



Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis

Marios K. Georgakis^{a,b,c,*}, Theano Beskou-Kontou^a, Ioannis Theodoridis^a, Alkistis Skalkidou^d, Eleni Th. Petridou^a

^a Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

^b Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

^c Graduate School of Systemic Neurosciences (GSN), LMU Munich, Munich, Germany

^d Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

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ABSTRACT

Introduction: Experimental and epidemiological studies suggest female sex hormones to have long-lasting neuroprotective and anti-ageing properties. Surgically-induced menopause leads to a premature cessation of exposure to female sex hormones and could thus impact late-life cognitive function. Yet, evidence remains controversial.

Methods: We systematically reviewed literature for articles investigating the association of surgical menopause (defined as bilateral oophorectomy before the onset of menopause) with risk of dementia, cognitive performance, cognitive decline, and Alzheimer's disease neuropathological indices later in life. We evaluated study quality with the Newcastle-Ottawa scale and performed random-effects meta-analyses.

Results: We identified 11 eligible studies (N = 18,867). Although surgical menopause at any age was not associated with risk of dementia (4 studies; HR: 1.16, 95%CI: 0.96–1.43), early surgical menopause (≤ 45 years of age) was associated with a statistically significantly higher risk (2 studies; HR: 1.70, 95%CI: 1.07–2.69). Surgical menopause at any age was associated with faster decline in verbal memory, semantic memory, and processing speed, whereas early surgical menopause was further associated with faster global cognitive decline. No heterogeneity was noted. Among women undergoing surgical menopause, a younger age at surgery was associated with faster decline in global cognition, semantic and episodic memory, worse performance in verbal fluency and executive function, and accumulation of Alzheimer's neuropathology.

Conclusions: Current evidence is limited, but suggests surgical menopause induced by bilateral oophorectomy at ≤ 45 years of age to be associated with higher risk of dementia and cognitive decline. Additional large-scale cohort studies are necessary to replicate these findings.

1. Introduction

Cognitive impairment and dementia are major causes of disability, dependency, and death worldwide (DALYs and Collaborators, 2016; The, 2017). As many as 50 million people suffer from dementia globally, a figure which is expected to triple by 2050 (The, 2017; WHO, 2017a), raising dementia to a major public health concern (Shah et al., 2016; WHO, 2017b). Several lines of evidence suggest sex differences in the epidemiology of dementia (Rocca et al., 2014b). The incidence of dementia is higher in elderly women compared to men, a difference that cannot be fully explained by increased longevity (Andersen et al.,

1999). Experimental studies further demonstrate neuroprotective and anti-ageing properties of estrogens and progesterone (Pike et al., 2009), suggesting that their deprivation after menopause could explain women's vulnerability to cognitive decline (Levine et al., 2016; Nebel et al., 2019; Rocca et al., 2014a; Rocca et al., 2014b).

In this context, previous studies have investigated whether age at menopause, as a proxy of lifetime exposure to endogenous female sex hormones and an indicator of the period of hormone deficit, might influence cognitive function and the risk of dementia in post-menopausal women. A meta-analysis by our group, found no strong evidence supporting earlier menopause as a risk factor for dementia,

* Corresponding author at: Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, National and Kapodistrian University of Athens, 75M. Asias Str., Athens, 11745, Greece.

E-mail address: marios.georgakis@med.uni-muenchen.de (M.K. Georgakis).

¹ Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilians-University (LMU), Feodor-Lynen-Str. 17, 81377 Munich, Germany.

albeit there was evidence that a younger age at menopause was associated with faster cognitive decline (Georgakis et al., 2016a).

Surgical menopause, induced by bilateral oophorectomy before the onset of natural menopause, leads to a premature cessation of exposure to female sex hormones that might have deleterious consequences (Henderson and Sherwin, 2007). Indeed, surgical menopause has been associated with higher risk of coronary artery disease and stroke, higher cardiovascular and all-cause mortality, and a higher multimorbidity burden (Evans et al., 2016; Poorthuis et al., 2017; Rocca et al., 2016). As the results of published studies are inconsistent (Geerlings et al., 2001; Rocca et al., 2007), it remains unclear whether surgical menopause may also contribute to an increased risk of dementia or if -and to what extent- confounding factors may shape this relationship (Rocca et al., 2014a). More than 10% of women may undergo onset a hysterectomy before natural menopause (Howe, 1984; Phung et al., 2010; Redburn and Murphy, 2001), which in the majority of cases is combined with bilateral oophorectomy leading to surgical menopause (Howe, 1984; Phung et al., 2010; Rocca et al., 2016). Thus, any effect of surgical menopause on the risk of dementia could have a major public health impact.

Here, we set out to leverage data from published literature in order to explore whether surgical menopause influences cognitive function later in life. Specifically, we aimed to assess the association of surgical menopause induced by bilateral oophorectomy before the onset of natural menopause, with risk of dementia and Alzheimer's disease, as well as global and domain-specific cognitive performance and cognitive decline. To explore potentially gradient effects, we also aimed to explore among women having undergone a surgical menopause, whether a younger age at surgery is associated with cognitive outcomes.

