Reproductive Factors and the Risk of Incident Dementia: Results From the UK Biobank

Jessica Gong (jgong@georgeinstitute.org.au)
The George Institute for Global Health https://orcid.org/0000-0001-6027-7640
Katie Harris
The George Institute for Global Health
Sanne A E Peters
: The George Institute for Global Health UK
Mark Woodward
The George Institute for Global Health UK

Research

Keywords: dementia, reproductive health, hormone, UK Biobank, women's health

Posted Date: March 31st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-359787/v1

Version of Record: A version of this preprint was published at Alzheimer's & Dementia on December 1st, 2021. See the published version at https://doi.org/10.1002/alz.049993.

Abstract

Background: To examine the risk of incident all-cause dementia associated with reproductive factors in women, and the number of children in both sexes; and whether the effects vary by age, socioeconomic status (SES), smoking status and body mass index in the UK Biobank.

Methods: A total of 273,265 women and 228,966 men without prevalent dementia from the UK Biobank were included in the analyses. Cox proportional hazard regressions estimated hazard ratios (HRs) for reproductive factors with incident all-cause dementia.

Results: Over a median of 11.3 years follow-up, 1,680 dementia were recorded in women and 2,021 in men. Adjusted HRs (95% confidence intervals (CIs)) for dementia were 1.20 (1.08, 1.35) for menarche <12 years, and 1.24 (1.10, 1.39) for menarche ≥15 years compared to 13 years; 0.86 (0.74, 1.00) for ever been pregnant; 0.80 (0.69, 0.93) for each abortion; 1.29 (1.12, 1.49) for menopause at <47 compared to 50 years; 1.13 (1.01, 1.27) for hysterectomy; 0.80 (0.72, 0.90) for oral contraceptive pills use; and 1.56 (1.40, 1.73) for hormone replacement therapy (HRT) use. The U-shaped associations between the number of children and the risk of dementia were similar for both sexes. There was evidence for early (natural and artificial) menopause, and a greater number of children were associated with a higher risk of dementia among women of relatively lower SES only.

Conclusions: Shorter cumulative endogenous estrogen exposure in women is associated with higher dementia risk, although female biological factors involved in childbearing are unlikely to account for risk variation.

Introduction

The dementia epidemic confronts the world as a major challenge, with extensive impact on individuals, carers, families and societies at large.[1, 2] Fifty million people live with dementia globally, and this number is projected to triple by 2050.[1] There is no effective course-modifying treatment for dementia to date;[2] mitigation and modification of risk factors, therefore, present opportunities to reduce the burden associated with dementia at a population level.[2]

The age-standardised global prevalence and death rates for dementia were estimated to be higher in women than men.[3] While the risk of developing dementia increases with age, the extent to which the female predominance is simply due to women's longer lifespan remains far from conclusive, and female-specific reproductive factors may be able to explain these sex disparities.[4, 5]

Several endogenous estrogen changes occur throughout a woman's reproductive life. Estradiol (E2) is the most predominant form of estrogen during reproductive life (from menarche to menopause)[6] and estriol (E3) is the primary estrogen during pregnancy.[7] Exogenous hormone use, such as oral contraceptives during reproductive years, and hormone replacement therapy (HRT) in later life can also influence

estrogen level. Few studies evaluated the long-term effect of reproductive factors on dementia risk, such that conclusions remain equivocal, and the putative mechanisms are not well-understood.[4, 8–13]

This study examined the reproductive factors and exogenous hormone use in relation to the risk of incident all-cause dementia in women in the UK Biobank. We assessed whether the effects of these factors vary by age, socioeconomic status, smoking status and body mass index (BMI).

Methods

Study population

The UK Biobank is a prospective population-based cohort, recruited over 500,000 (aged 40 to 69 years) women and men between 2006 and 2010.[14] Individuals were invited to attend one of the 22 centres across the UK for baseline assessment, which included questionnaires soliciting information on lifestyle, medical history, and reproductive history. Physical measurements were collected, and a blood sample was taken. Written informed consent was obtained for all participants electronically.

Measurement of reproductive factors

Self-reported reproductive factors included in this study were age at menarche, pregnancy history, number of live births, age at first live birth, number of stillbirths, number of miscarriages, number of abortions, reproductive lifespan, age at menopause, (age at) hysterectomy, (age at) oophorectomy. Exogenous hormone exposures included oral contraceptive pills use, age started using oral contraceptive pills, use of HRT, age at HRT initiation, and duration of HRT use. Early menarche was defined as age at the first menstrual period before 12 years of age. Early natural menopause was defined as the permanent absence of a menstrual period before 47 years of age. The reproductive lifespan was defined as the difference between the age at menopause and the age at menarche. Age at hysterectomy and oophorectomy were used to determine the timing of these procedures. The number of children fathered was also recorded for men and was thus analysed here.

Study endpoint

The primary endpoint in this study was incident (i.e. fatal or non-fatal) all-cause dementia, as defined by the UK Biobank Outcome Adjudication Group, using International Classification of Diseases (ICD)-10 codes A81.0, F00, F01, F02, F03, F05, G30, G31.0, G31.1, G31.8, and I67.3.[15] Hospital inpatient data from England, Scotland, and Wales, as well as the national death registers were used to identify the date of the first known dementia after the date of baseline assessment. Follow-up for all participants started at the entry to the study, with data from the death registers ended on the 30th June 2020, and hospital inpatient data ended on the 31st May 2020; or when fatal, non-fatal all-cause dementia or death was recorded.

Covariates

Socioeconomic status (SES) was determined using the Townsend Deprivation Index. Smoking status was self-reported and categorised as never, former, or current smokers. Systolic blood pressure was taken at study baseline using the Omron HEM-7015IT digital blood pressure monitor as the mean of two sitting measures. BMI was calculated as the weight of the individual in kilograms, measured using the Tanita BC-418 MA body composition analyser, divided by the square of the individual's standing height in metres. Diabetes status was self-reported: if the age at diagnosis was younger than 30, and the participant was using insulin, they were classified as type 1 diabetes, otherwise as type 2 diabetes. Total cholesterol was measured using the Beckman Coulter AU580. Self-reported medication use was also recorded.

Statistical analysis

The present analyses excluded participants with prevalent dementia at baseline (N = 263). Baseline characteristics are presented as mean with standard deviation (SD) for continuous variables and number with percentage for categorical variables.

Sex-specific crude incidence rates of dementia were estimated using Poisson regression models, with a log offset for person-years. We estimated the unadjusted and multiple-adjusted rates for dementia per 10,000 person-years in all risk factor categories. Multiple adjusted models included age at study entry, SES, smoking status, systolic blood pressure, BMI, history of diabetes mellitus, total cholesterol, antihypertensive drugs and lipid-lowering drugs.

The associations between reproductive factors and dementia were assessed using Cox proportional hazard regression models that estimated the hazard ratios (HRs) with 95% confidence intervals (95% CIs). When more than two groups were compared, the 95% CIs were estimated using floating absolute risks.[16] Covariate adjustments were the same as those made in the Poisson models. The association between the number of children fathered and dementia was assessed in men, fitted with the same set of covariates, to make a direct comparison with the number of live births in women.

