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RESEARCH ARTICLE

Menopause

Long-term effects of premenopausal risk-reducing salpingo-oophorectomy on cognition in women with high familial risk of ovarian cancer: A cross-sectional study

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Abstract

Objective: To examine the effect of a premenopausal risk-reducing salpingo-oophorectomy (RRSO) in women at increased risk of ovarian cancer on objective and subjective cognition at least 10 years after RRSO.

Design: A cross-sectional study with prospective follow-up, nested in a nationwide cohort.

Setting: Multicentre in the Netherlands.

Population or Sample: 641 women (66% *BRCA1/2* pathogenic variant carriers) who underwent either a premenopausal RRSO ≤ age 45 (n = 436) or a postmenopausal RRSO ≥ age 54 (n = 205). All participants were older than 55 years at recruitment.

Methods: Participants completed an online cognitive test battery and a questionnaire on subjective cognition. We used multivariable regression analyses, adjusting for age, education, breast cancer, hormone replacement therapy, cardiovascular risk factors and depression.

Main Outcome Measures: The influence of RRSO on objective and subjective cognition of women with a premenopausal RRSO compared with women with a postmenopausal RRSO.

Results: After adjustment, women with a premenopausal RRSO (mean time since RRSO 18.2 years) performed similarly on objective cognitive tests compared with women with a postmenopausal RRSO (mean time since RRSO 11.9 years). However, they more frequently reported problems with reasoning (odds ratio [OR] 1.8, 95% confidence interval [95% CI] 1.1–3.1) and multitasking (OR 1.9, 95% CI 1.1–3.4) than women with a postmenopausal RRSO. This difference between groups disappeared in an analysis restricted to women of comparable ages (60–70 years).

Conclusions: Reassuringly, approximately 18 years after RRSO, we found no association between premenopausal RRSO and objective cognition.

KEYWORDS
BRCA1/2 pathogenic variant carriers, cognitive functioning, premature menopause, risk-reducing salpingo-oophorectomy

1 | INTRODUCTION

Women carrying a *BRCA1/2* germline pathogenic variant (*BRCA1/2pv*) have an increased life-time risk of breast and/or ovarian cancer.[1] To prevent ovarian cancer, guidelines recommend risk-reducing salpingo-oophorectomy (RRSO) after completing childbirth for *BRCA1pv* carriers between ages 35 and 40 and for *BRCA2pv* carriers between ages 40 and 45.[2,3] Although this preventive surgery reduces the risk of ovarian cancer, it induces immediate menopause long before natural menopause occurs at an average age of 51 years.[4] This may adversely impact cognition, as studies have shown neuroprotective effects of estrogens.[5] The uptake of RRSO in *BRCA1/2pv* carriers is high (86–91%).[6] Therefore, knowledge about long-term health consequences of RRSO, such as cognitive effects, is important for effective counselling.

Several studies have reported conflicting findings on the association between (bilateral) oophorectomy before natural menopause and cognition later in life. Some studies showed that an oophorectomy is associated with cognitive impairment and long-term increased risk of dementia.[7–10] This association is argued to be dependent on age at oophorectomy. A recent study observed that women with a bilateral oophorectomy before age 46 had an increased risk of cognitive impairment 20 years later compared with women without bilateral oophorectomy.[9] However, in *BRCA1/2pv* carriers who underwent RRSO before age 46 compared with carriers with RRSO at later ages, such an association between age at oophorectomy and cognitive decline was not found after approximately 9 years.[9,11]

It is difficult to compare results across studies, as these had several methodological limitations.[12,13] First, studies did not always take into account the indication for oophorectomy in the exposure group (e.g. ovarian cancer or a benign ovarian condition), nor were data provided on whether a bilateral oophorectomy, unilateral oophorectomy or a hysterectomy without oophorectomy was performed. Secondly, studies use different comparison groups (e.g. general population, premenopausal women without oophorectomy). Thirdly, adjustment for confounding (e.g. hormone replacement therapy [HRT]) was done inconsistently.[14] Also, many studies did not adjust for comorbidities such as depression and hypertension, which are known risk factors for dementia,[15] or for cancer, which can also negatively affect cognition.[16] Last, no studies examined the relation between RRSO and subjective cognition. As such, while there is some

evidence for an association between premenopausal RRSO and cognitive impairment at later ages, many questions remain unanswered.

