Bilthoven, Utrecht; Germany: Heidelberg, Potsdam; Denmark; Aarhus, Copenhagen). Of the 2708 self-reports in these centers, 2030 were confirmed to have diabetes (75%).

Assessment of menopausal status and age at menopause

The analyses in this paper are based on menstrual status at baseline and retrospective recall of age at menopause. Menopausal status was defined according to information on menstruation status and age at enrollment. Women were considered as post-menopausal if they reported not having had any menses over the past 12 months. Women were considered premenopausal when they reported having had regular menses over the past 12 months. Women were considered perimenopausal if they reported having irregular menses over the past 12 months or if they indicated having had menses over the past 12 months, but were no longer menstruating at the time of enrollment.

Menopausal age was defined as the self-reported age at the last menstrual period. Information on hysterectomy and oophorectomy status was also obtained through self-administered questionnaires. We considered women surgically post-menopausal if they had had a hysterectomy and/or uni- or bilateral oophorectomy before reaching natural menopause (Cooper and Thorp, 1999; Hardy and Kuh, 1999; Farquhar *et al.*, 2005; Yasui *et al.*, 2012). Women with missing or incomplete questionnaire data on menstruation status were classified as premenopausal when they were younger than 46 years, as perimenopausal when they were between 46 and 55 years of age, and as post-menopausal when they were older than 55 years at enrollment in which case they were excluded from the present analysis because of lack of information on age at menopause.

Assessment of other covariates

Information on smoking, alcohol consumption, physical activity and education level was based on self-report. Baseline questionnaires also included questions on reproductive factors such as age at first menstruation, number of live and stillbirths, and current and past use of OCs and hormone replacement therapy (HRT). Except for the Bilthoven cohort (The Netherlands), all centers collected information on the number of full-term pregnancies (the sum of live and stillbirths). In the Bilthoven cohort, the number of children was used as a proxy for the number of full-term pregnancies. Women were also asked to give their age of starting and quitting smoking, and starting age and duration of OC use (in years). Information on the starting age of HRT use was collected slightly differently in each center. For this reason, start of HRT use was recoded in a uniform categorical variable ($\leq$40 years, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, $\geq$55 years) to maximize comparability across centers.

In most centers, trained health professionals measured weight and height during a visit to the study center. Weight was corrected for the clothing worn during measurement in order to reduce heterogeneity due to protocol differences among centers and for self-reporting in Oxford participants using a prediction equation based on a comparison of self-reported and measured data (Haftenberger *et al.*, 2002). For the French cohort, we had to rely on self-report for 71% of the participants. BMI was calculated from the participant's weight (kilograms) divided by the square of their height (square meters).

Data analysis

Missing values for covariates (all $< 5\%$) were imputed using single imputation. Data were analyzed using a survival analysis approach, which allows for the inclusion of incomplete or censored observations in the estimation of ANM. Women who had had a hysterectomy and/or oophorectomy prior to menopause were censored at their age at surgery and pre- and perimenopausal women were censored at their age at enrollment. In all analyses, age from birth to menopause or censoring was used as the underlying time scale. We first used Kaplan–Meier analysis to estimate the median age at menopause for the entire cohort and after stratification for participant characteristics. We then used Cox proportional hazards models to estimate the association between participant characteristics and ANM. Hazard ratios (HRs) derived from these models represent the risk of becoming naturally menopausal at a given age, with HRs less than 1 indicating a later menopause and HRs greater than 1 indicating an earlier menopause compared with the reference. To account for the immortal person-time, which is the interval between birth and diabetes onset, representing a period of follow-up during which the outcome (menopause or censoring) cannot occur in exposed women (Rothman and Greenland, 1998; van Walraven et al.,

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2004; Sylvestre et al., 2006; Shariff et al., 2008), diabetes status was modeled as a binary time-dependent variable, changing from unexposed at birth to exposed at the self-reported age at diagnosis. To investigate the impact of diabetes timing, we also entered age at diagnosis as a time-dependent categorical variable (age at diagnosis ≥50 years, 45–49 years, 40–44 years, 30–39 years, 20–29 years, 10–20 years, <10 years) into the model.

