Fertile lifespan characteristics and all-cause and cause-specific mortality among postmenopausal women: the Rotterdam Study

Loes Jaspers, M.D.,[a] Maryam Kavousi, M.D., Ph.D.,[a] Nicole S. Erler, Dipl.-Stat.,[a,b] Albert Hofman, M.D., Ph.D.,[a,c] Joop S. E. Laven, M.D., Ph.D.,[d] and Oscar H. Franco, M.D., Ph.D.[a]

[a] Department of Epidemiology, [b] Department of Biostatistics, and [d] Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Erasmus University Medical Centre, Rotterdam, the Netherlands; and [c] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

Objective: To characterize the relation between established and previously unexplored characteristics of the fertile life with all-cause and cause-specific mortality.
Design: Prospective cohort study.
Setting: Not applicable.
Patient(s): A total of 4,076 postmenopausal women.
Intervention(s): Women's fertile lifespan (age at menarche to menopause), number of children, maternal age at first and last child, maternal lifespan (interval between maternal age at first and last child), postmaternal fertile lifespan (interval between age at last child and menopause), lifetime cumulative number of menstrual cycles, and unopposed cumulative endogenous estrogen (E) exposure.
Main Outcome Measure(s): Registry-based all-cause and cause-specific mortality.
Result(s): A total of 2,754 women died during 14.8 years of follow-up. Compared with women with 2–3 children, a 12% higher hazard of dying was found for women having 1 child (hazard ratio [HR], 1.12; 95% confidence interval [CI] 1.01–1.24), which became nonsignificant in models adjusted for confounders (HR, 1.08; 95% CI 0.96–1.21). Late age at first and last birth were associated with a 1% lower hazard of dying (HR, 0.99; 95% CI 0.98–1.00). Longer maternal and postmaternal fertile lifespan (HR 1.01; 95% CI 1.00–1.02), longer fertile lifespan (HR 1.02; 95% CI 1.00–1.05), and unopposed cumulative E exposure (HR, 1.02; 95% CI 1.00–1.04) were significantly harmful for all-cause mortality. Findings differed with regard to direction, size, and statistical significance when stratifying for cardiovascular disease, cancer, and other mortality.
Conclusion(s): Overall, we found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, postmaternal fertile lifespan, and E exposure were harmful for all-cause mortality. More research is needed in contemporary cohorts with larger sample sizes and more extreme ages of birth. (Fertil Steril® 2017;107:448–56. ©2016 by American Society for Reproductive Medicine.)
Key Words: Fertility, longevity, mortality

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/13103-22973

Received August 24, 2016; revised and accepted November 3, 2016; published online December 2, 2016.
L.J. reported receiving research support from Metagenics Inc. M.K. is supported by the Netherlands Organisation for Scientific Research (NWO) Veni grant (Veni, 91616079). N.S.E. has nothing to disclose. A.H. has nothing to disclose. J.S.E.L. has received unrestricted research grants from the following pharmaceutical companies (in alphabetical order): Ferring, Merck Sharpe & Dome (MSD), Merck Serono, Organon, Serono, Schering Plough. O.H.F. reported receiving grants or research support from Metagenics Inc.
Joop S.E. Laven and Oscar H. Franco should be considered similar in author order.
Supported by Erasmus Medical Centre and Erasmus University, Rotterdam, the Netherlands; the Netherlands Organisation for Scientific Research (NWO); the Netherlands Organisation for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. This study was sponsored and funded by Metagenics Inc. Metagenics Inc. with the steering committee were not involved in study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit for publication. The funder/sponsor did not have the ability to veto publication of study results.
Reprint requests: Loes Jaspers, M.D., Department of Epidemiology, Erasmus University Medical Center, Dr. Molewaterplein 50, PO Box 2040, Office NA-2914, Rotterdam 3000 CA, the Netherlands (E-mail: l.jaspers@erasmusmc.nl).

Fertility and Sterility® Vol. 107, No. 2, February 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.11.006

During the past decades there has been a major interest in the role of fertility characteristics, including parity and timing of childbirth, in later life health (1). This research area has intensified during the past 20 years given the demographic trends wherein couples tend to postpone childbirth to later life stages (2). Since the 1970s, the proportion of European women aged ≥30 years at first childbirth increased from 8%–40% and the mean age hereof increased by 4–5 years (3). The paradigm shift in reproductive choices is not without risk as it could lead to involuntary childlessness and

unattained desired family sizes (4). In addition, pregnancy complications and maternal mortality rates are higher during late motherhood at advanced ages (5). Nevertheless, benefits from these changing fertility patterns on mortality and longevity have also been widely observed (1).

Several measures of fertility potential have been suggested, some of which include late reproduction, parity, and age of menopause (6). The fertile lifespan (the interval between menarche and menopause), which has been used as a proxy for endogenous sex steroid exposure in cardiometabolic studies (7), could serve as physiologic index for fertility capacity (8, 9). In addition, because most women do not use their entire reproductive period to bear children, it may be of interest to look at more precise measures of the childbearing potential through extra characteristics, which include maternal lifespan (the interval between age at first birth and age at last birth) and postmaternal fertile lifespan (the interval between age at last child and age of menopause).

The full spectrum of fertile lifespan characteristics in association with all-cause or cause-specific mortality has not been examined. Particularly for several characteristics, such as age at last birth in relation to cause-specific mortality, the evidence is limited. In the present study we cover a range of established and previously unexplored characteristics of the fertile lifespan and expand the scope from all-cause to cause-specific mortality. Hence, we aimed to assess the associations between eight characteristics of the fertile lifespan (number of children, age at first birth, age at last birth, maternal lifespan, postmaternal fertile lifespan, fertile lifespan itself, lifetime cumulative number of menstrual cycles, and lifetime unopposed endogenous estrogen [E] exposure) with all-cause and cause-specific mortality in the prospective population-based Rotterdam Study.