Multiple-adjusted restricted cubic splines (with kernel density plots) were constructed to assess the shape of continuous reproductive factors associated with dementia risk. The top and bottom 2.5% of the distributions, where precision is poor, were excluded, with the median value of the distribution taken as the reference.

Pre-defined subgroup analyses were conducted by age group (categorised as ≥ 65 versus < 65 years, to yield an approximately equal number of events in each group), SES (Townsend deprivation index at or below versus above the national median (-0.56)), smoking status (ever versus never smoker) and BMI (> 25 kg/m^2 versus ≤ 25 kg/m^2), to examine the effect modifications by these characteristics. The

interaction term was fitted between the exposure of interest and the pre-specified subgroup to obtain the p-value.

For sensitivity analysis, we excluded women who underwent hysterectomy or oophorectomy.

All analyses were performed on complete case data using R version 4.0.2 (R Core Team, 2020) and Stata 16.0 (StataCorp, 2019).

Results

Over a median of 11.3 years follow-up, 1,680 incident dementia were recorded among 273,265 women. At the study baseline, the mean age of women was 56 years; the mean age at menarche and age at first live birth was 13 and 26 years, respectively; 85% reported they have been pregnant at least once, and 44% reported having two children. Sixty-one percent of the women were postmenopausal, and the mean age at natural menopause was 50 years. The percentage of women who reported a history of hysterectomy and oophorectomy were 19% and 8%, respectively; 81% reported ever used oral contraceptive pills, and 38% reported ever used HRT, with a mean age of 47 years for HRT initiation, and a mean duration of 6.0 years.

Among 228,966 men, 2,021 incident cases of dementia were recorded. The mean age for men at baseline was 57 years, with 41% reported fathering two children (Table 1).

Table 1
Baseline characteristics of study participants in the UK Biobank.

	Women (n = 273 265)	Men (n = 228 966)
Dementia, n %	**1 680 (0.6)**	**2 021 (0.9)**
Age, years	56.3 (8.0)	56.7 (8.0)
Socioeconomic status, %:		
Highest (≤ -2.08)	138 675 (50.7)	115 580 (50.5)
Middle (-2.08–1.40)	81 867 (30.0)	66 667 (29.1)
Lowest (≥ 1.40)	52 396 (19.2)	46 423 (20.3)
Smoking status, %:		
Never smoker	161 981 (59.3)	111 406 (48.7)
Former smoker	85 413 (31.3)	87 535 (38.2)
Current smoker	24 359 (8.9)	28 593 (12.5)
Blood pressure:		
Systolic blood pressure (Mean (SD))	135.3 (19.2)	140.9 (17.5)
Diastolic blood pressure (Mean (SD))	80.7 (10.0)	84.1 (10.0)
Body Mass Index (Mean (SD))	27.1 (5.2)	27.8 (4.2)
Diabetes, %:		
Type 1 diabetes	564 (0.2)	652 (0.3)
Type 2 diabetes	9 946 (3.6)	15 514 (6.8)
Total cholesterol (Mean (SD))	5.87 (1.1)	5.48 (1.1)
Antihypertensive drugs	38 406 (14.1)	47 966 (20.9)
Lipid lowering drugs	29 503 (10.8)	45 731 (20.0)
Age at menarche, years	13.0 (1.6)	-
Ever pregnant, %	231 372 (84.7)	-
Number of children, %		
None	51 086 (18.7)	47 100 (20.6)
One child	36 459 (13.3)	28 636 (12.5)
Two children	119 121 (43.6)	94 267 (41.2)

	Women (n = 273 265)	Men (n = 228 966)
Three children	48 277 (17.7)	38 129 (16.7)
Four or more children	17 494 (6.4)	16 562 (7.2)
Age at first live birth, years	25.9 (5.1)	-
Number of miscarriages, %:		
None	171 528 (62.8)	-
One	40 044 (14.7)	-
Two or more	15 876 (5.8)	-
Number of stillbirths, %:		
None	220 602 (80.7)	-
One	6 074 (2.2)	-
Two or more	963 (0.4)	-
Number of abortions, %:		
None	180 114 (69.2)	-
One	30 544 (11.2)	-
Two or more	7 351 (2.7)	-
Number of reproductive years	37.3 (4.8)	-
Menopause:		
Postmenopausal, %	165 865 (60.7)	-
Age at menopause, years	50.3 (4.5)	-
Surgical menopause:		
History of hysterectomy, %	51 233 (18.7)	-
Age at hysterectomy, years	43.9 (8.0)	-
History of oophorectomy, %	21 938 (8.0)	-
Age at oophorectomy, years	47.4 (7.8)	-
History of both hysterectomy and oophorectomy	20 904 (7.6)	
Exogenous hormone use:		
Oral contraceptive pills use:		
Ever used oral contraceptive pills, %	220 367 (80.6)	-

	Women (n = 273 265)	Men (n = 228 966)
Age first taken oral contraceptive pills, years	21.5 (4.7)	-
Hormone replacement therapy (HRT) use:		
Ever used HRT, %	104 142 (38.1)	-
Age initiated HRT, years	47.4 (5.4)	-
HRT duration, years	6.3 (5.3)	-

Dementia rates

The crude incidence rate for dementia was 5.48 (5.23, 5.75) for women and 7.99 (7.65, 8.35) for men per 10,000 person-years.

The multiple-adjusted rates of dementia per 10,000 person-years were the highest among those with shorter reproductive span (< 33 years: 7.36 (5.86, 8.87); 33–35 years: 7.46 (5.99, 8.94)); and earlier age at menopause (< 47 years: 7.45 (6.09, 8.81)) (Table 2). For the number of children, the rates were higher among men than women across all the categories, especially among men with four or more children, the multiple-adjusted rate was 11.32 (9.75, 12.89) for men, and 5.67 (4.56, 6.77) for women [See Additional file 1].

Table 2

Unadjusted and multiple-adjusted rates of incident dementia for reproductive risk factors in women.

Risk factors	Unadjusted rates/10 000 person years (95% CI)	Multiple-adjusted rates/10 000 person years (95% CI) *
Age at menarche		
<12	5.75 (5.14, 6.36)	5.09 (4.38, 5.81)
12	5.32 (4.72, 5.92)	4.98 (4.25, 5.71)
13	4.57 (4.08, 5.07)	4.58 (3.95, 5.21)
14	5.02 (4.45, 5.59)	4.82 (4.13, 5.51)
≥15	6.34 (5.64, 7.03)	5.81 (4.99, 6.62)
Ever been pregnant		
No	4.72 (4.09, 5.35)	5.93 (4.95, 6.91)
Yes	5.60 (5.31, 5.89)	5.04 (4.70, 5.37)
Number of live births		
0	4.45 (3.90, 4.99)	5.73 (4.84, 6.62)
1	4.85 (4.17, 5.52)	5.61 (4.63, 6.60)
2	5.19 (4.81, 5.58)	4.77 (4.31, 5.23)
3	6.49 (5.82, 7.17)	5.07 (4.38, 5.76)
4 or more	8.82 (7.50, 10.13)	5.67 (4.56, 6.77)
Parous		
No	4.45 (3.90, 4.99)	5.73 (4.84, 6.63)
Yes	5.71 (5.41, 6.00)	5.05 (4.71, 5.39)
Age at first live birth		
<21	7.78 (6.86, 8.70)	6.97 (5.89, 8.06)
21–22	7.62 (6.65, 8.58)	5.35 (4.46, 6.25)
23–24	7.55 (6.67, 8.45)	6.09 (5.20, 6.99)
25–26	4.88 (4.19, 5.58)	3.95 (3.21, 4.69)
27–29	4.46 (3.87, 5.04)	4.71 (3.92, 5.51)
>29	3.35 (3.04, 4.04)	4.97 (4.06, 5.88)

* Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs.