2. Methods

2.1. Search strategy

This systematic review was based on a predefined protocol that followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Stroup et al., 2000), as detailed in the checklists in **Supplementary Tables 1 and 2**, respectively. Two reviewers (T.B.-K. and I.T.) searched Medline and Embase for relevant articles up to January 1st 2019, without language or publication year restrictions using a combination of search terms (detailed in the **Supplementary Methods**). We subsequently further hand-searched the reference lists of eligible articles and relevant reviews ("snowball" procedure). All studies were evaluated for potential population overlap based on geographical setting and recruitment periods. In case of overlapping populations, we retained the study with the largest sample size. Disagreement between reviewers in the selection process were resolved with consensus.

2.2. Eligibility criteria

We included the following two types of studies in this systematic review:

(i) cohort and cross-sectional studies comparing risk of dementia and Alzheimer's disease, cognitive performance (single cognitive assessment in a cross-sectional setting), rate of cognitive decline (time-series assessments in a longitudinal setting), and the extent of neuropathological indices of Alzheimer's disease, between postmenopausal women having undergone a surgical menopause and postmenopausal women having experienced a natural menopause

(ii) cohort or cross-sectional studies of only women having undergone a surgical menopause exploring the association of the age at surgery with the same outcomes (risk of dementia and Alzheimer's disease, cognitive performance, rate of cognitive decline, Alzheimer's neuropathology indices).

The population of interest was postmenopausal women who had either undergone surgical or natural menopause. We excluded studies that examined specific populations, like exclusively women with estrogen-related malignancies or women with Down syndrome that is associated with intellectual disability and premature cognitive decline; no other exclusion criteria related to the genetic characteristics of the population were applied. Studies comparing postmenopausal having undergone surgical menopause with premenopausal women were also excluded.

Surgical menopause was defined as bilateral oophorectomy performed before the onset of natural menopausal transition. Studies defining surgical menopause more broadly, as either bilateral oophorectomy or hysterectomy performed before the onset of natural menopausal transition were also included in this review. Studies examining solely hysterectomy or solely unilateral oophorectomy as the exposure variable were excluded. Similarly, we excluded studies that pooled in the exposed group women who underwent hysterectomy or oophorectomy both before and after their natural menopausal transition, thus not leading to surgical menopause. In addition to surgical menopause at any age, to explore a potential gradient effect we examined premature and early surgical menopause, defined as bilateral oophorectomy performed at ≤ 40 years and ≤ 45 years of age, respectively (Faubion et al., 2015; Golezar et al., 2019; Stuenkel et al., 2015).

Our primary outcomes of interest were all-cause dementia, defined by standard clinical criteria or by validated cognitive tests, and clinical Alzheimer's disease defined according to clinical criteria. We further examined global and domain-specific cognitive performance, determined by validated structured tests administered at a single time point in the postmenopausal period and cognitive decline, determined by multiple serial assessments (> 1 time points) in the postmenopausal period. Finally, we examined neuropathological indices of Alzheimer's disease, as determined in autopsy findings.

2.3. Data extraction and quality assessment

Publication details (year, authors), study information (region, study period, design, follow-up, inclusion-exclusion criteria and number of cases-controls/ cohort-size), age of participants, definition of surgical menopause, type of surgery, age at surgery, method of exposure ascertainment, use of hormone therapy, definition and diagnostic criteria used for dementia diagnosis, number of dementia cases, methods of ascertainment of cognitive performance and cognitive decline, statistical analysis details (effect estimate, effect size, confidence intervals, p-values), and adjustment variables were extracted in a pre-designed spreadsheet. Maximally adjusted effect estimates were extracted in case of multiple presented analyses.

The quality of the included studies was evaluated using the 9-item Newcastle-Ottawa Scale for cohort studies (Wells et al., 2011). For representativeness of the exposed cohort, the studies should be based on community-based samples to be awarded a point. Studies should specifically define surgical menopause as bilateral oophorectomy performed before natural menopause and confirm the exposure status by cross-checking medical records or hospital-based registry data to be awarded a point for exposure ascertainment. Regarding presence of the outcome at study onset, we considered studies examining dementia to inherently not be biased because of reverse causation, as at the time of menopause it is highly unlikely that women might have been diagnosed with dementia. However, in order for studies examining cognitive performance or cognitive decline to be awarded a quality point, adjustment for baseline cognitive performance at the time of surgical menopause should be performed. For comparability questions, we set age *a priori* as the most important adjusting factors. Regarding outcome assessment, dementia and Alzheimer's disease should be defined by standardized clinical guidelines (e.g. DSM-IV, ICD-10, NINDS-ADRDA), whereas validated cognitive tests should be used for the assessment of cognitive performance and cognitive decline. We further examined the

time interval between menopausal transition and last examination for outcome assessment (dementia occurrence or neuropsychological testing). A minimum interval of ≥ 5 years between menopause onset and outcome assessment was required to award a quality point, so as to avoid bias due to reverse causation. An attrition rate of $< 20\%$ was set as a criterion for the item of follow-up adequacy. Studies starting their recruitment after menopause were not awarded this quality point for follow-up adequacy independently of their attrition rates, as they were considered to be inherently biased due to left censoring.