MATERIALS AND METHODS

Study Population

The study was embedded within a prospective, population-based cohort study among subjects ≥ 55 years in the municipality of Rotterdam, the Netherlands: the Rotterdam Study (RS). The rationale and study design have been described in detail elsewhere (10).

The baseline examination was completed between 1990 and 1993 (RS-I). Of the 4,878 women enrolled in the RS at baseline, 4,076 postmenopausal women were included in the present study. Women without informed consent (n = 187), missing data in >50% of the covariates (n = 123), missing age of menarche or menopause (n = 473), or missing age at first birth, last birth, or number of children (n = 19) were excluded from the analyses. An overview of the participant flow can be found in the flowchart (Supplemental Fig. 1, available online). The RS has been approved by the Medical Ethics Committee of the Erasmus Medical Centre and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Assessment of Fertile Lifespan Characteristics

The self-reported number of children, age of the mother at first and last birth, and age at menarche and menopause were assessed during the baseline interview using a questionnaire. Age at menopause was defined in retrospect as the age at final menstrual period, after a 12-month period of amenorrhea (11). Maternal lifespan was defined as the interval between maternal age at first and last birth in women that had two or more children, and may be a more precise measure of the childbearing period compared with the fertile lifespan, considering the fact that women do not use the entire fertile period to bear children. The postmaternal fertile lifespan was made by subtracting maternal age at last birth from age of menopause. Both age of menopause and age at last birth could be considered indirect proxies for fertility (6). Fertile lifespan in years was calculated by subtracting the age at menarche from the age at menopause. Lifetime cumulative number of menstrual cycles was calculated by subtracting 9 months for each pregnancy, 4 months of breastfeeding for every born child (12, 13), and contraceptive use duration in months from the reproductive lifespan in months. This value, the cumulative endogenous E exposure, was then converted to years, after which it was multiplied by the reported mean number of menstrual cycles per year (12, 14). To get the unopposed cumulative endogenous E exposure, the total postovulatory period in months ({lifetime number of menstrual cycles $\times$ 2}/4), was subtracted from the cumulative endogenous E exposure in months (12).

Assessment of All-cause and Cause-specific Mortality

Mortality data were obtained by several complementary approaches to ascertain (cause of) death for all participants of the RS. Data sources included the central registry of the Municipality of Rotterdam, records from collaborating general practitioners, and information obtained during follow-up rounds. If the vital status of participants was missing, the Central Registry of Genealogy of the Netherlands was consulted. Two research physicians independently classified the cause of death according to the International Classification of Diseases, 10th revision (15), from which cause-specific mortality was assessed. In case of disagreement, consensus was sought in a separate session. All causes of death were approved by experienced field-specific experts for final classification. For all-cause mortality participants were followed until March 3, 2015, and for cause-specific mortality until January 1, 2013. For the study of cause-specific mortality, we created three groups: cardiovascular mortality, cancer mortality, and other deaths (Supplemental Methods, available online).

Assessment of Covariates

Socioeconomic and environmental conditions and family planning can greatly impact the potential biological association between fertility and mortality (6). Therefore, the following covariates were considered for inclusion in the statistical models: baseline age, education level, marital status,

household income, ethnicity, smoking, alcohol intake, diet, physical activity, hormonal contraceptive use, female hormone use, prevalent chronic disease, cycle regularity at 25 years of age, menopause type, and waist-to-hip ratio. In addition, women of the same age can have different ages of menopause. Timing of menopause is associated with fertile lifespan characteristics and with postmenopausal health (16). Hence, time since menopause was included as a covariate in statistical models. All covariates were self-reported, except for body mass index (BMI) and waist-to-hip ratio, which was measured by research assistants at the study center. A description of the definitions and coding of all covariates can be found in the Supplemental Methods section.

Statistical Analysis

As a first step the distributions of all fertile lifespan characteristics was assessed. Because all of these variables were approximately normally distributed, no transformation was necessary. The correlations between the variables number of children, age of the mother at first and last birth, and age at menarche and menopause (the variables used to make the eight fertile lifespan characteristics), were assessed using the Pearson's correlation coefficient.

The association between the eight fertile lifespan characteristics (all analyzed continuously) and all-cause and cause-specific mortality were assessed using Cox regression. P-splines were used to characterize the shape of the effect of each continuous exposures with all-cause mortality and to identify any potential nonlinear associations (17). In addition, fertile lifespan characteristics were analyzed categorically using categories adapted from literature; if no evidence-based categorizations were available, quartiles were used (18–21). The proportional hazards assumption was checked by testing the significance of the interaction term of each exposure with time in the Cox models (e.g., Time × Number of children), and this assumption held for all exposures.

Model 1 was adjusted for age and time since menopause. Model 2 was additionally adjusted for education level, marital status, household income, hormonal contraceptive use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, and waist-to-hip ratio. These covariates were chosen because they were statistically associated with the exposure (e.g., fertile lifespan characteristic) and the outcome (mortality) at $\alpha<0.2$ (22). The same models were created for all-cause and cause-specific mortality. Covariates were imputed using fully conditional specification using the Markov chain Monte Carlo method (n = 5 imputations).

Two prespecified interactions were tested in model 2: Age × Exposure (e.g., age × age at last child) and Number of children × Exposure (e.g., number of children × age at last child). If the interaction term was significant, the analyses were stratified to show potential differential effects.

As a sensitivity analysis, a complete case analysis was performed to assess whether the imputation process influenced the findings. Furthermore, in a second sensitivity analysis, the population was restricted to women who never used hormonal contraceptives, to assess the magnitude of the effect of family planning behavior through fertility control (23). In addition, in a third sensitivity analysis, we restricted the population to healthy individuals by means of excluding all women with prevalent chronic disease at baseline or women who died within the first 3 years after baseline (these women may have underlying unknown chronic diseases).