Risk factors	Unadjusted rates/10 000 person years (95% CI)	Multiple-adjusted rates/10 000 person years (95% CI) *
Number of miscarriages		
0	5.76 (5.42, 6.10)	5.42 (5.02, 5.83)
1	4.80 (4.16, 5.44)	4.72 (3.90, 5.55)
2 or more	5.41 (4.33, 6.49)	4.32 (3.06, 5.59)
Number of stillbirths		
0	5.47 (5.17, 5.76)	5.23 (4.88, 5.59)
1	9.04 (6.77, 11.31)	5.49 (3.58, 7.40)
2 or more	9.49 (3.61, 15.37)	6.98 (1.39, 12.58)
Number of abortions		
0	5.99 (5.66, 6.32)	5.31 (4.94, 5.69)
1	3.95 (3.29, 4.62)	5.10 (3.94, 6.26)
2 or more	1.59 (0.73, 2.46)	3.51 (1.33, 5.69)
Reproductive years		
<33	7.89 (6.69, 9.10)	7.36 (5.86, 8.87)
33–35	7.03 (5.94, 8.12)	7.46 (5.99, 8.94)
36–37	5.48 (4.58, 6.37)	5.70 (4.52, 6.88)
38–39	4.88 (4.09, 5.68)	4.84 (3.82, 5.86)
40–42	5.46 (4.65, 6.27)	5.16 (4.18, 6.14)
>43	7.18 (5.91, 8.44)	5.28 (4.04, 6.53)
Age at menopause		
<47	8.22 (7.11, 9.32)	7.45 (6.09, 8.81)
47–49	5.78 (4.83, 6.74)	6.44 (5.07, 7.80)
50	6.52 (5.51, 7.52)	6.68 (5.42, 7.93)
51–52	4.98 (4.20, 5.76)	4.59 (3.62, 5.57)
53–54	4.51 (3.60, 5.41)	4.71 (3.53, 5.90)

* Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs.

Risk factors	Unadjusted rates/10 000 person years (95% CI)	Multiple-adjusted rates/10 000 person years (95% CI) *
>54	7.23 (6.17, 8.31)	5.57 (4.51, 6.64)
Hysterectomy		
No	4.77 (4.50, 5.05)	4.96 (4.60, 5.33)
Yes	8.46 (7.71, 9.21)	5.63 (4.99, 6.28)
Oophorectomy		
No	5.15 (4.88, 5.41)	4.99 (4.65, 5.32)
Yes	7.89 (6.77, 9.00)	5.43 (4.45, 6.41)
Ever taken oral contraceptive pills		
No	10.37 (9.53, 11.20)	5.90 (5.30, 6.50)
Yes	4.31 (4.05, 4.57)	4.76 (4.38, 5.14)
Ever used HRT		
No	4.04 (3.75, 4.33)	5.31 (4.84, 5.78)
Yes	7.69 (7.19, 8.20)	4.93 (4.50, 5.36)
* Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs.		

Age at menarche

Overall, the relationship between age at menarche and dementia appeared to be U-shaped (Table 3, Fig. 1A): the multiple-adjusted HRs (95% CI) of the age at menarche < 12 associated with dementia was 1.20 (1.08, 1.35), and at the age of ≥ 15 was 1.24 (1.10, 1.39), compared to women who had their menarche at 13.

Table 3
Multiple-adjusted hazard ratios for reproductive factors in association with incident dementia.

Risk factors	No. of events	Multiple-adjusted HR (95% CI)*
Age at menarche		
<12	341	1.20 (1.08, 1.35)
12	299	1.08 (0.96, 1.23)
13 (ref)	331	1.00 (0.89, 1.12)
14	294	0.95 (0.84, 1.08)
≥15	317	1.24 (1.10, 1.39)
Ever been pregnant	1454	0.86 (0.74, 1.00)
Number of live births		
0	254	1.16 (1.02, 1.33)
1	198	1.09 (0.94, 1.26)
2 (ref)	695	1.00 (0.92, 1.08)
3	352	1.03 (0.92, 1.15)
4 or more	172	1.14 (0.96, 1.34)
Parous vs not	1417	0.89 (0.77, 1.03)
Per live birth	-	0.99 (0.95, 1.03)
Age at first live birth		
<21	192	1.47 (1.29, 1.68)
21–22	239	1.25 (1.09, 1.43)
23–24	280	1.34 (1.19, 1.52)
25–26 (ref)	222	1.00 (0.86, 1.16)
27–29	276	1.16 (1.01, 1.33)
>29	194	1.15 (0.99, 1.34)
Per additional year of age at first live birth	-	0.98 (0.97, 0.99)
Number of miscarriages		
0 (ref)	1108	1.00 (0.94, 1.06)

*Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs

Risk factors	No. of events	Multiple-adjusted HR (95% CI)*
1	216	0.86 (0.74, 0.99)
2 or more	96	1.01 (0.81, 1.25)
Miscarriage vs not	312	0.90 (0.79, 1.03)
Per miscarriage	-	1.00 (0.93, 1.08)
Number of stillbirths		
0 (ref)	1353	1.00 (0.94, 1.06)
1	61	1.21 (0.92, 1.58)
2 or more	10	1.10 (0.52, 2.31)
Stillbirth vs not	71	1.20 (0.92, 1.55)
Per stillbirth	-	1.09 (0.90, 1.32)
Number of abortions		
0 (ref)	1272	1.00 (0.94, 1.07)
1	135	0.92 (0.77, 1.10)
2 or more	13	0.37 (0.20, 0.70)
Abortion vs not	148	0.83 (0.69, 1.00)
Per abortion	-	0.80 (0.69, 0.93)
Reproductive years		
<33 (ref)	165	1.00 (0.85, 1.18)
33–35	160	1.00 (0.85, 1.18)
36–37	144	0.77 (0.65, 0.92)
38–39	145	0.69 (0.58, 0.82)
40–42	174	0.72 (0.61, 0.84)
>43	123	0.82 (0.68, 0.98)
Age at menopause		
<47	214	1.29 (1.12, 1.49)
47–49	141	1.05 (0.88, 1.25)

*Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs

Risk factors	No. of events	Multiple-adjusted HR (95% CI)*
50 (ref)	162	1.00 (0.85, 1.18)
51–52	156	0.81 (0.68, 0.96)
53–54	95	0.78 (0.63, 0.96)
>54	176	0.95 (0.81, 1.11)
Hysterectomy vs not	483	1.13 (1.01, 1.27)
Oophorectomy vs not	192	1.05 (0.89, 1.23)
Ever taken oral contraceptive pills	1067	0.80 (0.72, 0.90)
Age started oral contraceptive pills (per year)	-	1.01 (1.00, 1.03)
Ever used HRT	895	1.56 (1.40, 1.73)
Age started HRT (per year)	-	0.96 (0.95, 0.98)
Duration of HRT use (per year)	-	0.99 (0.98, 1.01)
*Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs		

Parity-related factors

The HR for dementia who had ever been pregnant was 0.86 (0.74, 1.00) compared with never pregnant. Younger age at first live birth was associated with a higher dementia risk (Fig. 1B). Compared with women who never had an abortion, the HR for dementia in women who had two or more abortions was 0.37 (0.20, 0.70). Stillbirth and miscarriage were not associated with dementia risk.

Number of children

Compared with those who had two children, the associations between the number of children and dementia were similar for women and men and were U-shaped (Fig. 2). Some heterogeneity by SES was observed, where each additional child was associated with lower dementia risk in women of higher SES (0.92 (0.87, 0.98)), but a greater risk in women of lower SES (1.07 (1.01, 1.14)) (Table 4); this difference by SES was not observed in men.

Menopause-related factors

A longer reproductive lifespan and an older age at menopause had inverse log-linear associations with dementia risk (Table 3, Fig. 1C, Fig. 1D). The HR of dementia associated with menopause before the age of 47 was 1.29 (1.12, 1.49) compared to women who had their menopause at the age of 50. For women who reported a history of hysterectomy, the HR for dementia was 1.13 (1.01, 1.27) compared with women who never had a hysterectomy. Oophorectomy was not significantly associated with dementia; the HR was 1.05 (0.89, 1.23)). Younger age at hysterectomy was associated with increased dementia risk (Fig. 1E), whereas the relationship for age at oophorectomy and dementia was U-shaped (Fig. 1F). In addition, the timing of hysterectomy and oophorectomy did not appear to be associated with dementia risk, although some exposure categories were based on a small number of events [See Additional file 2]. For early menopause, hysterectomy and oophorectomy, there was some evidence of heterogeneity by SES, such that women of relatively lower SES had a greater dementia risk, but not for women of high SES (Table 4).

Exogenous hormone use

The HR for dementia in women who reported oral contraceptive pill use was 0.80 (0.72, 0.90) (Table 3). There was some evidence of heterogeneity by age, such that the lower risk was only statistically significant in women younger than 65 years at study baseline (Table 4). The HR for dementia associated with a 1-year increment in the age first taking oral contraceptive pills was 1.01 (1.00, 1.03)) (Table 3, Fig. 1G). The HR for dementia in women who reported HRT use was 1.56 (1.40, 1.73) compared with those who never used HRT. The HR for dementia associated with a 1-year increment in the age at HRT initiation was 0.96 (0.95, 0.98) (Table 3, Fig. 1H). There was no evidence for HRT duration affecting dementia risk (0.99 (0.98, 1.01) per year) (Table 3, Fig. 1I).

Table 4
Multiple-adjusted hazard ratios for incident dementia associated with reproductive factors, by age, SES, smoking, BMI.

Risk factors	Age			Socioeconomic status		
	< 65 years	≥ 65 years	P-value	Higher SES	Lower SES	P-value
Early menarche* vs. not	1.14 (0.95, 1.37)	1.14 (0.96, 1.36)	0.91	1.13 (0.96, 1.34)	1.13 (0.90, 1.43)	0.78
Age at first live birth per year	0.98 (0.96, 1.00)	0.98 (0.97, 1.00)	0.35	0.99 (0.97, 1.01)	0.97 (0.95, 1.00)	0.12
Each child†						
Women	0.97 (0.91, 1.03)	1.00 (0.95, 1.06)	0.47	0.92 (0.87, 0.98)	1.07 (1.01, 1.14)	< 0.001
Men	1.05 (1.01, 1.09)	1.01 (0.97, 1.06)	0.19	1.02 (0.97, 1.08)	1.04 (1.01, 1.08)	0.54
Stillbirth vs. not	1.08 (0.69, 1.70)	1.26 (0.92, 1.74)	0.70	1.17 (0.82, 1.68)	1.24 (0.83, 1.86)	0.79
Miscarriage vs. not	0.93 (0.76, 1.14)	0.88 (0.73, 1.05)	0.64	0.84 (0.70, 1.00)	1.07 (0.85, 1.36)	0.07
Abortion vs. not	0.77 (0.59, 1.00)	0.89 (0.69, 1.15)	0.54	0.75 (0.58, 0.98)	0.91 (0.69, 1.21)	0.16
Early menopause‡ vs. not	1.57 (1.23, 2.00)	1.30 (1.04, 1.62)	0.16	1.19 (0.96, 1.49)	1.80 (1.37, 2.38)	0.02
Hysterectomy vs. not	1.14 (0.95, 1.36)	1.13 (0.97, 1.30)	0.81	0.98 (0.85, 1.14)	1.32 (1.08, 1.61)	0.03
Oophorectomy vs. not	1.12 (0.87, 1.43)	1.01 (0.81, 1.24)	0.47	0.81 (0.64, 1.02)	1.37 (1.06, 1.79)	< 0.001
Oral contraceptive pill use vs. not	0.66 (0.55, 0.79)	0.93 (0.81, 1.06)	< 0.001	0.88 (0.76, 1.02)	0.71 (0.59, 0.87)	0.37
HRT use vs. not	1.08 (0.92, 1.28)	0.94 (0.82, 1.08)	0.25	0.94 (0.82, 1.07)	1.14 (0.94, 1.38)	0.26

Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs. P-values are the interaction between subgroups.

*Early menarche was defined as age at first menstrual period before the age of 12 years.

†Each livebirth in women and each child fathered in men.

‡Early menopause was defined as the permanent absence of menstrual periods before the age of 47 years.