2.4. Statistical analysis

We applied random-effects meta-analyses to pool relative risks (RR) estimating the associations between surgical menopause and risk of dementia in individual studies. Random-effects models were *a priori* preferred over fixed-effects models due to the expected heterogeneity between studies with regards to exposure and outcome definition (Higgins and Green, 2011). For global or domain-specific cognitive performance (assessment of cognitive function at a single time point) and cognitive decline (longitudinal difference between serial assessments of cognitive function at > 1 time points), we calculated standardized mean differences (Cohen’s *d*) based on available data from individual studies (Lipsey MW, 2000) and pooled them in random-effects meta-analyses. The significance level for the overall effect was set at $p < 0.05$. Between-study heterogeneity was assessed by the I^2 and the Cochran Q test; significance level was set at $p < 0.10$. Due to the paucity of studies examining age at surgical menopause, as a continuous variable, no meta-analysis could be performed. Due to the limited number of studies included in each analysis, no statistical assessment of publication bias could be performed. All analyses were performed using Stata version 13.0 (Stata Corp., College Station, TX).

3. Results

3.1. Search strategy results

The flowchart of the study selection process is depicted in Fig. 1. The search of the two Medline and Embase along with the “snowball” procedure yielded 2459 unique articles for assessment. Following

screening of titles and abstracts, we evaluated the full-text of 39 articles, out of which 26 were excluded for specific reasons (detailed in Supplementary Table 3). A total of 13 studies eventually met our inclusion criteria. Two articles were excluded due to population overlap (Rocca et al., 2008b, 2012), thus leading to a final set of 11 studies (Bove et al., 2014; Geerlings et al., 2001; Kritz-Silverstein and Barrett-Connor, 2002; Kuh et al., 2018; Kurita et al., 2016; McLay et al., 2003; Nappi et al., 1999; Rice et al., 2000; Rocca et al., 2007, 2016; Ryan et al., 2014) for inclusion in the systematic review.

3.2. Description of studies

Table 1 summarizes the characteristics of the 11 eligible studies. Eight of the studies had cohort design, 1 study comprised a retrospective analysis of a randomized controlled trial (Kurita et al., 2016), whereas 2 studies were of cross-sectional design (Kritz-Silverstein and Barrett-Connor, 2002; Nappi et al., 1999). However, only three of the cohort studies started following women before or at the time of surgical menopause (Kuh et al., 2018; Rocca et al., 2007, 2016). Nine of the studies were population-based, whereas 1 study examined women presenting to an endocrinology department with menopausal complaints (Nappi et al., 1999). Information on ever use of hormone therapy after menopause was reported in 10 studies, with figures varying greatly, from 0% to 72.7%.

There was variability in the definition of surgical menopause. Five of the studies examined bilateral oophorectomy performed before the onset of natural menopause (either with or without concurrent hysterectomy) (Kuh et al., 2018; Kurita et al., 2016; Rocca et al., 2007, 2016; Ryan et al., 2014), whereas two studies examined hysterectomy with bilateral oophorectomy performed before natural menopausal transition (Kritz-Silverstein and Barrett-Connor, 2002; Nappi et al., 1999). Three studies defined surgical menopause as either hysterectomy or bilateral oophorectomy performed before natural menopause (Bove et al., 2014; McLay et al., 2003; Rice et al., 2000), whereas Geerlings et al. examined any medically induced menopause, but was included, as the vast majority of women (83%) had undergone surgically-induced menopause (Geerlings et al., 2001). Three studies specifically provided results for surgical menopause performed at an age ≤ 45 years of age, thus leading to an early menopause (Kurita et al.,

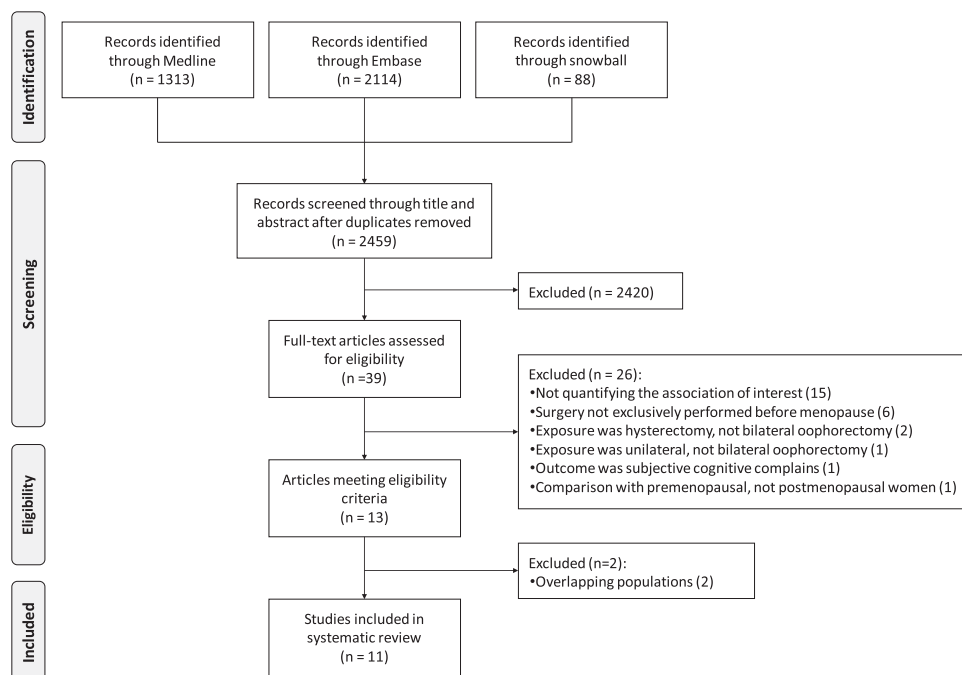


Fig. 1. Flowchart on the selection process of eligible studies.

Table 1
Characteristics of the included studies.