Analyses were adjusted for potential confounders in three consecutive models and all models were stratified by center to account for study center effects (i.e. questionnaire design and covariate measurement). The first model was adjusted for age. Next, we added reproductive factors to the model: age at menarche (continuous), number of full-term pregnancies (0, 1, 2, ≥3) and OC and HRT use (yes/no). In the final multivariable model, we further adjusted the analyses for known diabetes risk factors including BMI (continuous), smoking (yes/no), alcohol consumption (<10, 10–24, 25–50 and >50 g/day), physical activity (inactive, moderately inactive, moderately active, active) and education level (none, primary school, technical or professional school, secondary school, longer education). Similar to diabetes status, premenopausal exposures to smoking and OCs were modeled as binary time-dependent covariates with exposure starting at the self-reported age at smoking and OC initiation, and ending at cessation or censoring. HRT use before reaching natural menopause was modeled as a categorical variable (yes versus no).

The proportional hazards assumption was assessed by visual inspection of the Schoenfeld residual plots, which did not indicate violation of the assumption.

We also performed several sensitivity analyses. Hormone use prior to menopause may mask a woman's true menopausal age. To investigate the impact of this potential misclassification, we performed a separate analysis in which we excluded women who used HRT prior to menopause and women who used OCs in the year before or after their menopause. Because the age at entry varied between 20 and 97 years, a cohort effect may have confounded the association. To investigate this, we additionally adjusted the analyses for date of birth.

Some EPIC centers validated the self-reported diagnosis of diabetes at baseline by cross-referencing with additional information sources [including: verification by a medical practitioner, use of diabetes medication, repeated self-report of diabetes diagnosis in follow-up questionnaires, linkage to diabetes registries, or a glycated hemoglobin (HbA1c) concentration of above 6% (42 mmol/mol; values based on registry information, Malmø only)]. To investigate the impact of potential misclassification due to self-reporting of diabetes, we also repeated the analyses in centers with verified diabetes cases only. All statistical analyses were performed using STATA, version 11.0 (Stata Corp., College Station, TX, USA).

Results

Participant characteristics of the study population are summarized in Table I. The mean (SD) age was 50.6 (10.2) years and 131 923 (51.0%) women were still menstruating. The estimated median ANM in the entire study population was 52.0 years. The mean age at diabetes diagnosis was 47.3 years old (SD = 13.2). Table II shows the crude ANM across strata of participant characteristics and the corresponding HRs after multivariable adjustment. Current and former smoking and a low educational level were associated with an earlier onset of menopause, while late menarche, OC use and being parous were associated with a later menopause. Menopause was also delayed in women who were physically active and women who consumed alcoholic drinks.

In total, 5999 women had a self-reported diagnosis of diabetes of whom 2752 had diabetes before menopause (defined as age at diagnosis < age at menopause or censoring). Table III shows the HRs for natural menopause according to diabetes status. Overall, diabetics did not have a statistically significant lower risk of becoming menopausal than non-diabetics (HR = 0.94; 95% CI 0.89–1.01). Analyses for age at diagnosis showed that women with diabetes before the age of 20 years were more likely to have an earlier menopause (10–20 years: HR = 1.43; 95% CI 1.02–2.01, <10 years: HR = 1.59; 95% CI 1.03–2.43), whereas women with diabetes at age 50 years and older were more

Table I Characteristics of the study population (*N* = 258 898) from the European Prospective Investigation into Cancer and Nutrition (EPIC), enrolled between 1992 and 2000.