Risk factors	Age			Socioeconomic status		
	< 65 years	≥ 65 years	P-value	Higher SES	Lower SES	P-value
Risk factors	**Smoking status**			**BMI**		
	Never	Ever	P-value	≤ 25 kg/m^2	> 25 kg/m^2	P-value
Early menarche* vs. not	1.06 (0.89, 1.26)	1.22 (1.02, 1.47)	0.33	1.22 (0.97, 1.53)	1.10 (0.94, 1.28)	0.61
Age at first live birth per year	0.98 (0.96, 0.99)	0.99 (0.97, 1.01)	0.46	0.98 (0.96, 1.00)	0.98 (0.97, 1.00)	0.74
Each child†						
Women	0.96 (0.91, 1.02)	1.02 (0.96, 1.09)	0.13	1.02 (0.95, 1.09)	0.98 (0.93, 1.03)	0.46
Men	1.05 (0.99, 1.11)	1.03 (0.99, 1.07)	0.70	1.01 (0.95, 1.07)	1.05 (1.01, 1.08)	0.33
Stillbirth vs. not	1.05 (0.71, 1.54)	1.35 (0.95, 1.93)	0.30	1.27 (0.80, 2.01)	1.15 (0.84, 1.58)	0.71
Miscarriage vs. not	0.79 (0.65, 0.95)	1.04 (0.86, 1.25)	0.05	0.77 (0.61, 0.98)	0.97 (0.82, 1.14)	0.12
Abortion vs. not	0.79 (0.59, 1.04)	0.87 (0.68, 1.11)	0.60	0.93 (0.69, 1.24)	0.77 (0.60, 0.97)	0.34
Early menopause‡ vs. not	1.40 (1.11, 1.77)	1.42 (1.13, 1.78)	0.90	1.38 (1.06, 1.81)	1.41 (1.15, 1.74)	0.88
Hysterectomy vs. not	1.18 (1.01, 1.37)	1.08 (0.91, 1.28)	0.43	1.01 (0.83, 1.24)	1.20 (1.05, 1.38)	0.16
Oophorectomy vs. not	1.08 (0.87, 1.34)	1.01 (0.80, 1.29)	0.69	0.97 (0.73, 1.30)	1.08 (0.89, 1.31)	0.52
Oral contraceptive pill use vs. not	0.79 (0.68, 0.91)	0.82 (0.70, 0.98)	0.84	0.83 (0.69, 1.00)	0.80 (0.70, 0.92)	0.90

Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs. P-values are the interaction between subgroups.

*Early menarche was defined as age at first menstrual period before the age of 12 years.

†Each livebirth in women and each child fathered in men.

‡Early menopause was defined as the permanent absence of menstrual periods before the age of 47 years.

Risk factors	Age			Socioeconomic status		
	< 65 years	≥ 65 years	P-value	Higher SES	Lower SES	P-value
HRT use vs. not	0.93 (0.81, 1.07)	1.05 (0.90, 1.23)	0.26	0.87 (0.73, 1.03)	1.08 (0.94, 1.23)	0.08
Analyses were adjusted for age, Townsend index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs. P-values are the interaction between subgroups.						
*Early menarche was defined as age at first menstrual period before the age of 12 years.						
†Each livebirth in women and each child fathered in men.						
‡Early menopause was defined as the permanent absence of menstrual periods before the age of 47 years.						

Sensitivity analysis

After excluding women who underwent hysterectomy or oophorectomy, the associations for age at menarche, reproductive years and age at menopause in relation to dementia risk were similar to the main results [See Additional file 3].

Discussion

In this large population-based cohort study, we found several associations between reproductive factors and exogenous use of hormone with the dementia risk later in life. Both early and late menarche, younger age at first live birth, and hysterectomy were associated with greater dementia risk. Ever been pregnant, ever had an abortion, longer reproductive span, older age at menopause were associated with lower dementia risk. There was some evidence of heterogeneity by SES for early menopause, hysterectomy and oophorectomy, such that the elevated dementia risk associated with these risk factors was confined to women of lower SES. U-shaped associations were found for the number of children and dementia risk, similar for both sexes. For exogenous hormone exposures, the use of oral contraceptive pills was associated with a lower risk, while HRT use was associated with a greater risk of dementia.

Surrogates for endogenous hormone exposures

Reproductive events indicating shorter cumulative exposure to estradiol, including later menarche, early menopause, shorter reproductive span and hysterectomy, were all associated with an elevated risk of dementia in our study. Nevertheless, previous studies on the relationship between these risk factors have reported mixed results. Consistent with our findings, the Kaiser Permanente (KP) study showed that

reproductive events contributing to shorter estradiol exposure were associated with elevated dementia risk.[10] A nation-wide study from South Korea also reported these comparable findings.[13] These findings may be driven by the effects of estradiol on brain health; in experimental studies, estradiol has shown to confer neuroprotective effects by promoting neuronal dendritic spline regeneration[17] as well as reducing apoptosis and inflammation.[18] In contrast, the Gothenburg H70[9] and Rotterdam study[11] reported that a longer reproductive span and later menopause were associated with greater dementia risk,[9] while the 10/66 study reported no association for reproductive span and dementia.[12] The discrepancy in findings cannot be explained by the exclusion of women who reported hysterectomy or oophorectomy in the two studies reported opposite findings.[9, 11] However, the studies that reported null or opposite results included older women at study baseline (mean age around 70 years),[11, 12] or the women were followed into their late life.[9] Notably, the Gothenburg H70[9] only found significant associations with dementia for longer reproductive span and older age at menopause, among those with the older onset of dementia (75 years and above).[9] As such, we hypothesise that the risk exposure in midlife and older life may be different.

Surgically-induced menopause (hysterectomy and oophorectomy), when performed before the onset of natural menopause, can cease the secretion of endogenous sex hormones prematurely.[19] The KP study found the dementia risk is greater among women who underwent a hysterectomy,[10] which was consistent with our findings. Similarly, a pooled analysis of two cohorts found that the risk of cognitive impairment and dementia was higher in women who underwent a hysterectomy, and the risk was even greater in those who had a hysterectomy and bilateral oophorectomy.[20] A meta-analysis did not find an overall association between surgical menopause and dementia;[21] but surgical menopause before the age of 45 was associated with greater dementia risk.[21] We similarly demonstrated that younger age at hysterectomy and oophorectomy were inversely associated with dementia risk, providing further evidence for early cessation of hormones having a detrimental effect on cognition.

When disaggregated by SES, early natural menopause, hysterectomy, and oophorectomy were only associated with a greater risk of dementia in women of relatively low SES. Previous studies reported SES might adversely influence the age at entry to perimenopause.[22, 23] Further, social disadvantage can modulate the level of cortisol.[24] During the menopausal transition, increased cortisol level has been associated with vasomotor symptoms and depressed mood,[25] which are key determinants for cognitive function.[26, 27]

Parity-related factors

Pregnancy induces marked changes in endogenous estrogen levels [7, 28] and estrogen can be both neuroprotective or neurotoxic, depending on the concentration.[28, 29] A pooled study from the Cohort Studies of Memory in an International Consortium (COSMIC) found that the risk of Alzheimer's disease doubled for women who had four or more completed pregnancies.[28] Another COSMIC analysis showed that having five or more children was associated with increased dementia risk, while nulliparity and

having two to four children showed similar associations with primiparous women.[30] In our study, the number of children was similarly associated with dementia risk for women and men. As such, the risk variation in women appears to be more related to social and behavioural factors involved in parenthood rather than biological factors associated with childbearing. Further, each additional child was adversely associated with dementia in women of lower SES but protective in women of higher SES. This difference by SES was not apparent in men. A plausible explanation for this could be related to the additional expenditures and responsibilities associated with the number of dependents, which could lead to economic hardships and increase psychological distress in parents.[31] In particular, mothers are more likely to bear the brunt of childcare than fathers in a low-income household; hence the impact of parenthood on mothers of lower SES may be more adverse.[31]

Our study showed that abortion was associated with a lower risk of dementia, while we did not find any link for stillbirth or miscarriage. The COSMIC study by Jang et al. also found the risk of Alzheimer's disease in women who had incomplete pregnancies was half that of those who never experienced an incomplete pregnancy;[28] however, incomplete pregnancies in this study encompassed surgical or medical-induced abortion and spontaneous miscarriage. A Danish register-based cohort study that excluded women who had a surgical and medical abortion found stillbirth was associated with 86% greater risk of dementia, while miscarriage was not associated with dementia.[32] Both studies[28, 32] had limitations that precluded the effect of spontaneous miscarriage and abortion from being differentiated. The course of pregnancy and childbirth can have a considerable influence on lifestyle and health,[28] although we did not find any effect modifications to explain some of the findings in pregnancy-related factors. Further clarification for the mechanism which underpins these observations is needed.