Our aim was to examine the effect of a premenopausal RRSO on long-term cognitive functioning. We compared objective and subjective cognitive functioning at least 10 years after RRSO between women at high familial risk of ovarian cancer with a premenopausal RRSO ≤ age 45 and women with a postmenopausal RRSO ≥ age 54.

2 | METHODS

2.1 | Participants

Participants were women participating in the HARMOny study (ClinicalTrials.gov NCT03835793), a multicentre cross-sectional study assessing long-term effects of RRSO on (sub)clinical cardiovascular disease, bone health, cognition and quality of life by comparing women with a premenopausal RRSO and women with a postmenopausal RRSO.

Study design and procedures have been described previously.[17] Briefly, between 2018 and 2021, we invited 1271 women from the well-established HEBON cohort study of Dutch families with a high familial risk of breast/ovarian cancer to participate in the HARMOny study (Appendix S1).[18] Women were eligible if they had a RRSO ≤ age 45 and were currently aged ≥55 years, resulting in at least 10 years since RRSO. We compared them with women currently aged ≥55 years with a RRSO ≥ age 54, aiming to frequency-match on age. We chose the cut-off of 45 years based on clinical recommendations for *BRCApv* carriers.

Exclusion criteria were ovarian carcinoma, metastatic disease, early-onset dementia and insufficient understanding of the Dutch language. These criteria were checked via medical files and questionnaires. A history of breast cancer was not an exclusion criterion. This study was approved by the Institutional Review Board of the Netherlands Cancer Institute. All participants provided written informed consent.

2.2 | Study assessments

After inclusion to the HARMOny study, participants completed an online questionnaire on socio-demographic data, general health, cancer-specific outcomes, cardiovascular health and medical treatments, including cancer treatment and use of HRT.

To study objective cognition, participants completed the Amsterdam Cognition Scan (ACS), an online neuropsychological assessment that is completed on the computer at home without supervision.[19] The ACS consists of seven cognitive tests, based on traditional neuropsychological tests covering four domains: verbal memory, attention, executive functioning and processing speed (10 outcome variables; see Table S1). The ACS takes approximately 1 hour to complete and is tailored to detect cognitive dysfunction associated with cancer (treatment). The ACS has shown concurrent validity and test–retest reliability, and normative data have been collected.[20]

Subjective cognition was assessed by the Medical Outcomes Study cognitive functioning scale (MOS-cog), measuring the frequency of self-reported cognitive problems in daily life.[21] The MOS-cog is a validated questionnaire consisting of six questions on reasoning, memory, attention, concentration, multitasking and thinking speed (score: 0–5). Higher scores indicate a higher frequency of cognitive complaints.

2.3 | Outliers objective cognition

Outliers were removed in two steps. For each cognitive outcome, non-legitimate test scores (i.e. impossible scores due to computer malfunction, non-adherence to test instructions or low motivation) were removed using predefined cut-offs based on test instructions and clinical expertise. The cut-offs per test are depicted in Table S8. After removing impossible scores, we excluded outliers on the speed-based tests with the median absolute deviation (MAD) method.[22] The MAD was applied separately in participants below age 60 and above to adequately take age into account.

2.4 | Age-corrected cognitive domain scores

Based on the demographically adjusted normative dataset of the ACS (women aged ≥55 only, $n = 157$),[19] we calculated age-corrected z-scores for test outcomes. Performance on the online versions of the Trail Making Test A (TMT-A) and TMT-B, Visual Reaction Time, Tower of London and Grooved Pegboard were reversed (z-score times −1), so that higher scores indicated better performance.

We calculated cognitive domain scores by averaging the means of the age-corrected z-scores of the subtests belonging to the same domain. This led to four cognitive domain scores: verbal memory, executive functioning, processing speed and attention (Table S1).