Age at entry (years), mean (SD)	50.6 (10.2)
BMI (kg/m^2), mean (SD)	25.2 (4.6)
Menopausal status, % (*N*)	
Pre- or perimenopausal	51.0 (131 923)
Natural post-menopausal	34.4 (88 992)
Surgical post-menopausal	14.7 (37 983)
Age at menarche (years), mean (SD)*	13.0 (1.6)
Number of full-term pregnancies, % (*N*)*	
0	14.9 (38 575)
1	15.9 (41 273)
2	40.2 (104 128)
≥3	26.0 (67 381)
Ever OC use, % (*N*)*	58.4 (151 138)
Ever HRT use, % (*N*)*	19.2 (49 799)
Smoking status, % (*N*)*	
Never	58.5 (151 559)
Former	21.8 (56 556)
Current	18.0 (46 714)
Alcohol consumption, % (*N*)*	
<10 g/day	69.3 (179 485)
10–24 g/day	20.8 (53 837)
25–50 g/day	7.5 (19 334)
>50 g/day	1.5 (3897)
Education, % (*N*)*	
None	5.8 (14 942)
Primary school	24.3 (62 982)
Technical or professional school	19.6 (50 814)
Secondary school	22.9 (59 356)
Longer education	23.7 (61 365)
Physical activity, % (*N*)*	
Inactive	24.6 (63 696)
Moderately inactive	34.9 (90 439)
Moderately active	23.7 (61 228)
Active	15.7 (40 596)
Diabetes, % (*N*)	2.3 (5999)
Age at diabetes diagnosis, (years) mean (SD)	47.3 (13.2)

OC, oral contraceptives; HRT, hormone replacement therapy.
*Variables with missing values (all < 5%).

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Table II Associations of reproductive and lifestyle factors with age at natural menopause.

Participant characteristic	Median ANM (IQR)[a]	Adjusted HR (95% CI)*,[b]
Age at menarche		
<12 years	52 (49–54)	REF (1.00)
≥12 years	52 (50–54)	0.95 (0.93–0.96)
Number of full-term pregnancies		
0	51 (49–54)	REF (1.00)
1	52 (49–54)	0.89 (0.87–0.92)
2	52 (50–55)	0.86 (0.84–0.88)
≥3	52 (49–54)	0.85 (0.83–0.87)
Ever use of oral contraceptives		
Never	51 (49–54)	REF (1.00)
Ever	52 (50–55)	0.93 (0.92–0.95)
BMI		
<25 kg/m^2	52 (50–55)	REF (1.00)
25–30 kg/m^2	52 (49–54)	1.02 (1.01–1.04)
≥30 kg/m^2	52 (49–54)	1.01 (0.99–1.03)
Smoking status		
Never	52 (50–54)	REF (1.00)
Former	52 (50–55)	1.05 (1.03–1.07)
Current	51 (49–54)	1.35 (1.32–1.37)
Alcohol consumption		
<10 g/day	52 (49–54)	REF (1.00)
10–25 g/day	52 (50–55)	0.94 (0.93–0.96)
25–50 g/day	52 (50–55)	0.91 (0.89–0.93)
>50 g/day	52 (50–55)	0.91 (0.86–0.97)
Physical activity		
Inactive	51 (49–54)	REF (1.00)
Moderately inactive	52 (50–54)	0.96 (0.94–0.97)
Moderately active	52 (50–55)	0.92 (0.91–0.94)
Active	52 (50–55)	0.96 (0.94–0.98)
Education		
None	50 (48–53)	1.54 (1.49–1.58)
Primary school	51 (49–54)	1.31 (1.28–1.34)
Technical or professional school	52 (49–54)	1.18 (1.15–1.20)
Secondary school	52 (50–55)	1.04 (1.01–1.06)
Longer education	52 (50–55)	REF (1.00)

ANM, age at natural menopause; IQR, interquartile range; CI, confidence interval; REF, reference.
*The hazard ratios (HRs) represent the risk of becoming naturally menopausal at a given age, with HRs less than 1 indicating a later menopause and HRs greater than 1 indicating an earlier menopause compared with the reference.
aMedian ANM was estimated using Kaplan–Meier analyses.
[b]HRs derived from multivariable adjusted Cox proportional hazards models including reproductive factors (age at menarche, number of full-term pregnancies, ever use of OCs and HRT) and diabetes risk factors (BMI, smoking status, alcohol consumption, physical activity and education).

likely to enter menopause at a later age (HR = 0.81; 95% CI 0.70–0.95). None of the other categories of age at diagnosis were associated with ANM (Table III, models 1–3).

