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Age at natural menopause and life expectancy with and without type 2 diabetes.

Menopausal age, life expectancy and diabetes.

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ABSTRACT

Objective: Effective interventions of future health-care require a better understanding of the health risks associated with early onset of menopause and diabetes, but the necessary data are scarce. Little quantitative information is available about the combined association of early menopause and diabetes on life expectancy and the number of years lived with and without diabetes.

Methods: We included 3,650 postmenopausal women aged 45+ years from the Rotterdam Study, a prospective population-based cohort study. Age at menopause categories were defined as: early (≤44 years old), normal (45-54 years old) and late (≥55 years old). For life table calculations, we used prevalence, incidence rates and hazard ratios for three transitions (free of diabetes to diabetes, free of diabetes to death and diabetes to death) stratifying by age at menopause categories and adjusting for confounders.

Results: Compared to late menopause, the difference in life expectancy for women who experienced early menopause was -3.5 95%CI: -6.6,-0.8 years overall and -4.6 95%CI: -8.9,-0.9 years without diabetes. Compared to age at normal menopause, the difference in life expectancy for women who experienced early menopause was -3.1 95%CI: -5.1,-1.1 years overall and -3.3 95%CI: -6.0,-0.6 years without diabetes.

Conclusions: Women who experienced early menopause lived less long and spent fewer years without diabetes than women who experienced normal or late menopause.

Keywords: Age at menopause; life expectancy; type 2 diabetes

ABBREVIATIONS

T2D, Type 2 diabetes

RS, The Rotterdam Study

LE, Life expectancy

HR, Hazard Ratio

CI, Confidence Interval

IQR, Interquartile range

SD, Standard deviation

VIF, Variance inflation factor

INTRODUCTION

Diabetes is one of the major causes of premature illness and death in most countries and imposes a substantial financial burden to society, especially in women [1, 2]. Almost 1 in 2 women will develop type 2 diabetes (T2D) during their lifetime, and recent data has shown that the age-standardised prevalence of diabetes among adult women has increased in the past 30 years from 5.0% to 7.9% [3, 4].

In women, T2D often manifests during mid-life and thus coincides with the timing of the menopausal transition [5]. Emerging evidence shows an association between age at menopause and diabetes with studies reporting almost a 2-fold increased risk of T2D with early onset of menopause [6, 7]. Also, it is well established that early onset of menopause is associated with early death[8-10]. This could be important because, while mortality rates for women with non-T2D have declined over time [11], mortality rates for women with T2D may have instead increased [11].

Effective interventions and accurate projections of future health-care costs require a better understanding of the health risks associated with early onset of menopause, but the relevant data are scarce. To our knowledge, no study up to date has quantified (calculating the number of years lived with and without diabetes) the combined association of early menopause and T2D with life expectancy. Previous estimates reflecting the association of age at menopause with diabetes have been limited to absolute risks or lifetime risk without combining information about the number of the remaining years lived with or without diabetes, raising a gap in the intuitive understanding of risk and impact communicated among doctors and patients [6, 7, 12].

Two studies have examined the association of age at menopause with total life expectancy [13, 14]. Ossewaarde and colleagues, in a breast cancer-screening cohort, reported that both premature and early onset of menopause were associated with a decrease in life expectancy of approximately 1 to 2 years [13]. Snowdon et al. concluded that each-one year decrease in age at menopause was associated with a 0.47-year decrease in the age at death in women with natural menopause before the age of 47 years [14]. However, these studies did not distinguish between life expectancy with and without diabetes and did not provide a direct observation of a well-defined population, as the results were obtained through modelling and simulation using nation-wide mortality data.

In a large population of postmenopausal women, we aimed to calculate and compare the association of age at natural menopause with total life expectancy and the number of years lived with and without T2D.

METHODS

Population for analyses

The Rotterdam Study (RS) is a population-based prospective cohort study of individuals aged 45years and over, living in Rotterdam, the Netherlands. The rationale and design of the RS have been previously described [15].