2.5 | Statistical analyses

With a two-sided α of 0.05, with 200 women in the study we have 94% power to detect a difference in z-score of 0.5 between the two groups. With 750 women in the study, we have 98% power to detect a difference in z-score of 0.3, and 78% power to detect a difference in z-score of 0.2.

Patient characteristics were compared using independent samples t-tests, χ^2 tests or Fisher exact tests. To examine the effect of a premenopausal RRSO on long-term objective

cognition, age-corrected *z*-scores for the four cognitive domains were compared between the premenopausal and postmenopausal RRSO groups, and between the RRSO groups and the normative population using independent samples *t*-tests. In addition, we performed multivariable linear regression analyses with the four cognitive domains as dependent variables and RRSO (premenopausal or postmenopausal) as the independent variable, adjusting for current age, level of education, breast cancer, HRT, depression and cardiovascular risk factors (i.e. hypertension). Body mass index (BMI), diabetes and smoking were not confounding factors and were therefore omitted from our analyses.

To examine the effect of a premenopausal RRSO on long-term subjective cognition, independent sample *t*-tests were used to compare the six subjective cognition outcomes (score 0–5) between the premenopausal and postmenopausal RRSO groups. In addition, we performed ordered logistic regression analyses, adjusting for current age, level of education, breast cancer, HRT, depression and cardiovascular risk factors, yielding odds ratios (OR).

We performed several subgroup analyses for objective and subjective cognition. Because of the clinical recommendations for *BRCA1/2pv* carriers, we compared cognition between women with RRSO ≤ age 40 and between ages 41 and 45. Furthermore, because of the age difference between the pre- and postmenopausal RRSO groups, we compared cognition in participants whose ages overlapped (60–70 years). Additionally, to account for potential confounding effects of breast cancer history and HRT, we performed stratified analyses according to breast cancer history; within the premenopausal RRSO group we performed stratified analyses according to HRT use. Due to collinearity between premenopausal or postmenopausal RRSO and 'time since RRSO', we did not add 'time since RRSO' to the regression analyses. Subsequently, we performed sensitivity analyses with 'time since RRSO' as a continuous variable.

2.6 | Proportion cognitively affected

Participants who scored ≥1 standard deviation (SD) below the age-corrected normative mean on two tests from different cognitive domains were classified as cognitively affected. This criterion is used in studies in the field of cancer (treatment) and cognition.[23–25] The proportion of cognitively affected participants was compared between the premenopausal and postmenopausal RRSO groups using a χ^2 test, and compared with the expected proportion (30%) of cognitively affected based on the probability curves provided by Ingraham & Aiken.[26] To analyse the effect of a premenopausal RRSO on the proportion cognitively affected, we used multivariable logistic regression analyses, adjusting for current age, breast cancer history, HRT, depression, education and cardiovascular disease.

For all statistical analyses, STATA version 15.0 (StataCorp) was used. An α of 0.05 was used as the criterion for statistical significance.

3 | RESULTS

3.1 | Participation

In total, 758 women who met the eligibility criteria gave written informed consent (response rate 59.6%), of whom 505 were in the premenopausal RRSO group (RRSO ≤ age 45) and 253 in the postmenopausal RRSO group (RRSO ≥ age 54) (Figure S1).

The ACS was completed by 641 women: 436 with a premenopausal RRSO and 205 with a postmenopausal RRSO. Forty-one participants were unable to complete the ACS because they did not have access to a laptop or computer. Compared with ACS completers, noncompleters were older (mean age: 63.1 years [SD 6.1] versus 67.2 years [SD 6.1]; $p < 0.01$). They did not report cognitive complaints more frequently (*p*-values ranged from 0.08 to 0.31).