Results were not materially different when we excluded women who used HRT prior to menopause and/or OCs around the time of menopause, although the association with diabetes before the age of 10 years was slightly strengthened (Table IV). Results were also unchanged after adjusting the analyses for birthdate (Table IV). When restricting to verified diabetes cases, the associations yielded a similar HR for women with a late diabetes diagnosis, but the association with an early diabetes diagnosis attenuated toward the null and was no longer statistically significant, although numbers were very small in these groups (Table IV).

Discussion

In the present study, we found no statistically significant overall association between diabetes and ANM. However, when looking at age of diagnosis, women with diabetes before the age of 20 years reached menopause earlier, whereas menopausal onset was delayed in women having diabetes after 50 years of age. For diabetes onset between the ages 20 and 50 years, no association with ANM was found. All associations remained similar after adjusting for age, smoking, reproductive factors and diabetes risk factors.

There are several aspects that need to be considered when interpreting our findings. The strengths of our study include its large sample size and the measurement of a broad set of potential confounders. Except for BMI and number of full-term pregnancies, covariate measurement was fully standardized across centers. Well-known associations with smoking status, education and parity were replicated, which can be interpreted as an internal validation of our data.

A potential source of bias that cannot be controlled for is survival bias. In our study, participants were required to have survived the time between exposure and study entry. Participants with diabetes are probably less likely to participate in a study, because of their illness and poorer survival (Soedamah-Muthu *et al.*, 2006; Barr *et al.*, 2007). Indeed, the prevalence of diabetes in our study sample was somewhat lower than expected (King *et al.*, 1998; Wild *et al.*, 2004). Since mortality has been associated with early menopause (Atsma *et al.*, 2006), an association between early-onset diabetes and younger ANM could have been biased toward the null. On the other hand, the association between late-onset diabetes and older ANM might have been overestimated, although survival bias is probably less of a problem here, because the time between diabetes diagnosis and study entry is much smaller. Future prospective studies following women through menopause are needed to assess the impact of this potential bias.

Second, we cannot be certain about the exact sequence of diabetes and menopause in women in whom both events occur approximately around the same age (i.e. reverse causation). Moreover, the menopause transition is a process that takes at least 3 years but this is highly variable and can be much longer (Harlow *et al.*, 2012) and diabetes occurs at least 4–7 years prior to diagnosis (Harris *et al.*, 2012). Thus, we cannot rule out the possibility that women with a short interval between menopause and diabetes were misclassified in our study. Third, assessment of both diabetes and menopause status was based on self-report, not verified by medical records. However, previous studies have shown that the validity and reproducibility of self-reported age at menopause is acceptable (Colditz *et al.*, 1987; den Tonkelaar, 1997; Cairns *et al.*, 2011). Moreover, the replication

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Table III Hazard ratios of natural menopause according to diabetes status and age at diagnosis.

	HR (95% CI)*		
	Model 1 (*N* = 258 898)	**Model 2 (*N* = 258 898)**	**Model 3 (*N* = 258 898)**
Diabetes before menopause			
No (*N* = 256 146)	REF (1.00)	REF (1.00)	REF (1.00)
Yes (*N* = 2752)	0.97 (0.91–1.03)	0.95 (0.89–1.01)	0.94 (0.89–1.01)
Age at diabetes diagnosis (years)			
No diabetes before menopause	REF (1.00)	REF (1.00)	REF (1.00)
≥50 (*N* = 317)	0.85 (0.73–0.99)	0.82 (0.70–0.96)	0.81 (0.70–0.95)
45–49 (*N* = 649)	0.91 (0.81–1.02)	0.90 (0.81–1.01)	0.91 (0.81–1.02)
40–44 (*N* = 444)	1.02 (0.87–1.19)	1.01 (0.86–1.18)	1.00 (0.86–1.17)
30–39 (*N* = 715)	1.00 (0.87–1.14)	0.98 (0.85–1.12)	0.96 (0.84–1.10)
20–29 (*N* = 394)	1.07 (0.89–1.30)	1.03 (0.85–1.24)	0.99 (0.82–1.20)
10–20 (*N* = 161)	1.20 (0.85–1.69)	1.42 (1.01–1.99)	1.43 (1.02–2.01)
<10 (*N* = 72)	1.56 (1.01–2.39)	1.66 (1.08–2.55)	1.59 (1.03–2.43)