The present study used data from the third visit of the first cohort, RSI-3 (March 1997- December 1999) and the baseline examinations of the second, RSII-1 (February 2000-December 2001) and third cohort, RSIII-1 (February 2006-December 2008). Information about the visits and participants used for this study are presented in Supplemental Digital Content Figure S1. A total of 6816 women were

eligible for the analysis. Women who were not postmenopausal (N=741), had missing information on age of menopause (N=145), experienced non-natural (N=1408) or unknown type of menopause (N=20) were excluded from the analyses. Furthermore, we excluded 434 women who reported using oral contraceptives during the menopause transition, since these may mask or influence the onset of menopause [16] and are associated with an increased risk of T2D in postmenopausal women [17]. The remaining 3650 postmenopausal women were eligible for the analyses (Figure 1).

Study population

The Rotterdam Study (RS) is a population-based prospective cohort study ongoing since 1990 in the city of Rotterdam in The Netherlands. Potential participants aged 55 years and over were invited in random clusters. Names and addresses were drawn from the municipal register which is reliable, complete and up to date. The baseline cohort (RSI) included 7983 participants (78% of 10,215 invitees)[18]. Over the years, two more rounds were held. The first, in 2000–2001, included all inhabitants aged 55 years and over, recruiting 3011 participants (out of 4472 invitees) (RSII)[18]. The second extension initiated in 2006, included 3932 participants aged 45 years and over, out of 6057 invited (RSIII)[18]. Detailed information about the visits and participants of the Rotterdam study are presented in Supplemental Digital Content Figure S1. The overall response figure for all three cycles was 72.0% (14,926 of 20,744). RS complies with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus Medical Centre and complies with the Dutch Ministry of Health, Welfare and Sport. All participants provided written informed consent to obtain and process data from their treating healthcare providers.

Assessment of age at menopause

The self-reported age at menopause was assessed during the baseline interview using a questionnaire. Age at menopause was defined in retrospect as the age at final menstrual period, which was followed by cessation of menses that lasted at least 12 months [19]. In addition, to define the nature of menopause, women were asked to report if bleeding was ceased naturally or was ceased because of other reason. For all women reporting menopause after gynecologic surgery or radiation therapy and for those reporting any other operations that might have led to menopause, information on the exact date and type of operation was verified using general practitioners' records.

Ascertainment of type 2 diabetes

The participants were followed from the date of baseline center visit onwards. Cases of T2D were ascertained at baseline and during follow-up through: (i) active follow-up using general practitioners' records, (ii) hospital discharge letters and (iii) glucose measurements from RS visits that took place approximately every 4 years [20]. T2D was defined according to recent WHO guidelines, as a fasting blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were absent), or the use of glucose-lowering medication. Information regarding the use of glucose-lowering medication was derived from both structured home interviews and linkage to pharmacy records [20]. Two study physicians independently adjudicated all potential events of T2D. In case of disagreement, consensus was sought with an endocrinologist. Follow-up data were through January 1st 2012.

Follow-up for mortality

Mortality data were obtained by notification from the municipal administration. Participants were followed from the first day they entered the study till the day of death, the day of lost to follow-up or the last date of contact, whichever came first. Data on all-cause mortality and living status were updated biweekly until August 1st 2016. The method applied requires all outcomes to have the same end date. In our data, the follow up for diabetes was until January 1st 2012, therefore all the analyses were truncated accordingly.

Assessment of potential confounders

Based on previous literature[7, 10, 16, 17, 21-24], biological plausibility and data availability in the RS, potential confounding variables (including age, smoking, alcohol, education level, hormone therapy, physical activity, age at menarche, number of pregnancies and oral contraceptive use) were selected for the analyses. Also, to account for any potential effect of the cohorts in the RS, we additionally adjusted all our analyses for cohort (I, II and III). Information on current health status, medical history, medication use and smoking behavior was obtained at baseline (RSI-3, RSII-1 and RSIII-1). Participants were asked whether they were currently smoking cigarettes, cigars, or pipes. Alcohol intake was assessed in grams of ethanol per day. Education was defined according to the standard international classification of education as low (primary education), intermediate (secondary general or vocational education), or high (higher vocational education or university). Data on age at menarche were collected by asking women, “How old were you when you had your first menstrual period?”. The retrospective data on self-reported number of pregnancies and use of hormone therapy were collected by a questionnaire during the home interview. Physical activity was assessed using the LASA Physical Activity Questionnaire (LAPAQ) and is expressed in METhours/week.