RESULTS

Descriptive Statistics

An overview of the study characteristics can be found in Table 1. Women had a median age of 69.1 years (interquartile range, 62.2–76.6) and most women were of Northern European descent (98.4%). The median number of children women gave birth to was two (interquartile range, 1–3) and the mean age at first and last birth were 26.4 years (SD 4.5) and 32.1 years (SD 5.5), respectively.

During the study period, 2,754 women died of any cause and the median follow-up time was 16.6 years (interquartile range, 9.0–21.0). Until January 1, 2013, 780 women died of cardiovascular disease, 547 women of malignant cancers, and 1,024 of other causes (Supplemental Table 1, available online). All variables from which the fertile lifespan characteristics were derived were significantly correlated with each other, except for age at menarche, which was only correlated with age at last birth (Supplemental Table 2, available online).

Maternal Characteristics

The Cox regression results for the association between fertile lifespan characteristics and all-cause mortality can be found in Table 2. Compared with the reference group of women who had 2 or 3 children, a 12% higher hazard of dying was found for women having 1 child in model 1 (hazard ratio [HR], 1.12; 95% confidence interval [95% CI] 1.01–1.24), which became statistically nonsignificant in model 2 (HR, 1.08; 95% CI 0.96–1.21). A 1-year increase in age at first birth was associated with a 1% lower hazard of dying in models 1 and 2 (HR, 0.99; 95% CI 0.98–1.00). When compared to the reference group of women giving birth between 25 and 34 years, older women (e.g., ≥35 years) had a 25% lower hazard of dying in model 2 (HR, 0.75; 95% CI 0.61–0.93). For age at last birth, a 1-year increase was associated with a 1% lower hazard of dying in model 1 (HR, 0.99; 95% CI 0.98–1.00). A 1-year longer maternal and postmaternal fertile lifespan was significantly associated with a 1% higher hazard of dying in model 1 (HR, 1.01; 95% CI 1.00–1.02), but lost significance in model 2.

Some differences were observed when comparing the association of fertile lifespan characteristics with cause-specific mortality to the association with all-cause mortality (Supplemental Tables 3–5, available online). For number of children, having no children compared with having 2–3 children was associated with a 26% higher hazard for cardiovascular mortality (HR, 1.26; 95% CI 1.02–1.56). Late age at first birth (≥25 years) resulted in a 16% higher hazard for cancer mortality (HR, 1.16; 95% CI 0.94–1.46), whereas this was associated with a 15% lower hazard for other mortality (HR, 0.85; 95% CI 0.73–0.99). Late age at last birth (≥35 years) resulted in a 17% lower hazard for cardiovascular

TABLE 1

Characteristics of the study population (n = 4,076).

Characteristic	Value
Age (y), median (IQR)	69.1 (62.2–76.6)
Time since menopause (y), mean (SD)	21.2 (10.7)
Waist-to-hip ratio, mean (SD)	87.1 (8.9)
BMI (kg/m^2), mean (SD)	26.7 (4.0)
Education, n (%)	
Primary	1,230 (30.2)
Lower/intermediate or lower vocational	1,873 (45.9)
Intermediate vocational or higher general	812 (19.9)
Higher vocational or university	161 (4.0)
Marital status, living with partner, n (%)	2,087 (51.2)
Equivalent household income (/1000,-), median (IQR)	1.8 (1.2–2.5)
Ethnicity (white), n (%)	4,011 (98.4)
Menopause type (natural), n (%)	3,827 (93.9)
OC (yes), n (%)	1,172 (28.7)
Female hormone use (yes), n (%)	544 (13.3)
Prevalent chronic disease (yes), n (%)	629 (15.4)
Coronary heart disease	176 (4.4)
Heart failure	137 (3.4)
Stroke	89 (2.2)
Diabetes mellitus	206 (5.1)
Cancer	28 (2.3)
COPD	104 (2.6)
Smoking (current), n (%)	752 (18.4)
Alcohol intake (glasses/d), median (IQR)	0.1 (0–0.7)
Physical activity (ideal levels), n (%)[a]	3,655 (89.7)
Fertile lifespan characteristics	
Children (n), median (IQR)	2 (1–3)
Children, n (%)	
0	845 (20.7)
1	665 (16.3)
2	1,141 (28.0)
3	743 (18.2)
4	383 (9.4)
≥5	299 (7.3)
Age (y) at first birth, mean (SD)	26.4 (4.5)
Age (y) at first birth, n (%)	
≤19	166 (5.1)
20–24	1,166 (36.1)
25–34	1,745 (54.0)
≥35	154 (4.8)
Age (y) at last birth, mean (SD)	32.1 (5.5)
Age (y) at last birth, n (%)	
≤24	335 (10.4)
25–34	1,880 (58.2)
35–39	743 (23.0)
≥40	273 (8.4)
Maternal lifespan (y), median (IQR)	5.0 (2.0–9.0)
Postmaternal fertile lifespan (y), mean (SD)	16.8 (7.0)
Fertile lifespan (y), mean (SD)	35.2 (5.3)
Lifetime number of menstrual cycles, mean (SD)	331.4 (106.4)
Unopposed cumulative endogenous E exposure (y), median (IQR)	16.1 (12.8–18.6)

Note: BMI = body mass index; COPD = chronic obstructive pulmonary disorder; E = estrogen; IQR = interquartile range; OC = oral contraceptive.
[a] ≥150/≥75 min/wk of moderate and/or vigorous activity.

Jaspers. Fertility characteristics and mortality. Fertil Steril 2016.

mortality (HR, 0.83; 95% CI 0.68–1.00), whereas no effect was found for the other causes of death.