Exogenous hormone use

The use of oral contraceptive pills was associated with a lower risk of dementia, whereas HRT was associated with a greater risk. The link between premenopausal hormone use and dementia risk has hardly been characterised.[33] A previous study suggested that women who reported hormonal contraceptive use performed better in the visuospatial ability and speed and flexibility domains of the neuropsychiatric tests than those who had never used hormonal contraception.[33] On the other hand, the potential benefits of HRT to prolong estrogen supply in older women have not been corroborated by interventional studies,[34, 35] while the observational evidence remains conflicting.[4, 36–39] The Women's Health Initiative Study (WHIS), is the only clinical trial that evaluated postmenopausal hormone therapy on preventing dementia, concluded that the risk of dementia was doubled in women randomised to estrogen-progestin based HRT.[34] In a case-control study in Finland, long-term use of systemic HRT was associated with an increased risk of Alzheimer's disease.[39] As such, it is still largely contentious whether HRT can potentially prevent dementia. The timing of HRT use may be crucial, such that there is a critical window which exogenous hormone use can confer cognitive benefits in postmenopausal women.[29, 40]

Strengths and limitations

The strengths of our study were the large sample size and the prospective design, with linkage to national health records and death registers. Further, our study included a comprehensive list of reproductive factors and exogenous hormone use through the life-course. The limitations included retrospective and self-reported measures of reproductive factors, which may be inherently subject to recall bias and misclassification. The generalisability of the findings may be limited, given that the UK Biobank cohort is relatively healthier and more affluent than the UK general population. Dementia subtypes were not differentiated due to the currently small number of events in the UK Biobank. Lastly, although multiple adjustments were made to account for confounders, there may still be other unmeasured factors that can lead to residual confounding.

Conclusions

This study highlights that the reproductive and endocrine milieu in women can have a significant impact on their dementia risk, although the physical experiences of childbearing is unlikely to account for the risk variation in women. Our research supports a life-course approach for dementia prevention, particularly around the design of risk reduction strategies pertaining to reproductive factors which are unique to women. It is necessary to validate our findings on hormone use through rigorous clinical trials, and our findings may be helpful for identifying high-risk women to participate in future trials. Further, deprivation is likely to be an important determinant of dementia risk and other aspects of women's health, given that the elevated dementia risk associated with early (natural and artificial) menopause and a greater number of children were restricted to women of lower SES. These findings are pertinent given the recent recommitment to the Beijing Declaration to improve equity in sexual and reproductive health.

List Of Abbreviation

BMI	Body Mass Index
CI	Confidence Interval
COSMIC	Cohort Studies of Memory in an International Consortium
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
SES	Socioeconomic Status
WHIS	Women's Health Initiative Study

Declarations

Ethics approval and consent to participate

Written informed consent was obtained for all UK Biobank participants electronically. UK Biobank has obtained Research Tissue Bank approval from its governing Research Ethics Committee, as recommended by the National Research Ethics Service. This research has been conducted using the UK Biobank Resource (application No. 2495). Permission to use the UK Biobank Resource was approved by the access subcommittee of the UK Biobank Board. The Study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the UK Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The UK Biobank resources are however available from the authors upon reasonable request and can be accessed through applications on their website.

Competing interests

MW does consultancy for Amgen, Freeline and Kirin outside the submitted work; no support from any organisation for the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Funding

JG is supported by the Scientia PhD scholarship from the University of New South Wales, Sydney, Australia. SAEP is supported by a UK Medical Research Council Skills Development Fellowship [grant number MR/P014550/1]. MW is supported by an Australian National Health and Medical Research Council Investigator Grant [grant number APP1174120] and Program Grant [grant number APP1149987]. The funders had no role in the study design, collection, analysis, intepretation of data, writing of the manuscript or in the decision to submit the article for publication.

Authors' contributions

All authors were involved in the design of the study. JG carried out the statistical analyses, with support from KH, SAEP and MW. JG wrote the first draft of the manuscript. All authors edited further drafts and approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MW is the guarantor of the work.

Acknowledgements

Not applicable.

References

1. Patterson C. World Alzheimer report 2018: the state of the art of dementia research: new frontiers. Alzheimer's Disease International: London, UK. 2018. doi.
2. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248). doi: https://doi.org/10.1016/S0140-6736(20)30367-6.
3. Nichols E, Szoeke CE, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurology. 2019;18(1). doi: https://doi.org/10.1016/S1474-4422(18)30403-4.
4. Ferretti MT, Martinkova J, Biskup E, Benke T, Gialdini G, Nedelska Z, et al. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: Position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology. European Journal of Neurology. 2020;27(6). doi: https://doi.org/10.1111/ene.14174.
5. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimer's Dementia. 2018;14(9). doi: https://doi.org/10.1016/j.jalz.2018.04.008.
6. Henderson VW. Aging, estrogens, and episodic memory in women. Cognitive and behavioral neurology: official journal of the Society for Behavioral and Cognitive Neurology 2009;22(4). doi: https://doi.org/10.1097/WNN.0b013e3181a74ce7.
7. Tulchinsky D, Hobel CJ, Yeager E, Marshall JR. Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. American journal of obstetrics and gynecology. 1972;112(8). doi: https://doi.org/10.1016/0002-9378(72)90185-8.
8. Gannon O, Robison L, Custozzo A, Zuloaga K. Sex differences in risk factors for vascular contributions to cognitive impairment & dementia. Neurochemistry international. 2019;127. doi: https://doi.org/10.1016/j.neuint.2018.11.014.
9. Najar J, Östling S, Waern M, Zettergren A, Kern S, Wetterberg H, et al. Reproductive period and dementia: A 44-year longitudinal population study of Swedish women. Alzheimer's & dementia. 2020;16(8). doi: https://doi.org/doi.org/10.1002/alz.12118.
10. Gilsanz P, Lee C, Corrada MM, Kawas CH, Quesenberry CP, Whitmer RA. Reproductive period and risk of dementia in a diverse cohort of health care members. Neurology. 2019;92(17). doi: https://doi.org/10.1212/WNL.0000000000007326.
11. Geerlings MI, Ruitenberg A, Witteman JC, van Swieten JC, Hofman A, van Duijn CM, et al. Reproductive period and risk of dementia in postmenopausal women. JAMA. 2001;285(11). doi: https://doi.org/10.1001/jama.285.11.1475.