Data analysis

Data are presented as mean (± SD) for normally distributed continuous variables and median (range) for continuous variables that are not normally distributed. When fitting the models and checking for multicollinearity, in our analyses variance inflation factor (VIF) was lower than 3, suggesting no evidence of collinearity. The One-way ANOVA test (for continuous variables) and $\chi 2$ (for categorical variables) were used to compare parameters between the groups. We created population-based multistate life tables to calculate life expectancy and years lived with and without T2D in early (≤44 years old), normal (45-54 years old) and late menopause (≥55 years old, reference) categories. The multistate life table is a demographic tool that allows the experience of individuals in different health states to be combined in order to calculate the total life expectancy and the amount of years that individuals could expect to live in the different health states. We considered 3 different health states: free of T2D, T2D, and death. Participants could experience the following transitions: from free of T2D to T2D or death and from T2D to death. No backflows were allowed (eg. from having T2D to not having T2D), and only the first entry into a state was considered.

To obtain transition rates, we first calculated the overall age-specific rates for each transition. Next, we calculated the prevalence of early, normal, and late menopause by 10-year age groups, and separately for women with and without diabetes. Hazard ratios (HRs) comparing women who experienced early and normal menopause to women who experienced late menopause were calculated using Poisson regression ("Gompertz" distribution) in two models. In model 1 we adjusted for age and cohort. In model 2 we additionally adjusted for potential confounders including: smoking status (current smokers vs former/ever smokers), alcohol intake (continuous),

education level (low, intermediate and high), physical activity (continuous), use of oral contraceptives (yes vs. no), use of hormone therapy, and reproductive factors (age at menarche and number of pregnancies of at least 6 months). Finally, we calculated three sets of transition rates for each menopausal age category using (i) the overall transition rates, (ii) the adjusted HRs for T2D and mortality, and (iii) the prevalence of age at natural menopause categories by presence of T2D. Similar calculations have been described previously [25, 26]. Considering the age range of participants in RS and the small number of participants between 45 to 50 years old (N=34) we a priori decided to start the multistate life tables at the age of 50 years. We used Monte Carlo simulation (parametric bootstrapping) with 10,000 runs to calculate the 95 % confidence intervals of our life expectancy estimates with @RISK software (Palisade Corporation, Ithaca, New York) runs [27]. To deal with missing values, we used multiple imputation in SPSS (IBM SPSS Statistical for Windows, Armonk, New York: IBM). To calculate the HRs and the transition rates we used STATA version 12 for Windows (StataCorp, College Station, Texas).

Sensitivity analyses

Several sensitivity analyses were performed. To examine the impact of women who reported use of oral contraceptive at onset of menopause, we included them in the analyses (n=434). Also, to investigate both, the association of natural and non-natural menopause with T2D risk and life expectancy, we included in the analyses women with non-natural menopause. Furthermore, to explore whether there were significant differences between early and normal age at menopause in risk of T2D and mortality, life expectancy, and years lived with and without T2D, we repeated the analysis using normal age at menopause category as reference.

RESULTS

Baseline characteristics

Mean age at menopause in the early, normal and late categories were respectively 41years (SD = 3.0), 50 years (SD=2.5) and 56 years (SD=1.6) (Table 1). Compared to women who experienced late menopause, early menopausal women had lower education levels, drank less and were more likely to smoke (Table 1).

