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WOMEN'S REPRODUCTIVE HISTORY AND DEMENTIA RISK

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Background: Women have substantially higher prevalence of dementia compared to men but female sex-specific risk factors over the lifecourse are not well understood. There may be female-specific risk and protective factors which impact hormonal milieu and brain health. **Methods:** We evaluated 14,595 female members of Kaiser Permanente who were aged 40-55 in 1964-1973 and remained members as of 1/1/96. Between 1964-1973 women reported number of children, miscarriages, and age of menarche and menopause. Education, race, sex, and midlife health indicators (BMI, hypertension, and smoking) were collected between 1972-1973. Dementia diagnoses and late-life health indicators (stroke, heart failure, and diabetes) were abstracted from medical records from 1/1/1996-9/30/2017. Cox proportional hazard models (age as time scale) evaluated associations between aspects of reproductive history and dementia adjusted for sociodemographics and lifecourse health indicators. **Results:** 98% reported having ≥1 child. Mean age of menarche was 12.9 (SD=1.5 years) and mean age of menopause was 45.0 (SD=6.1 years). Of the 6,751 women who responded to questions regarding miscarriages, 75% reported ≥1 miscarriage. Compared to women with one child, women with 3 children and those with ≥4 children had a 12% lower risk of dementia (Table). Women with 3 children and those with ≥4 children continued to be at lower risk of dementia in fully adjusted models. Each additional report of a miscarriage was associated with an 8% increased risk of dementia (aHR=1.08; 95% CI: 1.05-1.12). Compared to women reporting no miscarriages, those with ≥3 miscarriages had 47% elevated dementia risk (aHR=1.47; 95% CI: 1.27-1.71). Compared to menarche between ages 10-13years, menarche at ≥16 was associated with 22% greater risk (aHR=1.22; 95% CI: 1.03-1.44). Menarche at ≤9 was associated with a non-significant 40% increased risk versus menarche at ages 10-13 (aHR=1.40; 95% CI: 0.83-2.37). There was no evidence of an association between age of menopause and dementia risk. **Conclusions:** This is the first large-scale epidemiological investigation of various aspects of reproductive history and dementia risk. We found that number of children, miscarriages and age at menarche was associated with dementia; future research should examine mechanistic pathway between reproductive events and brain health.

Table
Dementia hazard ratios associated with reproductive history from Cox proportional hazards models with age as time scale

	N	Dementia cases	Demographics	Demographics & midlife factors	Demographics & mid- and late-life factors
# children					
1 child	2,350	902	Ref	Ref	Ref
2 children	4,607	1,672	0.93 (0.86, 1.01)	0.94 (0.86, 1.01)	0.94 (0.87, 1.02)
3 children	3,534	1,258	0.88 (0.81, 0.96)	0.89 (0.81,0.97)	0.88 (0.81, 0.96)
	3,885	1,351	0.88 (0.80, 0.95)	0.87 (0.80, 0.95)	0.86 (0.79, 0.94)
# miscarriages					
Continuous	6,751	2,338	1.08 (1.05, 1.12)	1.08 (1.04, 1.11)	1.08 (1.04, 1.11)
0 miscarriages	1,669	512	Ref	Ref	Ref
1 miscarriage	3,077	1,094	1.21 (1.09, 1.35)	1.22 (1.09, 1.35)	1.21 (1.09, 1.35)
2 miscarriages	1,246	446	1.17 (1.03, 1.34)	1.17 (1.03, 1.34)	1.17 (1.03, 1.33)
	759	286	1.47 (1.27, 1.71)	1.45 (1.25, 1.67)	1.43 (1.23, 1.65)
Age at menarche					
≤9 years old	29	14	1.40 (0.83, 2.37)	1.42 (0.84, 2.41)	1.39 (0.82, 2.36)
10-13 years old	3451	1402	Ref	Ref	Ref
14-15 years old	1484	610	0.99 (0.90, 1.09)	1.01 (0.91, 1.11)	1.00 (0.91, 1.11)
	789	341	1.22 (1.03, 1.44)	1.25 (1.05, 1.47)	1.27 (1.07, 1.50)
Age at menopause					
≤41 years old	1219	483	1.06 (0.94, 1.20)	1.07 (0.94, 1.21)	1.08 (0.96, 1.22)
42-46 years old	1376	561	1.03 (0.92, 1.16)	1.05 (0.94, 1.18)	1.06 (0.95, 1.19)
47-49 years old	1050	424	0.95 (0.84, 1.07)	0.95 (0.84, 1.07)	0.96 (0.85, 1.08)
	1495	678	Ref	Ref	Ref

Note: Demographics include age, race/ethnicity, and educational attainment. Midlife factors include body mass index, hypertension, smoking status. Late life factors include stroke, diabetes, and heart failure.