Study	Region (study period)	Study design	Cohort characteristics	Cohort size	Mean follow-up (y)	Mean age at dementia assessment (mean ± SD)	Exposure variable definition (assessment)	HT users	Outcome, assessment method	Incident cases in cohort	Adjustment factors
Nappi et al., 1999	Pavia; Italy	Cross-sectional	Consecutive patients of a reproductive endocrinology unit for treatment of menopausal complaints	76	NA	52.4 ± 4.3	Hysterectomy and bilateral oophorectomy (clinical evaluation, interview, hormonal results)	0%	Cognitive performance: verbal memory (Serial Learning Test)	NA	None
Rice et al., 2000	Seattle, Washington; USA	Cohort	Local residents of ≥ 50% Japanese ancestry identified through census	837	2.0	73.4 ± 5.4	Hysterectomy and/ or bilateral oophorectomy (interview)	45.6%	Cognitive decline: global cognition, attention, verbal memory, verbal fluency, processing speed (CASI)	NA	Age, education, language spoken, baseline CASI score
Geerlings et al., 2001	Ommournd, Rotterdam; Netherlands (1990-1999)	Cohort	Local residents free of dementia at baseline, with complete gynecological history. Excluded if menopause induced after quitting oral contraceptives	2736	6.3	76.1 ± 9.2	Medically induced menopause (interview)	10.5%	Dementia: DSM-III-R Clinical AD: NINCDS-ADRD	167 (dementia), 135 (AD)	Age, education, smoking, alcohol intake, BMI, use of HT, number of children, APOE genotype
Kritz-Silversein & Barrett-Connor, 2002	Rancho Bernardo, California; USA (1972-1974)	Cross-sectional	All local residents aged 30-79 years at baseline (1972-1974) who survived to attend a follow-up visit in 1988-1991	885	NA	74.3 ± 7.5	Hysterectomy and bilateral oophorectomy (interview, medical records)	72.7%	Cognitive performance: global cognition (MMSE), verbal memory (Buschke selective reminding), visual memory (Visual Reproduction), verbal fluency (category fluency), executive function (TMT-B), attention (Serial Sevens, World Backward)	NA	Age, education, use of HT
McLay et al., 2003	East Baltimore, USA (1981–1996)	Cohort	Local residents who had not used hormone replacement therapy	361	12-15	63.4 ± 14.3	Hysterectomy and/ or bilateral oophorectomy (interview)	0%	Cognitive performance and cognitive decline: global cognition (MMSE), Dementia or cognitive impairment: questionnaire, modified and adapted for the study or reported by proxy respondent	NA	Age, education, race, childbirth, age at menopause, baseline cognitive function
Rocca et al., 2007	Olmsted County, Minnesota; USA (1950-1987)	Retrospective cohort	All local residents born before 1962 who underwent an oophorectomy before menopause (or before age 56 years if age at menopause was unknown) and referent women from the local population with the same year of birth. Excluded were women who underwent oophorectomy for ovarian or another estrogen-related cancer	2961	26.9	70	Bilateral oophorectomy (registry)	NR	248		Age, education, history of depression (ever vs never), type of interview (direct vs proxy).
Bove et al., 2014	USA (1994-2012)	Cohort	MAP: older women from Chicago free of known dementia at baseline; ROS: older Catholic nuns free of	607	up to 18	77.4 ± 7.7	Hysterectomy and/ or bilateral oophorectomy (interview)	52.9%	Clinical AD: NINCDS-ADRD Pathological AD: NIA-Reagan ^a	NR	Age, education, smoking, study

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Table 1 (continued)

Study	Region (study period)	Study design	Cohort characteristics	Cohort size	Mean follow-up (y)	Mean age at dementia assessment (mean ± SD)	Exposure variable definition (assessment)	HT users	Outcome, assessment method	Incident cases in cohort	Adjustment factors
			known dementia at baseline						AD neuropathology: global, neuritic plaques, NFL tangles, diffuse plaques ^a Cognitive decline: global cognition, episodic memory, semantic memory, attention, visuospatial ability, processing speed (combinations from a battery of 19 tests)		
Ryan et al., 2014	Montpellier,Bordeaux, Dijon;France (1999–2008)	Cohort	Non-institutionalized individuals randomly recruited from electoral rolls, free of dementia at baseline	4868	77	80.8 ± 5.4	Bilateral oophorectomy (interview)	20.3%	Dementia: DSM-IV-R ^b Cognitive performance and cognitive decline ^b ; global cognition (MMSE), verbal fluency (Isaacs Set test), visual memory (BVRT), processing speed (TMT-A), executive function (TMT-B)	393	Age, education, baseline cognitive function, recruitment centre physical limitations, chronic illness, depression, use of HT, APOE4 genotype
Kurita et al., 2016	California; USA (2000–2008)	Retrospective analysis of trials	Postmenopausal women without diabetes mellitus, uncontrolled hypertension, signs/symptoms of cardiovascular disease, psychiatric conditions, thyroid disease and a life expectancy of > 5 years participating in trials testing interventions (folic acid, vitamin B12, vitamin B6; soy isoflavones; oral estradiol) on progression of subclinical atherosclerosis. Excluded were women with missing history of bilateral oophorectomy and women with history of unilateral oophorectomy	926	2.7	66.1 ± 7.2	Bilateral oophorectomy (interview, medical records, hormonal results)	71.2%	Cognitive performance and cognitive decline: global cognition, executive function, semantic memory, visual memory (combinations from a battery of 14 tests)	NA	Age, education, race/ethnicity, BMI, treatment indicator, baseline cognitive function, trial
Rocca et al., 2016	Olmsted County, Minnesota; USA (1988–2007)	Retrospective cohort	All local residents who underwent an oophorectomy before 50 years between 1988 and 2007 and individually matched referent women from the local population with the same year of birth. Excluded were women who underwent oophorectomy for ovarian	3295	14.5	60	Bilateral oophorectomy (registry)	NR	Dementia: ICD-9	63	Age, education, baseline presence of chronic conditions (including dementia), race, BMI, smoking, calendar year