Diabetes events and death

Of the 3240 postmenopausal women free of diabetes at baseline, 305 women developed incident T2D over a median follow-up of 9.2 years (Table 2). Among women free of diabetes, 489 women died during the follow-up (median= 6.9 years), whereas 164 women died among women with T2D (median follow-up= 4.9 years). Both models yielded similar estimates; therefore, we further report the results of the most adjusted model (model 2). Compared to late menopause, early (HR=1.42, 95% CI: 1.01, 2.00), but not age at normal menopause (HR=1.13, 95% CI: 0.85, 1.49) was associated with an increased risk of mortality among women free of diabetes. Among diabetic women with early and normal menopause, the HRs for mortality were 1.64 95% CI: 0.93, 2.88, and 0.85 95% CI: 0.52, 1.39 respectively, relative to those with late menopause (Table 2).

Total life expectancy and life expectancy with and without type 2 diabetes.

The association of early, normal, and late menopause with the risk of each health/disease/death transition was translated into the number of years lived with and without diabetes (Figure 2). Total life expectancy at the age of 50 years was lower in women who had an early menopause and higher in women who had a late menopause. Compared to women with late menopause, the difference in life expectancy for women with normal and early age at menopause was 0.5 95% CI: -2.1, 1.3 and 3.5 95% CI: -6.6,-0.8 years, respectively. Compared to women with late menopause, the difference in life expectancy for women with normal and early age at menopause was 1.3 95% CI: -4.3, 0.8 and 4.6 95% CI: -8.9,-0.9 years without T2D as well as 0.8 years 95% CI: -1.3, 2.4 and 1.1 years 95% CI: -1.8, 4.4 years with T2D, respectively.

Sensitivity analyses

Total life expectancy and the number of years lived with and without T2D did not significantly differ after including women who reported using oral contraceptives. These results are presented in Supplemental Digital Content Table S1, Table S2, Figure S2. The results were attenuated, but did not substantially change after the inclusion of women with non-natural menopause (results are shown in Supplemental Digital Content Table S3, Table S4 and Figure S3). Furthermore, the difference in life expectancy for women who experienced early menopause, compared to women with normal age at menopause was -3.1 95% CI: -5.1,-1.1) and -3.3 95% CI: -9.5, -0.6 years overall and without T2D respectively, and 0.2 95% CI: -2.0,2.8 years with T2D, although the latter was not a statistically significant difference. Results using the normal menopause group as the reference category are presented in Supplemental Digital Content Figure S2, Table S5 and S6.

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DISCUSSION

At the age of 50 years, women who experienced early menopause lived less years and spent fewer years without diabetes than women who experienced normal or late menopause. Compared to women with normal or late age at menopause, women with early menopause lived at least 3.1 years fewer overall and at least 3.3 years fewer without diabetes, respectively.

The decreased life expectancy without diabetes among women with early menopause might be due to the increased risk of T2D and mortality associated with early menopause. The higher risk of diabetes in women with early age at natural menopause might reflect an earlier diagnosis of diabetes across the lifespan and therefore, a decreased life expectancy without T2D, although the difference in years lived overall and without T2D did not differ significantly. Furthermore, early menopause was also associated with an increased mortality risk among participants without T2D, resulting in a further decrease in total life expectancy and number of years lived without T2D. The number of years lived with diabetes was a result of incident diabetes risk and mortality risk among those with diabetes. In our study, no significant association was observed of age at menopause with mortality among women with diabetes, which could be due to the small number of cases in this transition (transition 3). Life expectancy with diabetes was at least 0.2 and 1.1 years more for women with early age at menopause compared with those who experienced normal and late menopause respectively. This reflects two opposing results: 1) higher incidence of diabetes in women who experienced early menopause increasing the time spent with diabetes; and 2) increased mortality associated with early menopause in diabetic patients, decreasing the time spent with diabetes. The net result is that women who experienced early menopause lived shorter and did not spend more years with diabetes.