Proxies for E Exposure

A 1-year longer fertile lifespan was associated with a 2% higher hazard for all-cause mortality in models 1and 2 (HR, 1.02; 95% CI 1.00–1.05). The observed effects were similar for unopposed cumulative endogenous E exposure. No associations were found between lifetime number of menstrual cycles and all-cause mortality (Table 2).

Fertile lifespan and unopposed cumulative endogenous E exposure were associated with a 5% and 4% higher hazard for cardiovascular mortality (HR, 1.05; 95% CI 1.00–1.10 and HR, 1.04; 95% CI 1.00–1.09, respectively), but not with cancer and other mortality (Supplemental Tables 3–5). More lifetime number of menstrual cycles was significantly associated with other mortality, although the effect size reflected unity (HR, 1.00; 95% CI 1.00–1.00) (Supplemental Table 5).

Linearity and Interaction Terms

In Figure 1 the shape of the effects for each fertile lifespan characteristic and all-cause mortality are shown. There was evidence against linearity only for number of children (*P* values for each imputed set ranged from .0073–.0192), for which the association was J-shaped.

The interaction terms with baseline age were not significant (NS) for any of the fertile lifespan characteristics, whereas the interaction terms with number of children were significant for age at last birth (*P*=.03), postmaternal fertile lifespan (*P*=.03), and cumulative E exposure (*P*=.04). When stratifying the analysis for 0, 1, 2, or 3, and ≥4 children, we found that the associations were merely evident for the group of women bearing one child for age at last birth (HR, 0.97; 95% CI 0.95–0.99; *P*=.003), for postmaternal fertile lifespan (HR, 1.03; 95% CI 1.01–1.05; *P*=.003), and for endogenous E exposure (HR, 1.08; 95% CI 1.03–1.13; *P*=.002), whereas no significant associations were found for the other three groups (Table 3).

Supplemental Table 6, available online, details the multiple imputation process. In three sets of sensitivity analyses—the complete case analyses, the analyses restricted to the nondiseased population, and the analyses excluding women ever using oral contraceptives (OC)—the direction, size, and significance of the associations remained the same (data not shown). Finally, because of the 4,878 women enrolled in the RS at baseline, 4,076 postmenopausal women were included in the present study, we compared the characteristics of the included participants to the total population of women at baseline. Compared with the total female population of the RS, women included in this study were 0.8 years younger and had 0.6% less prevalent chronic disease, but did not differ for other baseline characteristics (Supplemental Table 7, available online).

DISCUSSION

Given the demographic changes in reproductive choices and their relevance for mortality and longevity, we characterized the relation between established and previously unexplored characteristics of the fertile life with mortality, and therein expanded the scope from all-cause to cause-specific mortality. Overall, we found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, postmaternal fertile lifespan, and E exposure were harmful for all-cause mortality. For late last

TABLE 2

Association between fertile lifespan characteristics and all-cause mortality.

			Model 1		Model 2	
Variable	**No.**	**Events**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Children (continuous), n	4,076	2,754	1.00 (0.98–1.02)	.83	1.00 (0.97–1.02)	.76
Children (categorical), n						
0	845	602	1.06 (0.96–1.17)	.24	1.10 (0.98–1.23)	.10
1	665	470	1.12 (1.01–1.24)	.04	1.08 (0.96–1.21)	.20
2 or 3	1,884	1,194	Reference		Reference	
≥4	682	488	1.06 (0.95–1.17)	.32	1.07 (0.95–1.19)	.28
Age (y) at first birth (continuous)	3,231	2,152	0.99 (0.98–1.00)	.003	0.99 (0.98–1.00)	.01
Age (y) at first birth (categorical)						
≤19	166	114	1.19 (0.98–1.44)	.08	1.09 (0.89–1.35)	.41
20–24	1,166	740	1.01 (0.92–1.10)	.89	0.99 (0.89–1.09)	.78
25–34	1,745	1,188	Reference		Reference	
≥35	154	110	0.79 (0.65–0.96)	.02	0.75 (0.61–0.93)	.01
Age (y) at last birth (continuous)	3,231	2,152	0.99 (0.98–1.00)	.04	0.99 (0.98–1.00)	.14
Age (y) at last birth (categorical)						
≤24	335	233	1.15 (1.00–1.32)	.06	1.17 (1.00–1.36)	.05
25–34	1,880	1,150	Reference			
35–39	743	554	0.99 (0.90–1.10)	.90	0.99 (0.89–1.11)	.87
≥40	273	215	0.97 (0.84–1.13)	.69	1.01 (0.85–1.19)	.95
Maternal lifespan, y	2,566	1,668	1.01 (1.00–1.02)	.05	1.01 (1.00–1.02)	.14
Postmaternal fertile lifespan, y	3,231	2,152	1.01 (1.00–1.02)	.04	1.01 (1.00–1.02)	.14
Fertile lifespan, y	4,076	2,754	1.02 (1.00–1.04)	.04	1.02 (1.00–1.05)	.04
Lifetime number of menstrual cycles	1,755	928	1.00 (1.00–1.00)	.15	1.00 (1.00–1.00)	.27
Unopposed cumulative endogenous E exposure, y	1,736	913	1.01 (0.99–1.03)	.24	1.02 (1.00–1.04)	.06

Note: Model 1 was adjusted for age and time since menopause. Model 2 was additionally adjusted for education level, marital status, household income, oral contraceptive (OC) use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, waist-to-hip ratio, and body mass index (BMI). CI = confidence interval; E = estrogen; HR = hazard ratio.