12. Prince MJ, Acosta D, Guerra M, Huang Y, Jimenez-Velazquez IZ, Llibre Rodriguez JJ, et al. Reproductive period, endogenous estrogen exposure and dementia incidence among women in Latin America and China; A 10/66 population-based cohort study. PloS one. 2018;13(2). doi: https://doi.org/10.1371/journal.pone.0192889.
13. Yoo JE, Shin DW, Han K, Kim D, Won HS, Lee J, et al. Female reproductive factors and the risk of dementia: a nationwide cohort study. European journal of neurology. 2020;27(8). doi: https://doi.org/10.1111/ene.14315.
14. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS med. 2015;12(3). doi: https://doi.org/10.1371/journal.pmed.1001779.
15. Wilkinson T, Schnier C, Bush K, Rannikmäe K, Henshall DE, Lerpiniere C, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. European journal of epidemiology. 2019;34(6). doi: https://doi.org/10.1007/s10654-019-00499-1.
16. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Statistics in medicine. 1991;10(7). doi: https://doi.org/10.1002/sim.4780100703.
17. Woolley CS, McEwen BS. Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. Journal of Neuroscience. 1992;12(7). doi: https://doi.org/10.1523/JNEUROSCI.12-07-02549.1992.
18. Azcoitia I, Arevalo M-A, De Nicola AF, Garcia-Segura LM. Neuroprotective actions of estradiol revisited. 2011;22(12). doi: https://doi.org/10.1016/j.tem.2011.08.002.
19. Henderson VW, Sherwin BB. Surgical versus natural menopause: cognitive issues. Menopause. 2007;14(3). doi: https://doi.org/10.1097/gme.0b013e31803df49c.
20. Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. Neurodegenerative diseases. 2012;10(1-4). doi: https://doi.org/10.1159/000334764.
21. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis. Psychoneuroendocrinology. 2019;106. doi: https://doi.org/10.1016/j.psyneuen.2019.03.013.
22. Wise L, Krieger N, Zierler S, Harlow BL. Lifetime socioeconomic position in relation to onset of perimenopause. Journal of Epidemiology and Community Health. 2002;56(11). doi: https://doi.org/10.1136/jech.56.11.851.
23. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. International of Epidemiology. 2014;43(5). doi: https://doi.org/10.1093/ije/dyu094.
24. Ouanes S, Popp J. High cortisol and the risk of dementia and Alzheimer's disease: a review of the literature. Frontiers in aging neuroscience. 2019;11. doi: https://doi.org/10.3389/fnagi.2019.00043.
25. Woods NF, Mitchell ES, Smith-DiJulio K. Cortisol levels during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Menopause.

2009;16(4). doi: https://doi.org/10.1097/gme.0b013e318198d6b2.

26. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. The Journal of steroid biochemistry & molecular biology. 2014;142. doi: https://doi.org/10.1016/j.jsbmb.2013.06.001.
27. Maki PM, Thurston RC. Menopause and Brain Health: Hormonal Changes Are Only Part of the Story. Frontiers in Neurology. 2020;11. doi: https://doi.org/10.3389/fneur.2020.562275.
28. Jang H, Bae JB, Dardiotis E, Scarmeas N, Sachdev PS, Lipnicki DM, et al. Differential effects of completed and incomplete pregnancies on the risk of Alzheimer disease. Neurology. 2018;91(7). doi: https://doi.org/10.1212/WNL.0000000000006000.
29. Liu JH. Does estrogen provide “neuroprotection” for postmenopausal women? Menopause. 2019;26(12). doi: https://doi.org/10.1097/GME.0000000000001459.
30. Bae JB, Lipnicki DM, Han JW, Sachdev PS, Kim TH, Kwak KP, et al. Does parity matter in women’s risk of dementia? A COSMIC collaboration cohort study. BMC medicine. 2020;18(1). doi: https://doi.org/10.1186/s12916-020-01671-1.
31. Bird CE. Gender differences in the social and economic burdens of parenting and psychological distress. Journal of Marriage and the Family. 1997. doi: https://doi.org/10.2307/353784.
32. Basit S, Wohlfahrt J, Boyd HA. Pregnancy loss and risk of later dementia: A nationwide cohort study, Denmark, 1977–2017. Alzheimer's & dementia: translational research & clinical interventions. 2019;5. doi: https://doi.org/10.1016/j.trci.2019.02.006.
33. Egan KR, Gleason CE. Longer duration of hormonal contraceptive use predicts better cognitive outcomes later in life. Journal of Women's Health. 2012;21(12). doi: https://doi.org/10.1089/jwh.2012.3522.
34. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20). doi: https://doi.org/10.1001/jama.289.20.2651.
35. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. 2012(7). doi: https://doi.org/10.1002/14651858.CD004143.pub5.
36. Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology. 1997;48(6). doi: https://doi.org/10.1212/wnl.48.6.1517.
37. Matyi JM, Rattinger GB, Schwartz S, Buhusi M, Tschanz JT. Lifetime estrogen exposure and cognition in late life: the Cache County Study. Menopause. 2019;26(12). doi: https://doi.org/10.1097/GME.0000000000001405.
38. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA. 1998;279(9). doi: https://doi.org/10.1001/jama.279.9.688.

39. Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364. doi: https://doi.org/10.1136/bmj.l665.

40. Maki PM, Girard LM, Manson JE. Menopausal hormone therapy and cognition. BMJ. 2019. doi: https://doi.org/10.1136/bmj.l877.