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Table 1 (continued)

Study	Region (study period)	Study design	Cohort characteristics	Cohort size	Mean follow-up (y)	Mean age at dementia assessment (mean ± SD)	Exposure variable definition (assessment)	HT users	Outcome, assessment method	Incident cases in cohort	Adjustment factors
Kuh et al., 2018	Great Britain (1946–2015)	Birth cohort	or another estrogen-related cancer All women born in Great Britain in a specific week of 1946	1315	69	69	Bilateral oophorectomy (interview, medical records)	63.5%	Cognitive performance and cognitive decline: verbal memory (15-item word-learning task), processing speed (visual search task)	NA	Age, education, use of HT, BMI, smoking, occupational class, childhood cognitive ability

NR: Not reported. NA: Not applicable.
 AD: Alzheimer's disease, APOE: Apolipoprotein E, BMI: body mass index, BYRT: Benton Visual Retention Test, CASI: Cognitive abilities screening instrument, DSM: Diagnostic and Statistical Manual of Mental Disorders, HT: Hormone therapy, ICD: International Statistical Classification of Diseases and Related Health Problems, MMSE: Mini-Mental State Examination, NINCDS-ADRD: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, ROS, Religious Order Study, TMT: Trail making test.
^a Analysis based on 179 individuals.
^b Analysis based on 3739 individuals.

2016; Rocca et al., 2007, 2016), but no studies provided results on premature surgical menopause (≤ 40 years of age). Three additional studies examined among women with a surgical menopause, if age at surgery was associated with cognitive outcomes (Bove et al., 2014; Kuh et al., 2018; Ryan et al., 2014).

Four studies assessed all-cause dementia as the main outcome; 3 of them defined dementia clinically based on the DSM or ICD criteria (Geerlings et al., 2001; Rocca et al., 2016; Ryan et al., 2014), whereas 1 study applied cognitive evaluation with the TICS or a questionnaire about dementia to the proxy informant (Rocca et al., 2007). Clinically defined Alzheimer's disease was the outcome in 2 studies, applying the NINCDS-ADRD criteria (Bove et al., 2014; Geerlings et al., 2001). Cognitive performance at a single time point, examined either as global cognitive function or performance in specific cognitive domains, was examined as an outcome in 6 studies (Kritz-Silverstein and Barrett-Connor, 2002; Kuh et al., 2018; Kurita et al., 2016; McLay et al., 2003; Nappi et al., 1999; Ryan et al., 2014) and 6 studies also examined cognitive decline between at least follow-up time points in intervals ranging from 2 to 24 years (Bove et al., 2014; Kuh et al., 2018; Kurita et al., 2016; McLay et al., 2003; Rice et al., 2000; Ryan et al., 2014). The majority of the studies (10 of 11) adjusted for basic variables in their analyses, including age and education, 4 studies adjusted for the use of hormone therapy after menopause (Geerlings et al., 2001; Kritz-Silverstein and Barrett-Connor, 2002; Kuh et al., 2018; Ryan et al., 2014), and 5 studies examining cognitive performance or decline adjusted for baseline cognitive function (Kuh et al., 2018; Kurita et al., 2016; McLay et al., 2003; Rice et al., 2000; Ryan et al., 2014).

3.3. Quality assessment

Fig. 2 graphically presents the quality assessment results for the eligible studies. With a maximum score of 9, the median score of the included studies was 7, ranging between 4 (Nappi et al., 1999) and 9 (Rocca et al., 2016). Five of the studies (Bove et al., 2014; Geerlings et al., 2001; McLay et al., 2003; Rice et al., 2000; Ryan et al., 2014) were compromised because of assessing surgical menopause status only through interview with the respondents or the proxies, whereas 2 studies lost a quality point in the item related to presence of outcome at the start of study, because of not considering baseline or premenopausal cognitive function in their analyses (Kritz-Silverstein and Barrett-Connor, 2002; Nappi et al., 1999). The majority of the studies (Bove et al., 2014; Geerlings et al., 2001; Kritz-Silverstein and Barrett-Connor, 2002; Kuh et al., 2018; Kurita et al., 2016; McLay et al., 2003; Nappi et al., 1999; Rice et al., 2000; Rocca et al., 2007; Ryan et al., 2014) were compromised due to high attrition rates or because they did not start following women at the time of their menopause. On the positive side, with the exception of one study (Nappi et al., 1999), all studies were awarded quality points for representativeness of the exposed cohort, selection of the non-exposed cohort, comparability between exposed and unexposed women, assessment of outcome, and interval duration between menopause and cognitive outcome assessments.