Jaspers. Fertility characteristics and mortality. Fertil Steril 2016.

reproduction, postmaternal fertile lifespan, and E exposure, these findings were merely evident in one-child mothers. In addition, the findings differed with regard to direction, size, and significance when stratifying for cardiovascular disease, cancer, and other mortality. From a clinical perspective, the magnitude of the associations ranged from 1%–5% lower or higher risk of dying per year increase of each fertile lifespan characteristic.

Strengths and Weaknesses

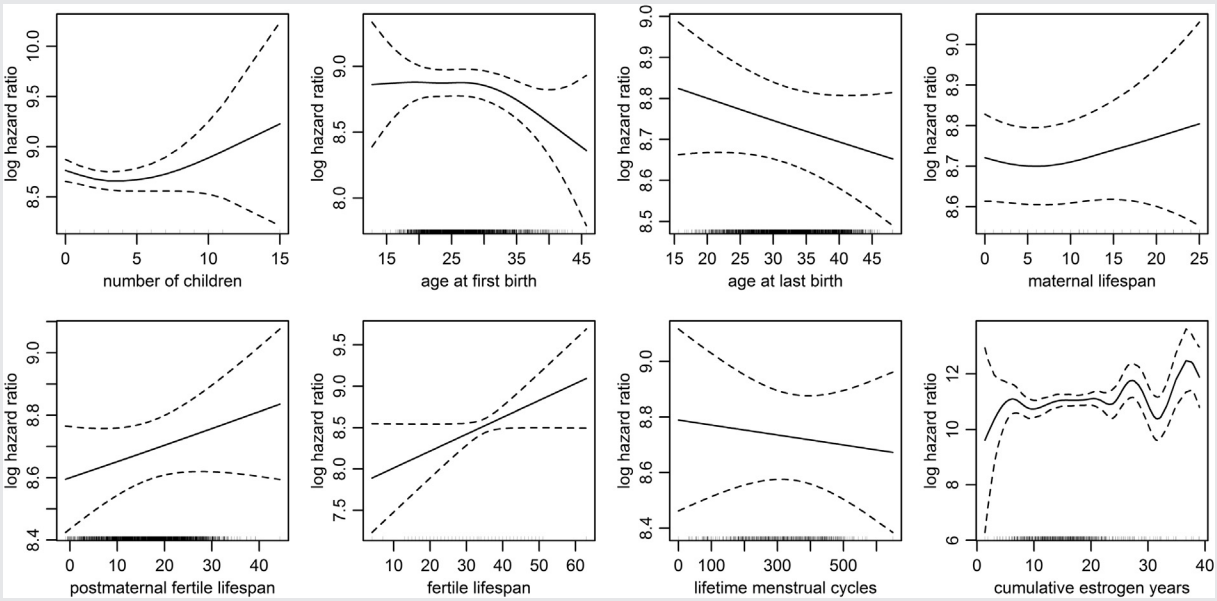
Strengths of this study included the consideration of the full spectrum of established as well as previously unexplored characteristics of the fertile lifespan, and access to the precise adjudicated causes of death information, which allowed us to study cause-specific mortality. Furthermore, the contemporary character of the cohort, in contrary to historic cohorts, provides a valuable insight into the role of fertility in longevity against a background of increasing reproductive choices and improved standards of care and therefore is applicable to the present time. In addition, the adjustment for many confounders, the graphic representation of the effects using p-splines and the stratified analysis for number of children, adds new information to the existing body of evidence in this field of work.

Several limitations merit careful consideration. Although we had information on marital status, no information was available on age at marriage and number of marriages. Furthermore, for the included women we had no information on fetal losses, abortions, and stillbirths. Assumptions were made for assembling the lifetime cumulative number of menstrual cycles and unopposed cumulative E exposure. Because fertile lifespan characteristics were assessed when women already reached menopause, retrospective recall could have occurred. However, because information on fertile lifespan characteristics were collected before the outcome (mortality) occurred, we reasonably do not expect this recall to have impacted our findings. Also, the RS comprises of men and women of ≥55 years. Hence, immortal time bias could have occurred given that women could have died during their reproductive life, for instance of maternal complications, and would therefore not be included in the studied population (24). However, even if it occurred, this would have led to an underestimation of the true effects in our study. Last, fertility characteristics may be of different importance for disease subtypes, such as breast, colorectal, and lung cancer. Our study was underpowered to stratify analyses for different disease and cancer subtypes.

Comparison with Other Studies and Possible Explanations

When comparing our findings to other studies, it is important to consider that the RS is a contemporary cohort and therefore conclusions with regard to natural fertility are limited. In contrast to historic cohorts from the 18th and 19th century where fertility followed precontraceptive patterns, in the current cohort there could have been a larger impact of

FIGURE 1



The shape of the log hazard ratio of each fertile lifespan characteristic using p-splines. The *solid line* represents the estimated log hazard ratio of each fertile lifespan characteristic; the *dashed lines* represent the 95% confidence intervals. cumu.estrogen.years = unopposed cumulative endogenous estrogen (E) exposure in years.

Jaspers. Fertility characteristics and mortality. Fertil Steril 2016.

reproductive choices. Among the included women, the youngest women were 27 years old at the time of the introduction of the first OC in the Netherlands in 1962, and only 30% of women indicated ever using OCs (24, 25). The mean age at first birth in our study was 26 years, meaning that the influence of contraceptive use was probably less pronounced for age at first birth, compared with the consecutive births thereafter. This may be supported by the large postmaternal fertile lifespan found in this study (17 years), indicating women stopped reproducing long before the onset of menopause. Where age of last birth may be influenced by family planning, economic circumstances, and socially acceptable propagation habits, age of menopause is less subject to these external factors (6). The interval between the two (e.g., postmaternal fertile lifespan) could provide insight in the potential influence of these external factors within our study population. The age at last birth was on average 32 years, whereas last reproduction was nearly 10 years later in historic cohorts (26). In sensitivity analyses we repeated the analyses excluding women who ever used OCs. The results did not substantially change with regard to significance, direction, and size of the effect.