In our study, total life expectancy in women aged 50 years and over was very similar between normal and late menopause and significantly decreased in the early menopause group. Consistent with our findings, data from a breast cancer screening cohort reported that a later menopause is associated with a longer overall survival and higher life expectancy [13]. In that study, women who experienced menopause at the age of 55 years or after lived 2 and 1 years longer than those who experienced menopause before the age of 40 and at age 40-44 respectively, which is slightly less than our findings. This discrepancy could be explained by differences in: (i) age of participants; (ii) categorization of age at menopause and (iii) in the calendar time of baseline measurements. Also, our study included only women who experienced natural menopause, whereas the previous study included women experiencing natural and not-natural menopause. Furthermore, in the previous study, the calculations for the life tables were made using a hypothetical population of women aged 50 years, obtaining estimates by modelling and simulation. In contrast, our study calculated the life expectancy with and without diabetes from direct observation of a well-defined population using multistate life tables.

Previous studies have reported that among major modifiable risk factors, never smoking was associated with the largest gain in total life expectancy in women (up to 4.1 years), followed by high physical activity (3.4 years) and normal weight (1.0 year) [28]. In our study, adjustment for these factors to rule out their influence on the association between age at menopause and T2D did not materially change the results. Previous studies investigating the association of age at menopause and mortality or diabetes, have also reported no changes in estimates when adjusting for smoking [7, 13], suggesting that smoking habits could not explain our findings. However, it would be of interest to explore whether smoking and early menopause are related through epigenetic mechanisms which can further affect women's health later in life.

To our knowledge, this is the first study that investigated the association of age at natural menopause with life expectancy with and without T2D. Other major strengths include the prospective design with a long-term follow-up; the large number of participants and the adjustments for a broad range of potential confounders.

Several limitations of this study should be addressed. Age at menopause was assessed by questionnaires that could be subject to some measurement error. Another limitation was the reliance on retrospective self-report of age at menopause that could be subject to memory and reporting bias, particularly in older women. In addition, inaccuracy from reporting bias would have been non-differential in relation to the menopausal categories. Hence, it is unlikely that this would have created any difference between groups. However, because T2D and mortality were assessed prospectively, the subjective measure of age at menopause would likely lead to non-differential misclassification with respect to the outcome, and therefore would likely bias our estimates toward the null. Furthermore, studies have reported that the validity and reproducibility of self-reported age at menopause is fairly good [8, 29].

Moreover, diabetes might have been subclinical at baseline and because age at menopause was retrospectively self-reported, the possibility of reverse causality should be considered. However, all women in our study were already postmenopausal years before incident diabetes occurred. Also, all women in RS had an assessment of fasting plasma glucose which would have helped to detect subclinical diabetes and therefore reverse causality is less likely to have happened.

Further, a time difference was observed between the start of the RS and the onset of menopause, which might have introduced immortal-time bias. Nevertheless, if immortal-time bias was present, the true point estimate for the relationship between early

menopause, T2D and mortality may be larger than we observed. Also, all population-based cohorts involving active participation are subject to the healthy volunteer effect [30] therefore the mortality rates in our study might be lower than those in the general population, thus leading to underestimation of the results [31]. Finally, the generalizability of our findings can be limited to middle-aged and older white European populations, and therefore, our results need confirmation in other populations.

These results support findings of prior studies that suggest that age at natural menopause might be a risk factor for mortality. Another hypothesis might be that both early menopause and premature death could be associated by a third factor, which may also partly explain the underlying mechanisms of the greater risk of T2D in women with early menopause. Epigenetic modifications such as DNA methylation of cytosine residues in CpG dinucleotides histone modification and micro RNAs might constitute an additional pathway linking the timing when menopause occurs with longevity and type 2 diabetes [32]. Future studies should explore epigenetic modifications associated with age at natural menopause and whether epigenetic signatures can explain the association between the onset of natural menopause with mortality and type 2 diabetes risk. In addition, our results provide supporting evidence for public health interventions aiming at delaying in menopause to reduce the incidence of T2D, postpone mortality and prolong total life expectancy as well as the years lived free of diabetes. Studies have shown that various lifestyle factors [22] such as smoking cessation [23, 33], low to moderate alcohol consumption [23], better nutrition and lower body mass index [21, 34], better socioeconomic status [22], are associated with a later menopause. Considering the observational nature of the studies so far, it is unclear whether these factors have a causal effect on age of menopause. Therefore, more research is needed to understand the direction of these associations

to help define better health policies. Also, our findings might be important for the health care sector since diabetes poses a significant financial burden on healthcare and nations' welfare budget [35].