3.4. Association of surgical menopause with cognitive outcomes

In the meta-analysis (Table 2), surgical menopause was not associated with higher risk of dementia (RR: 1.16, 95%CI: 0.94–1.43; 4 studies, 12,731 women; 891 dementia events; Supplementary Fig. 1A), but pooling the 2 studies specifically examining early surgical menopause (≤ 45 years of age), we found it to be associated with a higher risk of subsequent dementia (RR: 1.70, 95%CI: 1.07–2.69; 6256 women; 331 dementia events; Supplementary Fig. 1B). Studies examining cognitive decline (longitudinal difference between cognitive performance across serial measurements) showed surgical menopause at any age to be associated with faster cognitive decline in the domains of verbal memory, semantic memory, and processing speed. Surgical menopause before the age of 45 years was further associated with faster

global cognitive decline and a faster decline in semantic memory, as determined by a single study (Table 2; Supplementary Fig. 2). No evidence of heterogeneity was detected in any of these analyses (p from Cochran's $Q > 0.10$). In cross-sectional analyses examining cognitive performance at a single time point, we found no significant associations between surgical menopause and cognitive performance in any of the examined domains (Supplementary Figure 3).

3.5. Age at surgery in association with cognitive outcomes among women having undergone surgical menopause

Three studies examined whether age at surgery among women undergoing surgical menopause was associated with risk of dementia and Alzheimer's disease, cognitive performance, cognitive decline, and neuropathological indices of Alzheimer's disease (Bove et al., 2014; Kuh et al., 2018; Ryan et al., 2014). The results are summarized in Table 3. Bove et al., in a population-based study of 607 women found a younger age at surgical menopause to be associated with faster decline in global cognitive function (regression coefficient per 1 year increment in age at surgical menopause: -0.0024, 95%CI: -0.0044 to -0.0010), episodic memory (regression coefficient: -0.0032, 95%CI: -0.0061 to -0.0014), and semantic memory (regression coefficient: -0.0025, 95%CI: -0.0043 to -0.0009), as well as marginally increased risk for pathologically (OR: 0.96, 95%CI: 0.92–1.00) and clinically defined Alzheimer's disease (OR: 0.99, 95%CI: 0.98–1.00) in a follow-up period extending up to 18 years (Bove et al., 2014). Furthermore, a younger age at surgical menopause, in a subgroup of 179 women was associated with greater global Alzheimer's disease pathology (regression coefficient per 1 year increment in age at surgical menopause: -0.0077, 95%CI: -0.0086 to -0.0004), and particularly accumulation of neuritic plaques (regression coefficient: -0.0129, 95%CI: -0.0182 to -0.0027) (Bove et al., 2014). Ryan et al., in a group of 499 women having undergone surgical menopause reported that those having undergone the surgery at the age of 40–45 years or < 40 years were more likely to score in the range of cognitive impairment at a mean age of 74 years in the domain of verbal fluency (OR for 40–45 years vs. > 50 years: 2.64, 95%CI: 1.23–5.67 and OR for ≤40 years vs. > 50 years: 2.70, 95%CI: 1.28–5.68) (Ryan et al., 2014). Finally, Kuh et al., in the subsample of 151 women from a British birth cohort who had undergone surgical menopause, found age at surgery to not be significantly associated with cognitive performance in verbal memory (regression coefficient: 0.06, 95%CI: -0.03 to 0.14) and processing speed (regression coefficient: 0.44, 95%CI: -0.72 to 1.60) at the age of 69 years following adjustments for childhood IQ scores (Kuh et al., 2018).

4. Discussion

In this meta-analysis, we found surgical menopause induced by bilateral oophorectomy at ≤45 years of age to be associated with higher risk of dementia later in life. Surgical menopause was further associated with faster cognitive decline in verbal memory, semantic memory, and processing speed following the surgery. Finally, there was evidence among women undergoing surgical menopause that age at surgery is inversely associated with cognitive decline and accumulation of Alzheimer's disease pathology.

Our findings are in line with evidence suggesting that an early menopausal transition associates with epigenetic markers of biological aging (Levine et al., 2016), as well as neuroimaging evidence showing that bilateral oophorectomy before menopause is associated with medial temporal lobe structural abnormalities later in life (Zeydan et al., 2018). Moreover, surgical menopause has been associated with an accumulation of multimorbidity later in life (Rocca et al., 2016). Indeed, an earlier menopausal transition associates with increased risk of several age-related endpoints including all-cause mortality, coronary artery disease, stroke, late-life depression, and cognitive decline (Atsma et al., 2006; Evans et al., 2016; Georgakis et al., 2016a, b; Poorthuis et al., 2017; Rocca et al., 2016, 2008a; Ucar and Pandir, 2017). Interestingly, the higher risk of stroke and cerebrovascular disease in general might at least partially mediate an effect of oophorectomy on cognitive function and particularly on risk of vascular cognitive impairment and dementia.

Estrogens and progesterone have been reported to exert neuroprotective properties. Thus, it is plausible that an early cessation of the brain exposure to female sex hormones could be associated with short-term and long-term cognitive deficits. In animal studies, oophorectomy has been shown to lead to worse performance in cognitive tasks (Gibbs, 2000; Singh et al., 1994, 1995), to impact on synaptic transmission, neurotrophin expression, and neuronal plasticity (Jeziarski and Sohrabji, 2000; Luine, 1985; Singh et al., 1995; Woolley and McEwen, 1993), and to induce cognitive decline, amyloid accumulation, and a shift in brain glucose transport and metabolism in transgenic models of familial Alzheimer's disease (Ding et al., 2013). Estradiol administration on the contrary has been found to stimulate the synaptic formation in the hippocampus and the prefrontal cortex thus having an enhancing effect on memory (Luine, 2014). Furthermore, by directly binding to the glutamate receptor, estradiol might also act protectively in cases of cholinergic depletion (Greendale et al., 2011).