Maternal characteristics. In line with our findings, for number of children, contemporary cohorts consistently show a nonlinear effect, with the highest mortality in nulliparous women and women bearing $\geq$4 children (19, 27), whereas the findings from historic cohorts have shown negative, neutral, and positive effects (23, 28). For age at first birth, the empirical results are inconsistent, ranging from a beneficial effect of late first birth on longevity to no effect (1, 23). In our study, we found a linear protective effect of late first reproduction on mortality, of which the statistical significance attenuated after adjusting for socioeconomic factors and lifestyle. The effects of parity and first reproduction on mortality have been explained before by evolutionary fitness trade-off theories, balancing reproductive investment and somatic maintenance (29, 30). Two of such theories are the antagonistic pleiotropy theory (e.g., the same gene could be beneficial in early life, whereas being detrimental in later life) (31) and the disposable soma theory (e.g., the limited amount of energy has to be divided between reproductive activities and maintaining the soma) (32).

Late first parenthood was protective for other mortality. Whereas early parenthood has been associated with lower socioeconomic status, particularly during childhood, and with personality characteristics, such as a tendency toward more risk taking behavior, late parenthood could be characterized by less stress and better career prospects (33). We would have expected to find the same protective effect for cardiovascular mortality (33), for which the observed hazard was around unity. We did find a significant protective effect of late last reproduction with cardiovascular mortality, which attenuated after adjustment for covariates.

There has been a particular interest in late last reproduction, as studies from both contemporary and historic cohorts consistently point toward a protective effect of late last childbirth on postreproductive survival (1, 23). In our study, we found this effect, but less pronounced than in other studies.

TABLE 3

Association between fertile lifespan characteristics and all-cause mortality, stratified based on number of children.

Variable	0 children (n = 845) HR [95% CI]	*P* value	1 child (n = 665) HR [95% CI]	*P* value	2 or 3 children (n = 1,884) HR [95% CI]	*P* value	≥4 children (n = 682) HR [95% CI]	*P* value
Age (y) at last birth (continuous)	NA		0.97 (0.95–0.99)	.003	1.00 (0.99–1.02)	.82	1.00 (0.98–1.02)	.85
Age (y) at last birth (dichotomous)	NA							
≤34	NA		Reference		Reference		Reference	
≥35	NA		0.63 (0.46–0.85)	.003	1.06 (0.92–1.22)	.43	0.98 (0.80–1.21)	.85
Postmaternal fertile lifespan, y	NA		1.03 (1.01–1.05)	.003	1.00 (0.99–1.01)	.82	1.00 (0.98–1.03)	.85
Unopposed cumulative endogenous E exposure, y	1.02 [0.95–1.10]	.54	1.08 (1.03–1.13)	.002	1.01 (0.98–1.04)	.62	1.00 (0.95–1.04)	.82

Note: The presented results are adjusted for the covariates from model 2: age, time since menopause, education level, marital status, household income, oral contraceptive (OC) use, smoking, alcohol intake, physical activity, menopause type, female hormone use, prevalent chronic disease, waist-to-hip ratio, and body mass index (BMI). CI = confidence interval; E = estrogen; HR = hazard ratio; NA = not applicable.

Jaspers. Fertility characteristics and mortality. Fertil Steril 2016.

This could be explained by the fact that only 10 of the included women gave birth to their last child at >45 years, whereas in other studies these numbers were higher (18). The shape of the effect of age at last birth was linear and protective for mortality in our study. Although most studies did not comment on this extensively, one study by Helle and colleagues (1) did not find any evidence against linearity for age at last birth, in line with our findings. There have been several theories about which mechanisms could underlie the protective effect of late last reproduction (23). Reproductive performance, including measures such as late age of menopause and late last reproduction, could be viewed as a marker for later life health (21, 23, 34, 35). Studies have shown that that there is a genetic link between fertility and longevity that encompasses overlapping pathways and genes for telomerase activity, apoptosis mediated through p53/p73, Foxo transcription factors, the expression of APOE, and the role of the immune system, mitochondrial function, and oxidative stress in both processes (6). In addition, reproductive performance and longevity have shown to be linked by common genetic factors related to DNA repair and maintenance. Therefore, it could be that the occurrence of menopause is a consequence of the aging of the soma that results from the deterioration of these DNA repair mechanisms.

Other investigators have suggested that extended fertility and its association with a longer lifespan might be explained by the "rejuvenation theory." This theory describes that late pregnancy, childbirth, and breastfeeding could be rejuvenating at the physiologic level (36), and that the presence of young children in the postreproductive period could extend the lifespan (37).

Early versus late childbearing. Interestingly, we found a differential effect for age at last birth when stratifying the analysis for number of children. After stratification, the protective effect of late last reproduction (>35 years) on the risk of dying, compared with last childbearing at ≤34 years, was merely evident among women with one child only. A similar interaction was found in a study by Gagnon et al. (38) in a historic context.

For age at first reproduction, the median age was 37.1, 29.3, and 25.4 years in 1-child, 2- to 3-child, and ≥4-child mothers, respectively. The ages at last reproduction were 37.1, 37.5, and 38.7 years, respectively. Because for 1-child mothers the age at first and last reproduction is the same, there is a nearly 8-year difference in first reproductive event between 1-child and >1 child mothers. A possible explanation of the observed differential effect may be that 1-child mothers precisely planned when they wanted to have their first child but due to their age may have been unable to attain their desired family size with a second or third child. Some support for this explanation comes from the recent work performed by Habbema et al. (4) finding that to have a 90% chance of giving birth to 1 child, a woman should be no older than 35 years, and to have 2 children, women should start no later than 31 years. The social factors that caused these women to have their

child late may have protected them from dying (24). When looking into the characteristics of these women, we found that older mothers were more highly educated and less often smokers compared with younger mothers.