Cox proportional hazards models stratified by center and including diabetes status and age at diabetes diagnosis as time-dependent variables.
Model 1: adjusted for age.
Model 2: Model 1 plus reproductive factors (age at menarche, number of full-term pregnancies, OC use and HRT).
Model 3: Model 2 plus diabetes risk factors (BMI, smoking, alcohol consumption, education and physical activity).
*HRs represent the risk of becoming naturally menopausal at a given age, with HRs less than 1 indicating a later menopause and HRs greater than 1 indicating an earlier menopause compared with the reference.

Table IV Hazard ratios of natural menopause according to diabetes status and age at diagnosis—sensitivity analyses.

	HR (95% CI)*			
	Model 3 (*N* = 258 898)	**Model 4 (*N* = 234 240)**	**Model 5 (*N* = 258 898)**	**Model 6 (*N* = 119 613)**
Diabetes before menopause				
No (*N* = 256 146)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00) (*N* = 118 782)
Yes (*N* = 2752)	0.94 (0.89–1.01)	0.93 (0.87–1.00)	0.95 (0.89–1.01)	0.88 (0.79–0.98) (*N* = 831)
Age (years) at diabetes diagnosis				
No diabetes before menopause	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
≥50 (*N* = 317)	0.81 (0.70–0.95)	0.83 (0.71–0.98)	0.81 (0.70–0.95)	0.80 (0.62–0.95) (*N* = 171)
45–49 (*N* = 649)	0.91 (0.81–1.02)	0.88 (0.77–1.00)	0.91 (0.81–1.02)	0.80 (0.65–0.97) (*N* = 221)
40–44 (*N* = 444)	1.00 (0.86–1.17)	1.01 (0.85–1.19)	1.00 (0.86–1.17)	0.92 (0.72–1.18) (*N* = 164)
30–39 (*N* = 715)	0.96 (0.84–1.10)	0.92 (0.80–1.07)	0.97 (0.84–1.11)	1.12 (0.87–1.44) (*N* = 183)
20–29 (*N* = 394)	0.99 (0.82–1.20)	1.00 (0.82–1.22)	1.00 (0.82–1.20)	1.14 (0.79–1.65) (*N* = 69)
10–20 (*N* = 161)	1.43 (1.02–2.01)	1.41 (0.92–2.16)	1.44 (1.02–2.03)	1.02 (0.14–7.24) (*N* = 17)
<10 (*N* = 72)	1.59 (1.03–2.43)	1.79 (1.13–2.84)	1.59 (1.03–2.43)	No fit possible (*N* = 6)

Cox proportional hazards models stratified by center and including diabetes status and age at diabetes diagnosis as time-dependent variables.
Model 3: adjusted for age, reproductive factors (age at menarche, number of full-term pregnancies, OC use and HRT) and diabetes risk factors (BMI, smoking, alcohol consumption, education and physical activity).
Model 4: Model 3 after excluding women using HRT prior to menopause and/or women using OCs around menopause.
Model 5: Model 3 plus date of birth.
Model 6: Model 3 restricted to verified diabetes cases only (in a subset of EPIC: 13 centers in 5 countries (Italy: Florence, Milan, Naples, Ragusa, Turin; Spain: Pamplona, San Sebastian; Netherlands: Bilthoven, Utrecht; Germany: Heidelberg, Potsdam; Denmark; Aarhus, Copenhagen)).
*HRs represent the risk of becoming naturally menopausal at a given age, with HRs less than 1 indicating a later menopause and HRs greater than 1 indicating an earlier menopause compared with the reference.