3.2 | Participant characteristics

Several characteristics differed between the premenopausal and postmenopausal RRSO groups, partly due to the inclusion criteria (Table 1). The premenopausal RRSO group was younger at study participation than the postmenopausal RRSO group (59.9 versus 70.1 years; $p < 0.001$) and had a longer time since RRSO (18.1 versus 11.7 years; $p < 0.001$). Compared with the postmenopausal RRSO group, the premenopausal RRSO group more often completed at least middle level education (65.6% versus 51.2%; $p < 0.001$), more often received chemotherapy for breast cancer (76.9% versus 53.5%; $p = 0.01$), (had) more often used HRT (24.8% versus 10.3%; $p < 0.001$) and less often had cardiovascular risk factors (35.8% versus 56.2%; $p = 0.001$). There was no difference between the groups in occurrence of breast cancer and treatments other than chemotherapy, depression or *BRCA1/2pv* status (67% in the premenopausal RRSO group and 64.6% in the postmenopausal RRSO group). The premenopausal RRSO group reported more frequent computer use than the postmenopausal RRSO group.

Data were missing for 18 women (2.8%) with regard to breast cancer, for 22 women (3.4%) with regard to depression. Seventy-eight women (12.2%) did not remember whether they had taken HRT. We took this into account in our analyses by performing sensitivity analyses. We did not perform multiple imputation for the other missing confounders, as this was less than 5%.

3.3 | Outlier removal

In total, 3.0% of test scores was excluded from the analyses, resulting in different numbers per subtest available for analyses. Based on extreme value detection, 1.5% of test scores (106 scores) were excluded from analyses; 1.2% of

TABLE 1 Demographics of study participants that completed the online Amsterdam Cognition Scan.

	Premenopausal RRSO (n = 436)	Postmenopausal RRSO (n = 205)	p-Value[a]
Age (mean, SD)	59.9 (3.5)	70.1 (4.4)	<0.001
Age at RRSO, mean (SD)	41.8 (2.7)	58.5 (3.7)	<0.001
Time since RRSO, mean (SD)	18.1 (4.2)	11.7 (3.0)	<0.001
Age at menopause, mean (SD)	41.8 (2.8)	50.3 (5.0)	<0.001
Pathogenic genetic variants[b]			
BRCA1 germline mutation	209 (47.9%)	64 (31.2%)	0.41
BRCA2 germline mutation	83 (19.0%)	68 (33.2%)	
Non-carrier *BRCA1/2*	144 (33.0%)	73 (35.6%)	
Breast cancer, (yes)	247 (56.7%)	127 (62.0%)	0.19
Treatment of breast cancer			
Surgery	243 (97.9%)	120 (94.5%)	0.93
Chemotherapy	190 (76.9%)	68 (53.5%)	0.01
Radiotherapy	155 (62.5%)	65 (53.3%)	0.09
Endocrine therapy	93 (37.5%)	35 (28.7%)	0.09
HRT use			
Current user	23 (5.3%)	2 (1.0%)	<0.001
Past user	85 (19.5%)	19 (9.3%)	
Never user	287 (65.8%)	165 (80.5%)	
Unknown	41 (9.4%)	37 (18.0%)	
HRT duration in years, mean (SD)	1.6 (5.1)	0.4 (1.7)	0.13
Type HRT			
Tibolone	25 (23.1%)	2 (9.5%)	
Estradiol/progestogen	19 (17.6%)	0 (0.0%)	
Estradiol only	6 (5.6%)	1 (4.8%)	
Unknown	58 (53.7%)	18 (85.7%)	
BMI, mean (SD)	26.2 (5.0)	25.7 (4.4)	0.29
Educational level			
Primary school/lower level high school	111 (25.5%)	77 (37.6%)	<0.001
Middle level high school	143 (32.8%)	38 (18.5%)	
Advanced vocational/university	143 (32.8%)	67 (32.7%)	
Missing	39 (8.9%)	23 (11.2%)	
Hours of computer use per week	12.8 (12.3)	6.7 (7.6)	<0.001
Depression (yes)	63 (14.4%)	20 (9.8%)	0.10
Cardiovascular risk[c]	156 (35.8%)	123 (56.2%)	<0.001
Cardiovascular disease[d]	78 (19.1%)	51 (25.4%)	0.08
Hysterectomy (yes)[e]	60 (13.8%)	42 (20.5%)	0.002

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation.