Proxies for E exposure. The findings for fertile lifespan and unopposed cumulative E exposure were in the same line, both indicating that longer E exposure was hazardous for all-cause mortality, and cardiovascular mortality in particular, whereas no association was found between E exposure and cancer mortality. The latter could be explained by the fact that various subtypes of cancer that were included in the study, including hormonal and nonhormonal cancers. Findings from other studies reporting the association between endogenous E levels and cardiovascular outcomes have been inconsistent, particularly in the elderly. Estradiol is supposed to have a protective role in the cardiovascular system (39). However, in line with our findings, an increasing number of studies suggest the opposite (40–47).

Several potential mechanisms have been described. Visceral adiposity, which is associated with inflammation, insulin resistance/diabetes, and atherogenic dyslipidemia is suggested to increase E_2 levels through two pathways. Adiposity is negatively correlated with sex hormone-binding globulin, leading to a higher fraction of bioactive E_2. Also, central adiposity increases aromatase activity, and therefore the conversion of T into E_2 (44). Higher levels of E_2 were more strongly associated with atherothrombotic stroke in older postmenopausal women with greater central adiposity (43). In our study, adjusting for waist-to-hip ratio did not materially change the findings, indicating that pathways beyond adiposity may exist.

Another suggested explanation for this finding comes from the works of Naessen and colleagues (46, 47). They suggest that higher levels of endogenous E do not increase the risk of atherosclerosis, but that that the rise in endogenous E is a response to counteract the developing atherosclerosis (46, 47).

Conclusion and Directions for Future Research

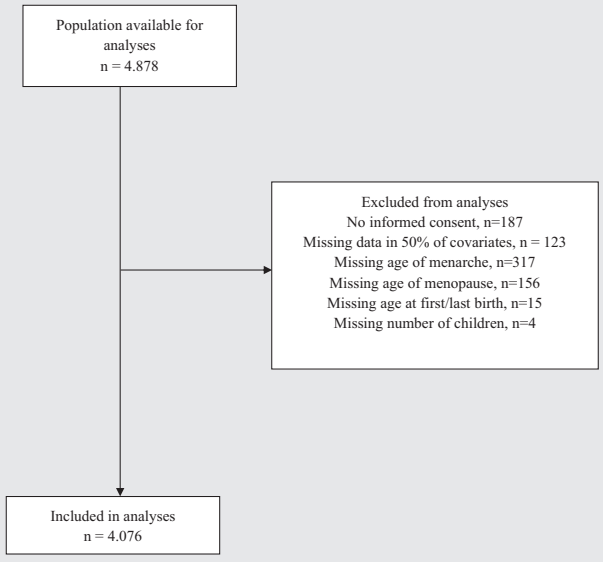
Overall, we found associations between established and previously unexplored fertile lifespan characteristics and mortality that differed for causes of death. We found that late first and last reproduction were protective for all-cause mortality, whereas a longer maternal lifespan, postmaternal fertile lifespan, and E exposure were harmful for all-cause mortality. Furthermore, with regard to late last reproduction, differences were found when comparing women with various number of children, which could partly be explained by socioeconomic status and overdue initiation of family planning. To broaden our understanding of the effect of changing fertility patterns on mortality in the present time, more research is needed in contemporary cohorts with larger sample sizes and more extreme number of children and ages of birth. The findings in contemporary cohorts may differ due to changes in women's reproductive choices, including use of hormonal contraception. The implications for women with diverse number of children for different causes of death should be further explored, taking into account insights in reproductive choices, and an extensive evaluation of the role of socioeconomic status.

REFERENCES

1. Helle S, Lummaa V, Jokela J. Are reproductive and somatic senescence coupled in humans? Late, but not early, reproduction correlated with longevity in historical Sami women. Proc Biol Sci 2005;272:29–37.
2. Laufer N. Introduction: fertility and longevity. Fertil Steril 2015;103:1107–8.
3. Lutz W, O'Neill BC, Scherbov S. Demographics. Europe's population at a turning point. Science 2003;299:1991–2.
4. Habbema JD, Eijkemans MJ, Leridon H, te Velde ER. Realizing a desired family size: when should couples start? Hum Reprod 2015;30:2215–21.
5. Sauer MV. Reproduction at an advanced maternal age and maternal health. Fertil Steril 2015;103:1136–43.
6. Wainer-Katsir K, Zou JY, Linial M. Extended fertility and longevity: the genetic and epigenetic link. Fertil Steril 2015;103:1117–24.
7. Brand JS, van der Schouw YT, Onland-Moret NC, Sharp SJ, Ong KK, Khaw KT, et al. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. Diabetes Care 2013;36:1012–9.
8. Snowdon DA, Kane RL, Beeson WL, Burke GL, Sprafka JM, Potter J, et al. Is early natural menopause a biologic marker of health and aging? Am J Public Health 1989;79:709–14.
9. Torgerson DJ, Thomas RE, Reid DM. Mothers and daughters menopausal ages: is there a link? Eur J Obstet Gynecol Reprod Biol 1997;74:63–6.
10. Hofman A, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, Ikram MA, et al. The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol 2013;28:889–926.
11. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159–68.
12. De Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. Am J Epidemiol 2002;155:339–45.
13. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. World Health Organization. Cochrane Database Syst Rev 2002:CD003517.
14. Atsma F, van der Schouw YT, Grobbee DE, Hoes AW, Bartelink ML. No added value of age at menopause and the lifetime cumulative number of menstrual cycles for cardiovascular risk prediction in postmenopausal women. Int J Cardiol 2008;130:190–5.
15. World Health Organization. International statistical classification of diseases and related health problems. 10th rev. Geneva: World Health Organization; 1992.
16. Laven JS, Visser JA, Uitterlinden AG, Vermeij WP, Hoeijmakers JH. Menopause: genome stability as new paradigm. Maturitas 2016;92:15–23.
17. Eilers PH, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci 1996;11:89–121.
18. Jaffe D, Kogan L, Manor O, Gielchinsky Y, Dior U, Laufer N. Influence of late-age births on maternal longevity. Ann Epidemiol 2015;25:387–91.
19. Kuningas M, Altmae S, Uitterlinden AG, Hofman A, van Duijn CM, Tiemeier H. The relationship between fertility and lifespan in humans. Age (Dordr) 2011;33:615–22.
20. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. Hum Reprod 2004;19:1548–53.
21. Perls TT, Alpert L, Fretts RC. Middle-aged mothers live longer. Nature 1997;389:133.
22. Hosmer D, Lemeshow S, May S. Chapter 5.2, Purposeful selection of covariates. In: Applied survival analysis: regression modeling of time to event data. 2nd ed. New York: Wiley-Interscience; 2008.
23. Gagnon A. Natural fertility and longevity. Fertil Steril 2015;103:1109–16.
24. Doblhammer G, Oeppen J. Reproduction and longevity among the British peerage: the effect of frailty and health selection. Proc Biol Sci 2003;270:1541–7.