Figures

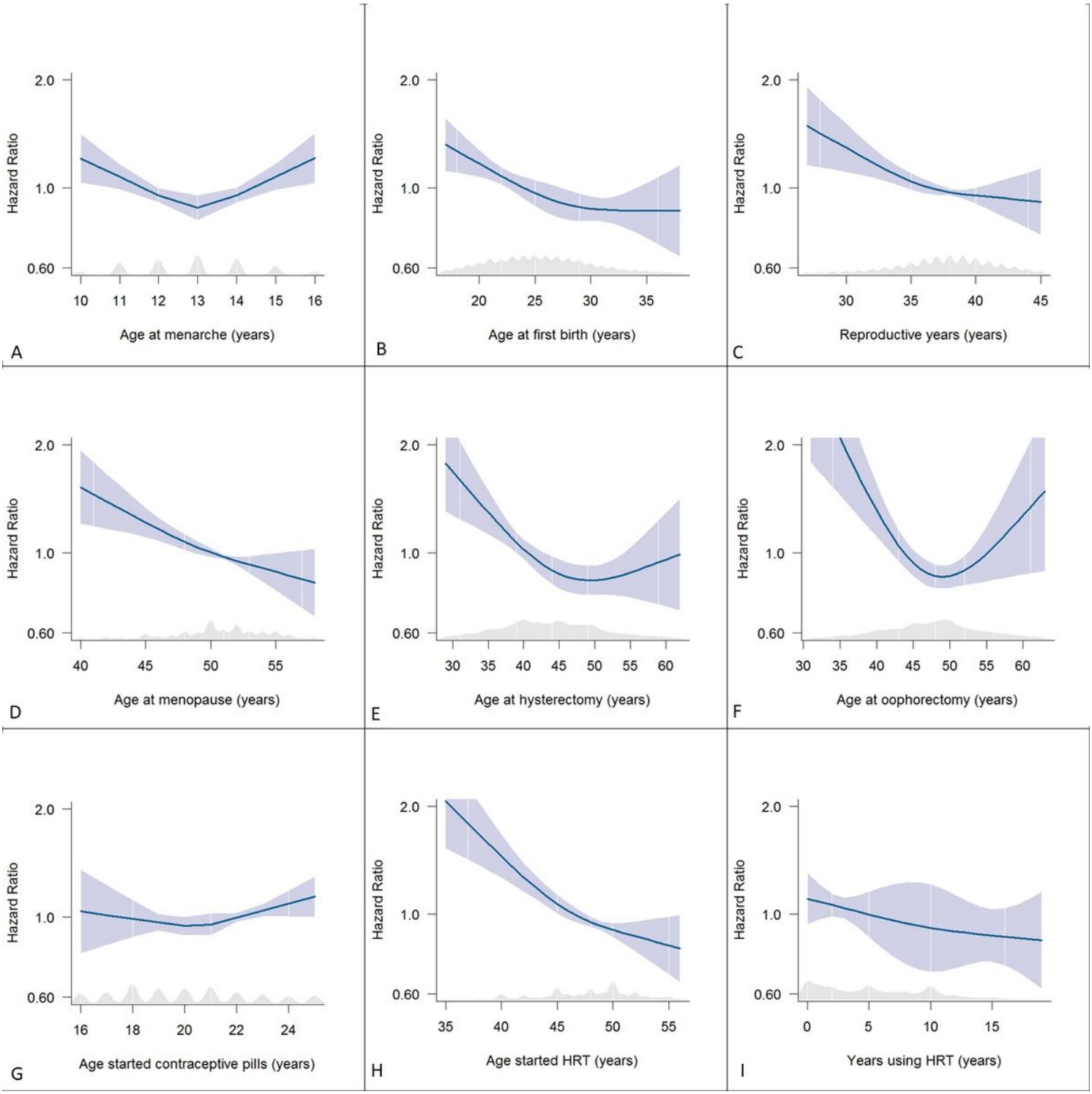

Figure 1

Multiple-adjusted restricted cubic splines (with kernel density plots) showing HRs for dementia and reproductive factors. After excluding the values from the top and bottom 2.5% of the distribution, with the median value being the reference. Splines adjusted for age, Townsend deprivation index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs.

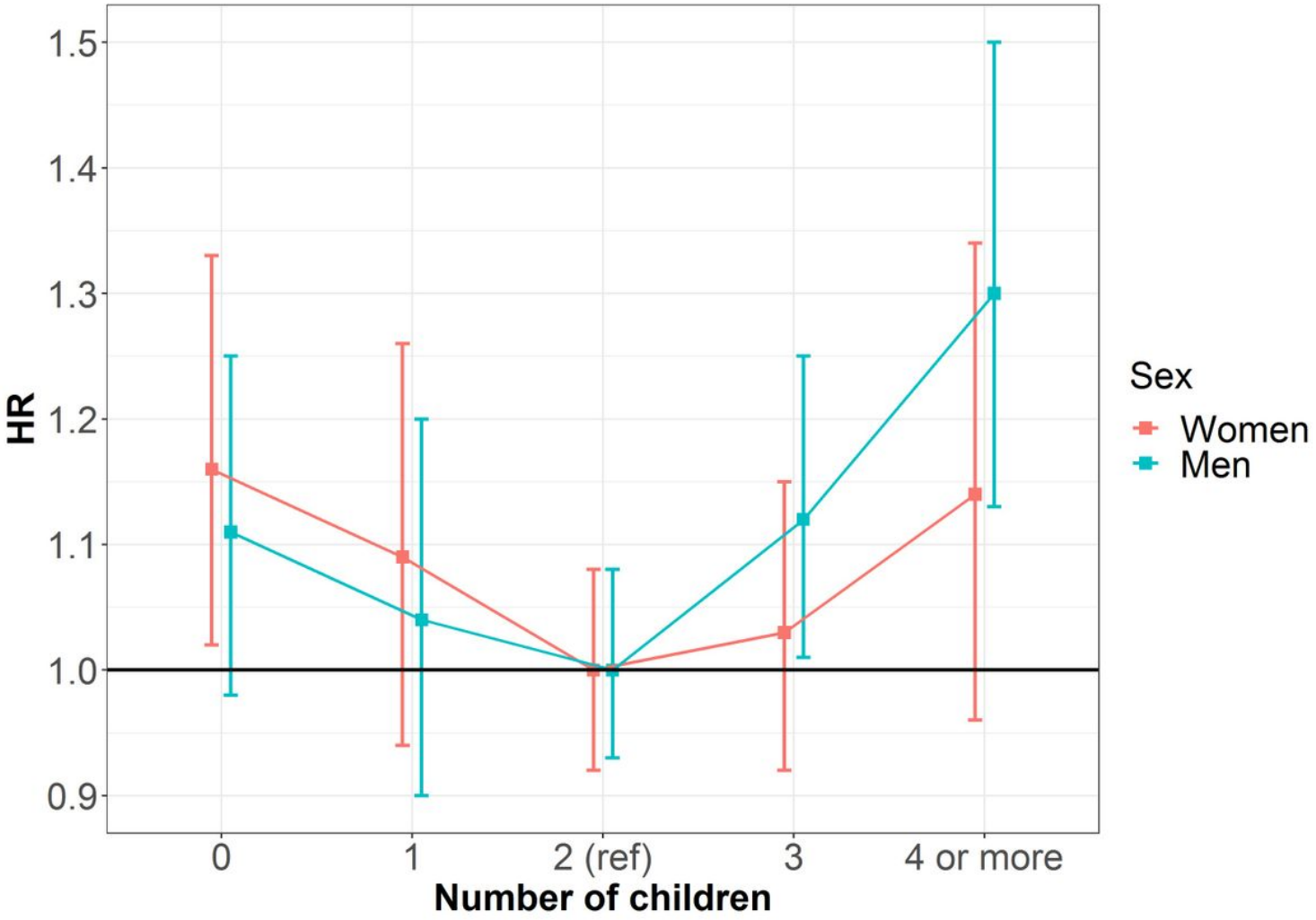

Figure 2

Multiple-adjusted hazard ratios for incident dementia associated with number of children for women and men. The HRs are plotted on a floating absolute scale. Analyses were adjusted for age, Townsend deprivation index, smoking status, systolic blood pressure, body mass index, diabetes, total cholesterol, antihypertensive drugs, lipids lowering drugs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistAlzResandTherapy.docx
- SummplementalmaterialsAlzResandTherapy.docx