Alternative explanations should be considered when interpreting these findings. First, shared risk factors between surgical menopause and dementia including gynecological and obstetric history that might

Study	Selection	Comparability	Outcome	Total score
Nappi (1999)	☆☆☆☆	☆☆	☆☆☆	4
Rice (2000)	☆☆☆☆	☆☆	☆☆☆	7
Geerlings (2001)	☆☆☆☆	☆☆	☆☆☆	7
Kritz-Silverstein (2002)	☆☆☆☆	☆☆	☆☆☆	7
McLay (2003)	☆☆☆☆	☆☆	☆☆☆	7
Rocca (2007)	☆☆☆☆	☆☆	☆☆☆	7
Bove (2014)	☆☆☆☆	☆☆	☆☆☆	7
Ryan (2014)	☆☆☆☆	☆☆	☆☆☆	7
Kurita (2016)	☆☆☆☆	☆☆	☆☆☆	8
Rocca (2016)	☆☆☆☆	☆☆	☆☆☆	9
Kuh (2018)	☆☆☆☆	☆☆	☆☆☆	8

Fig. 2. Quality assessment of eligible studies, as assessed by the Newcastle-Ottawa scale.

Footnote: Selection items include representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and exclusion of outcome presence at start of study; Comparability items include comparability for age and for any other risk factor; Outcome items include assessment of outcome, length of interval between menopausal transition and outcome assessment, and adequacy of follow-up cohorts.

Table 2Meta-analyses derived effect estimates of surgical menopause at any age and early surgical menopause induced at ≤ 45 years with cognitive outcomes.

	Surgical menopause at any age					Surgical menopause at ≤ 45 years				
	Studies	Population	Events	HR (95%CI)	I ² (%)	Studies	Population	Events	HR (95%CI)	I ² (%)
Dementia	4	12731	891	1.16 (0.94-1.43)	0	2	6256	331	1.70 (1.07-2.69)	0
Cognitive decline*	Studies	Population		d (95%CI)	I² (%)	Studies	Population		d (95%CI)	I² (%)
Global cognition	4	6992		-0.07 (-0.15, 0.00)	0	1	926		-0.40 (-0.72, -0.09)	-
Verbal memory	2	1763		-0.14 (-0.26, -0.03)	0	1	926		-0.23 (-0.55, 0.08)	-
Semantic memory	1	926		-0.25 (-0.48, -0.02)	-	1	926		-0.50 (-0.82, -0.19)	-
Executive function	2	5794		-0.09 (-0.24, 0.06)	32	1	926		-0.27 (-0.58, 0.05)	-
Attention	1	837		-0.07 (-0.20, 0.06)	-	-	-		-	-
Visual memory	2	5794		-0.11 (-0.29, 0.07)	52	1	926		-0.08 (-0.39, 0.24)	-
Processing speed	2	5705		-0.07 (-0.14, -0.004)	0	-	-		-	-
Verbal fluency	2	5705		0.05 (-0.04, 0.14)	0	-	-		-	-
Cognitive performance**	Studies	Population		d (95%CI)	I² (%)	Studies	Population		d (95%CI)	I² (%)
Global cognition	4	3009		-0.04 (-0.17, 0.08)	45	1	926		-0.01 (-0.35, 0.32)	-
Verbal memory	4	3202		-0.21 (-0.46, 0.05)	80 [†]	1	926		0.07 (-0.27, 0.40)	-
Semantic memory	1	926				1	926		-0.13 (-0.47, 0.20)	-
Executive function	3	7109		-0.08 (-0.27, 0.12)	73	1	926		-0.10 (-0.43, 0.23)	-
Attention	2	961		-0.10 (-0.26, 0.05)	0	-	-		-	-
Visual memory	3	6679		-0.01 (-0.14, 0.11)	39	1	926		0.20 (-0.13, 0.53)	-
Processing speed	2	6183		0.09 (-0.01, 0.19)	0	-	-		-	-
Verbal fluency	2	5753		0.10 (-0.01, 0.20)	63	-	-		-	-

The results are based on random-effects models. Bold indicates statistically significant results ($p < 0.05$).

* Negative association estimates indicate an association of bilateral oophorectomy with a faster cognitive decline.

** Negative association estimates indicate an association of bilateral oophorectomy with worse cognitive performance.

† Presence of significant heterogeneity.

relate to the reasons for surgery, educational background, personality traits, and pre-menopausal history of depression might underlie the observed association. Furthermore, common genetic susceptibility should be considered. For example, pleiotropic genetic loci shown in genome-wide association studies to be associated with age at menopause have also been reported to increase the risk for cardiovascular disease (Day et al., 2015; Sarnowski et al., 2018), which might mediate an effect on risk of vascular cognitive impairment and dementia.