CONCLUSIONS

In our study, women who experienced early menopause lived fewer years overall and spent less years without diabetes than women who experienced normal or late menopause. Future studies are needed to examine the mechanisms behind the association of age at natural menopause with type 2 diabetes and mortality, in order to tailor prevention and treatment strategies to improve women's health across all age-categories of menopause.

Author's contribution:

Study concept and design: TM and OHF

Acquisition, collection, analysis, or interpretation of data: EA, AB, MG, LJ, MAF, JSEL, HV, TM, OHF

Drafting of the manuscript: EA, TM

Critical revision of the manuscript for important intellectual content: AB, MG, LJ, MAF, JSEL, HV, TM, OHF

Statistical analyses: EA

Study supervision: TM, OHF

All authors approved the final version of the manuscript.

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335 FIGURES

336 **Figure 1.** Flow chart of participants in the study, the Rotterdam Study (1997-2012).

337 Abbreviations: RS the Rotterdam Study

338 Figure 1 shows the number of women eligible for the analysis after applying the inclusion and exclusion criteria to enter the study.

339

340 **Figure 2.** Life expectancy at 50 years old among women with late, normal and early menopause.

341 Abbreviations: LE life expectancy; T2D type 2 diabetes

342 In dark grey is depicted life expectancy free of diabetes and in light grey is depicted life expectancy with diabetes.

343 *Results after adjusted for: age, cohort, education levels, alcohol, smoking, age at menarche, hormone therapy, physical activity,

344 number of pregnancies and oral contraceptive use.

345 **Late menopause group is the reference category.

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Published in final edited form as: *Menopause*. 2019 Apr;26(4):387-394. doi: 10.1097/GME.0000000000001246.

Figure 1. Flow chart of participants in the study, the Rotterdam Study (1997-2012).