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of well-known associations with smoking status, education and parity suggests that recall of menopausal age was reasonably good. Although the probability of correct recall is lower when more time has passed (Colditz *et al.*, 1987; den Tonkelaar, 1997), it seems unlikely that recall of menopausal age is different for diabetes cases compared with non-cases. In our data the percentage of women that had missing data on menopausal status was indeed similar in diabetes cases compared with non-cases. Moreover, the level of agreement between self-reported diagnosis of diabetes and diagnosis based on medical records was fairly good (75%) (Langenberg *et al.*, 2011; Sluik *et al.*, 2011). Results restricted to verified cases yielded comparable estimates, although due to the small numbers associations were all non-significant and interpretation is difficult. Only self-reported cases were validated, and no information is available on medical diagnoses in those without a diabetes self-report. Therefore, false-negative cases may have been present. This may have led to an underestimation of the effect. However, as the prevalence of diabetes in our cohort is low (2.3%), and most of the cases will have been identified, the effect of false-negative reports will have been small. Although the mean age at diagnosis was a bit later compared with the self-reported mean age at diagnosis among the verified cases, it is unlikely that this will have impacted our findings, since the timing of diagnosis reporting is not likely to be influenced by menopausal status.

Finally, we could not distinguish between the effects of T1D and T2D, as this information was not available in EPIC. The decreasing age at T2D onset is a relatively recent phenomenon (Haines *et al.*, 2007; Chen *et al.*, 2012). Since women of the EPIC cohort were recruited in the mid-1990s, it seems reasonable to assume that the younger ANM observed in women with diabetes before the age of 20 years is a T1D effect. In women with diabetes diagnosed between the age of 20 and 30 the type of diabetes could also be gestational diabetes, making it even more difficult to draw firm conclusions.

Based on the literature, an accelerating effect of T1D on ANM might be plausible. Dorman *et al.* (2001) were the first to report an earlier onset of menopause in women with T1D, although the number of post-menopausal women was very small. In a more recent study among Finnish women with T1D, ANM was not associated with age at diabetes diagnosis, although patients with severe microvascular diabetes complications (proliferative retinopathy and nephropathy) were more likely to enter menopause early than those without (Sjoberg *et al.*, 2011). However, compared with the general Finnish population, women with T1D had a 1.5 years *later* median ANM (Sjoberg *et al.*, 2011). Both studies, however, were limited by small sample sizes and like ours were based on cross-sectionally collected data. There is some biological evidence that T1D may have a direct deleterious effect on ovarian function. Oocyte maturation and ovarian follicular development are impaired in animal models of T1D (Colton *et al.*, 2003; Chang *et al.*, 2005) and in women with T1D an earlier decrease in AMH levels has been reported (Soto *et al.*, 2009), which is indicative of a smaller ovarian reserve. Diabetes diagnosed after the age of 45 years is most likely T2D. A delaying effect of T2D on ANM has not been reported before (Lopez-Lopez *et al.*, 1999), and is not in agreement with recent studies suggesting the opposite association (Aydin, 2010; Isik *et al.*, 2012).

In conclusion, our results suggest that diabetes may influence ANM. Given the increasing prevalence of diabetes in women of childbearing age (Lawrence *et al.*, 2008; Patterson *et al.*, 2009), future longitudinal studies with continued follow-up of premenopausal women are needed to replicate these findings and to explore the underlying mechanisms of the observed association.

Authors' roles

J.S.B., N.C.O.-M. and Y.T.v.d.S. were responsible for the conception and design of the study, data analyses, interpretation of the results, and for drafting, reviewing and revising of the paper. M.J.C.E. was responsible for the data analyses and interpretation of the data. All other authors made a substantial contribution to the acquisition of the data. All authors contributed to the writing of the manuscript and agreed with manuscript results and conclusions. J.S.B., N.C.O.-M. and Y.T.v.d.S. are guarantors.

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Conflict of interest

None declared.

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