25. Eerelman M. Organon koppelde sex los van voortplanting. Available at: http://www.stadsarchiefoss.nl/Default.aspx?so=g&id=113. Accessed October 2, 2015.
26. Eijkemans MJ, van Poppel F, Habbema DF, Smith KR, Leridon H, te Velde ER. Too old to have children? Lessons from natural fertility populations. Hum Reprod 2014;29:1304–12.
27. Dior UP, Hochner H, Friedlander Y, Calderon-Margalit R, Jaffe D, Burger A, et al. Association between number of children and mortality of mothers: results of a 37-year follow-up study. Ann Epidemiol 2013;23:13–8.
28. Hurt LS, Ronsmans C, Thomas SL. The effect of number of births on women's mortality: systematic review of the evidence for women who have completed their childbearing. Popul Stud (Camb) 2006;60:55–71.
29. Kirkwood TB, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. Philo Trans R Soc Lond B Biol Sci 1991;332:15–24.
30. Westendorp RG, Kirkwood TB. Human longevity at the cost of reproductive success. Nature 1998;396:743–6.
31. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. Evolution 1957;11:398–411.
32. Kirkwood TB. Evolution of ageing. Nature 1977;270:301–4.
33. Grundy E, Kravdal T. Fertility history and cause-specific mortality: a register-based analysis of complete cohorts of Norwegian women and men. Soc Sci Med 2010;70:1847–57.
34. Laven JS. Genetics of early and normal menopause. Semin Reprod Med 2015;33:377–83.
35. Perls TT, Fretts RC. The evolution of menopause and human life span. Ann Hum Biol 2001;28:237–45.
36. Yi Z, Vaupel J. Association of late childbearing with healthy longevity among the oldest-old in China. Popul Stud (Camb) 2004;58:37–53.
37. Muller HG, Chiou JM, Carey JR, Wang JL. Fertility and life span: late children enhance female longevity. J Gerontol A Biol Sci Med Sci 2002;57:B202–6.
38. Gagnon A, Smith KR, Tremblay M, Vezina H, Pare PP, Desjardins B. Is there a trade-off between fertility and longetivity? A comparative study of women from three large historical databases accounting for mortality selection. Am J Hum Biol 2009;21:533–40.
39. Vitale C, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. Nat Rev Cardiol 2009;6:532–42.
40. Chen Y, Zeleniuch-Jacquotte A, Arslan AA, Wojcik O, Toniolo P, Shore RE, et al. Endogenous hormones and coronary heart disease in postmenopausal women. Atherosclerosis 2011;216:414–9.
41. Golden SH, Dobs AS, Vaidya D, Szklo M, Gapstur S, Kopp P, et al. Endogenous sex hormones and glucose tolerance status in postmenopausal women. J Clin Endocrinol Metab 2007;92:1289–95.
42. Kalyani RR, Franco M, Dobs AS, Ouyang P, Vaidya D, Bertoni A, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. J Clin Endocrinol Metab 2009;94:4127–35.
43. Lee JS, Yaffe K, Lui LY, Cauley J, Taylor B, Browner W, et al. Prospective study of endogenous circulating estradiol and risk of stroke in older women. Arch Neurol 2010;67:195–201.
44. Turgeon JL, Carr MC, Maki PM, Mendelsohn ME, Wise PM. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: insights from basic science and clinical studies. Endocrinol Rev 2006;27:575–605.
45. Vaidya D, Golden SH, Haq N, Heckbert SR, Liu K, Ouyang P. Association of sex hormones with carotid artery distensibility in men and postmenopausal women: Multi-Ethnic Study of Atherosclerosis. Hypertension 2015;65:1020–5.
46. Naessen T, Bergquist J, Lind L, Kushnir MM. Higher endogenous estrogen levels in 70-year-old women and men: an endogenous response to counteract developing atherosclerosis? Menopause 2012;19:1322–8.
47. Naessen T, Sjogren U, Bergquist J, Larsson M, Lind L, Kushnir MM. Endogenous steroids measured by high-specificity liquid chromatography-tandem mass spectrometry and prevalent cardiovascular disease in 70-year-old men and women. J Clin Endocrinol Metab 2010;95:1889–97.

SUPPLEMENTAL FIGURE 1



Flowchart of study participants.

Jaspers. Fertility characteristics and mortality. Fertil Steril 2016.