More than 20% of women may need to undergo a hysterectomy throughout their lifetime, with more than half of them being in premenopausal age at the time of the surgery. In most cases, hysterectomy is jointly performed with bilateral oophorectomy (Howe, 1984; Phung et al., 2010; Rocca et al., 2016). Given the very high prevalence of dementia in the elderly population (The, 2017; WHO, 2017a), an effect of bilateral oophorectomy in premenopausal women could translate to a major cause of disease burden. Although bilateral oophorectomy is associated with a lower risk of ovarian and breast cancers (Evans et al., 2016), the very high prevalence of the detrimental long-term outcomes associated with the surgery, especially when performed at a young age, necessitates decisions regarding ovary excision to be taken cautiously. It was not in the scope of the current meta-analysis to examine whether the risk of cognitive decline and dementia differs between women undergoing only hysterectomy, as compared to women undergoing both hysterectomy and oophorectomy. The lack of a significant result though among studies pooling in the exposed group women undergoing either hysterectomy alone or hysterectomy plus oophorectomy might provide indirect evidence for such an effect. In any case, future studies should examine whether ovarian conservation, when feasible, might actually attenuate the risk of dementia.

It remains controversial whether hormone therapy after menopause has a beneficial or detrimental effect on cognitive function. Large clinical trials have failed to show any benefit of hormone therapy on preventing cognitive decline after menopause even when prescribed to women with a history of oophorectomy (Henderson, 2010; Resnick et al., 2009; Shumaker et al., 2003). However, it has been hypothesized that the negative results from these early trials can be explained by the long interval between menopause and the initiation of treatment, as well as the old age of women (> 65 years) (Hogervorst, 2014). This

“critical period” hypothesis, supported by observational and experimental studies (Daniel et al., 2006; Shao et al., 2012) was tested in future trials, which also failed to show a protective effect (Espeland et al., 2013; Gleason et al., 2015). Whether estrogen replacement therapy initiated early after surgical menopause induced by bilateral oophorectomy at a young age (≤ 45 years) could reverse the observed higher risk for dementia and cognitive decline remains to be explored in future trials and could not be answered in the context of the current review of observational studies. Individual studies showed inconsistent results (Bove et al., 2014; Kurita et al., 2016; Ryan et al., 2014), which were biased by confounding, indication bias, and for not taking into account differences between type of treatment used (conjugated equine estrogens vs. estradiol).

Several methodological issues should be considered. First, the long gap between surgical menopause and the incidence of dementia might introduce survival bias in the analyses. Particularly, given the association of surgical menopause with higher all-cause mortality (Evans et al., 2016), it would be possible that natural menopause is overrepresented among women surviving until late life to be diagnosed with dementia, thus attenuating the observed effect of surgical menopause on dementia. Second, there was heterogeneity regarding the definition of surgical menopause with some studies pooling women that had undergone either bilateral oophorectomy or hysterectomy. This could have diluted the effect, but the primary result of higher risk of dementia following early surgical menopause was based on two studies examining only bilateral oophorectomy (Rocca et al., 2007, 2016). Third, recall bias might be an important limitation, especially for studies that have assessed the exposure mainly via interviews with demented patients, given both the memory problems of the patients but also the long interval between surgery and dementia diagnosis.

Fourth, indication for surgery might be an important confounder and was not considered in many studies. Yet, again the two studies examining the impact of bilateral oophorectomy at a young age on risk of dementia had excluded women who underwent oophorectomy due to ovarian cancer or treatment of an estrogen-related malignancy (mainly breast cancer) (Rocca et al., 2007, 2016). Fifth, it was not possible in the context of the current study to explore the potential impact that hormone replacement therapy after oophorectomy might have on

Table 3
Results from studies examining associations of age surgical menopause, as a continuous variable, with cognitive outcomes and Alzheimer's disease neuropathology indices.

Study	N	Cognitive decline/performance	N	Alzheimer's disease (AD) neuropathology
Bove et al., 2014	593	Significant associations of early age at bilateral oophorectomy with faster decline in global cognition, episodic memory and semantic memory in a follow-up of up to 18 years	179	Significant associations of early age at bilateral oophorectomy with global AD neuropathology, AD pathologic diagnosis, and accumulation of neuritic plaques
Ryan et al., 2014	499	Significant associations of early age at bilateral oophorectomy with worse performance in verbal fluency at a mean age of 74 years		
Kuh et al., 2018	151	No significant associations of age at bilateral oophorectomy with performance in verbal fluency at an age of 69 years		

prevention of cognitive decline and dementia since the majority of the included studies did not specifically examine this aspect; further, meta-regression analyses examining the effects of HT user proportion on the association estimates between surgical menopause and dementia or cognitive decline would be underpowered due to the paucity of studies included in each analysis. Sixth, with the exception of two studies (Geerlings et al., 2001; Ryan et al., 2014), the studies included in this review, did not take into account well-established genetic risk factors for dementia and cognitive decline, like the APOE genotype. Finally, because of the relative paucity of eligible studies, several of the analyses, like for specific cognitive domains or Alzheimer's neuropathological indices, were either underpowered or not feasible to perform.

5. Conclusion

In conclusion, current evidence supports that surgical menopause induced by bilateral oophorectomy at a young age may be associated with higher risk of dementia and cognitive decline later in life. Yet, our review further identified literature gaps and thus calls for additional research encompassing data from large cohorts that should shed light in this clinically relevant field.

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Conflicts of interest

None declared.

CRediT authorship contribution statement

Marios K. Georgakis: Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Theano Beskou-Kontou:** Formal analysis, Investigation, Project administration, Writing - original draft. **Ioannis Theodoridis:** Formal analysis, Investigation, Writing - original draft. **Alkistis Skalkidou:** Supervision, Writing - review & editing. **Eleni Th. Petridou:** Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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