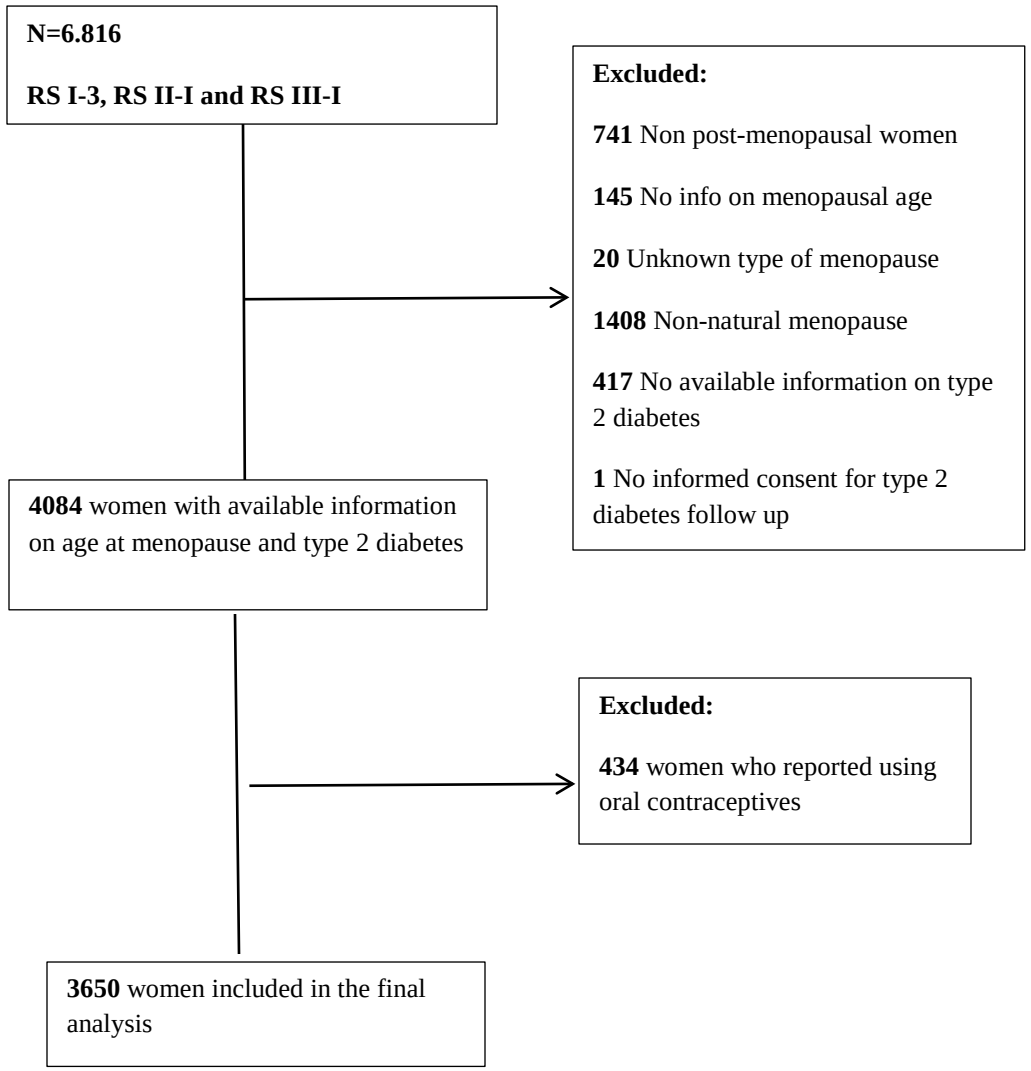

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Table 1. Baseline Characteristics of 3.650 Women by Age at Menopause Categories, the Rotterdam Study (1997-2012).

Characteristics	Categories of age at menopause*			P-value
	Early (n= 414)	Normal (n=2787)	Late (n= 449)	
Age, mean (SD), y	69.0 (10.6)	67.4 (9.8)	67.9 (8.6)	0.005
Age at menopause, mean (SD)	40.8 (3.0)	50.2 (2.5)	56.0 (1.6)	<0.001
Type 2 Diabetes, Yes (%)	54 (13.0)	304 (10.9)	52 (11.6)	0.11
Age at menarche, mean (SD)	13.4 (1.9)	13.4 (1.7)	13.6 (2.0)	0.216
Education, No. (%)				<0.001
Primary	97 (23.4)	427 (15.3)	55 (12.2)	
Lower	200 (48.3)	1451 (52.1)	234 (53.2)	
Intermediate	88 (21.3)	622 (22.3)	108 (23.0)	
Higher/university	29 (7.0)	287 (10.3)	52 (11.6)	
Smoking Status, Yes. (%)	119 (28.7)	539 (19.3)	54 (12.0)	<0.001
Alcohol, mean (SD), g/day	8.7 (11.9)	9.5 (12.5)	11.4 (13.6)	0.003
Physical activity (METhours/week)	81.4 (44.4)	85.3 (50.4)	83.5 (43.7)	0.297
Hormone therapy, Yes (%)	9 (2.2)	73 (2.6)	9 (2.0)	0.671
Oral contraceptive use, yes (%)	190 (45.9)	1464 (52.5)	230 (51.2)	0.041
Number of pregnancies, mean (SD)	2.5 (2.3)	2.3 (1.9)	2.3 (1.8)	0.235

*Menopause categories are defined as: Early ≤44 years old, Normal 45-54 and Late ≥55years old.
Abbreviations: SD; standard deviation

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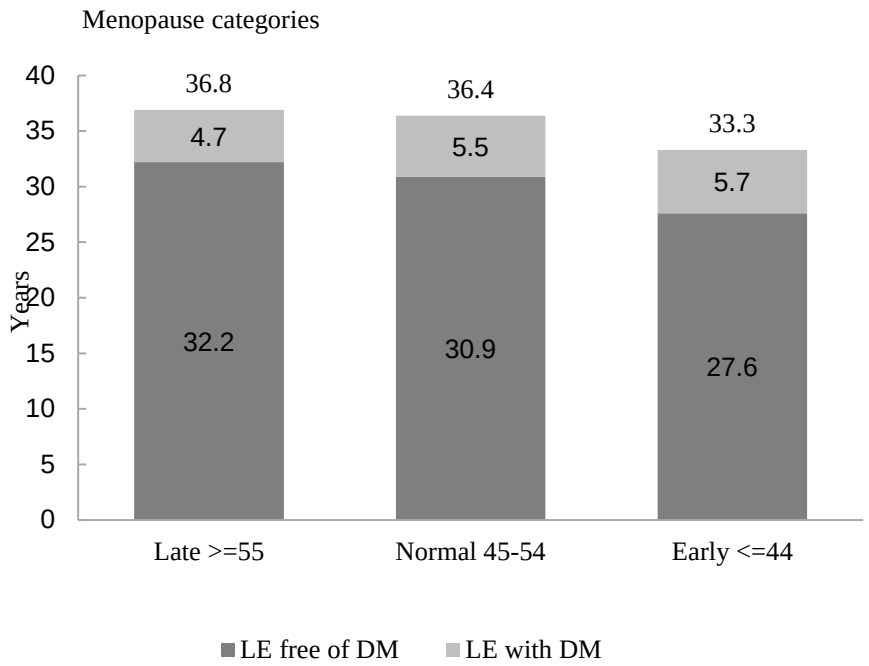
Table 2. Hazard Ratios by Transition Among Categories of Age at Menopause.*

Transition	No. Of Cases	Person-years	Age at Menopause Categories	HR†	95% CI	HR‡	95% CI
Incident T2D	28	2612	Late	1.00		1.00	
	234	21826	Normal	1.22	0.84,1.78	1.14	0.78,1.67
	42	3917	Early	1.89	1.20,2.97	1.69	1.07,2.67
No T2D to Death	68	2607	Late	1.00		1.00	
	519	19901	Normal	1.16	0.88,1.54	1.13	0.85,1.49
	97	3719	Early	1.49	1.05,2.09	1.42	1.01,2.00
T2D to Death	28	664	Late	1.00		1.00	
	148	3507	Normal	0.91	0.56,1.48	0.85	0.52,1.39
	44	1043	Early	1.73	0.99,3.00	1.64	0.93,2.88

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes.
*Age 50 and over at start of follow-up
† Adjusted for age and cohort
‡ Adjusted for age, cohort, smoking, alcohol, education, physical activity, oral contraceptive use, hormone therapy, age at menarche, number of pregnancies.

Figure 2. Life expectancy at 50 years old among women with late, normal and early menopause.



Abbreviations: HR, hazard ratio; LE life expectancy; T2D type 2 diabetes
*Results after adjusted for: age, cohort, education levels, alcohol, smoking, menarche, HT, physical activity, number of pregnancies and OC use.
**Late menopause group is the reference category.

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389 **Table 3.** Differences of age at menopause categories on life expectancy.

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Age at menopause categories	Difference in total LE		Difference in LE free of T2D		Difference in LE with T2D	
	Years	95% CI	Years	95% CI	Years	95% CI
Early vs. Late	-3.5	-6.6,-0.8	-4.6	-8.9,-0.9	1.1	-1.8,4.4
Normal vs. Late	-0.5	-2,1,1.3	-1.3	-4.3,0.8	0.8	-1.3,2.4
Early vs. Normal	-3.1	-5.1,-1.1	-3.3	-6.0,-0.6	0.2	-2.0,2.8

Abbreviations: LE life expectancy; T2D type 2 diabetes, CI confidence interval