[a]Groups compared using independent samples t-test or Fisher exact test when appropriate.

[b]All participants have a high familial risk of ovarian cancer. All women were tested for germline mutations; not all have a *BRCA1*/2 mutation. Among the established non-carriers there are, for example, CHEK2 mutation carriers.

[c]Cardiovascular risk factors: hypertension, hypercholesterolaemia and/or type 2 diabetes.

[d]Cardiovascular disease: myocardial infarction, angina, heart failure, arrhythmia, cardiac valve disorder, transient ischaemic attack and/or cerebrovascular accident.

[e]In the Netherlands, a hysterectomy is not standard of care when performing RRSO.

test scores (83 outliers) were from the verbal memory test. Some participants had difficulty understanding how to enter their answers or completed the recall phase longer than 1 hour after the learning phase. Participants with outliers on this subtest less frequently used the computer, were on average 2 years older and were less educated than participants without outliers. Using MADs, we removed an additional 103 outliers (27 from TMT-B, 32 from Visual Reaction Time, 19 from Tower of London, 7 from Corsi Block and 18 from Grooved Pegboard) due to improbably

low test scores that were likely to reflect technical glitches or a moment of inattention.

3.4 | Objective cognition

Based on independent samples *t*-tests, the premenopausal RRSO group performed better than the postmenopausal RRSO group on executive functioning (mean age-corrected *z*-score 0.20 and −0.01, respectively, $p = 0.005$), processing speed (mean age-corrected *z*-score 0.33 and −0.02, respectively, $p < 0.001$) and attention (mean age-corrected *z*-score 0.11 and −0.05, respectively, $p = 0.01$) (Figure 1, Table S2). However, after adjusting for confounders, a premenopausal RRSO was not associated with any of the cognitive domains (β-coefficient and 95% CI for a premenopausal RRSO on verbal memory: 0.07 (−0.26 to 0.39), processing speed: 0.05 (−0.29 to 0.38), executive functioning: 0.01 (−0.26 to 0.28) and attention: 0.14 (−0.10 to 0.38), see also Table S7). A higher level of education was associated with better cognitive performance. Longer time since RRSO did not influence the results.

Compared with the normative group, the premenopausal RRSO group performed better and the postmenopausal RRSO group similarly on attention, executive functioning and processing speed. Both groups performed slightly worse on verbal memory (Table S2).

3.5 | Proportion cognitively affected

In the postmenopausal RRSO group, the proportion of cognitively affected women (44.5%) was higher compared with the premenopausal RRSO group (33.3%; $p = 0.01$) and comparable to the 30% expected based on the probability curves.[26] After correcting for confounders, this difference in proportion of cognitively affected between the premenopausal and postmenopausal RRSO disappeared.

3.6 | Subgroup analysis objective cognition

Based on independent samples *t*-tests, the premenopausal RRSO ≤40 years group performed similarly on verbal memory, processing speed and attention, but better on executive functioning compared with the premenopausal RRSO in the 41–45 years age-group (Figure 2, Table S3). After adjusting for confounders, RRSO ≤40 compared with RRSO at ages 41–45 years was not associated with any cognitive outcome (Table S7).

The proportion of cognitively affected women with a premenopausal RRSO at 41–45 years was 36.4%, and 26.5% in women with a premenopausal RRSO ≤40 years. This difference was not statistically significant ($p = 0.06$). Also, neither proportion differed significantly from the expected 30% cognitively impaired in a healthy population given the number of tests administered.[26]

When comparing the premenopausal and postmenopausal RRSO groups in the overlapping age range of 60–70 years at study inclusion ($n = 222$), no differences were found in verbal memory, executive functioning, attention and processing speed (Table S4). After adjusting for confounders, we found no effect of RRSO on any cognitive domain (Table S7).

When stratifying by history of breast cancer, we also did not find differences between the premenopausal RRSO group and the postmenopausal RRSO group (Table S7). In addition, within the premenopausal RRSO group, there were no differences in cognitive test performance between women with and without breast cancer or between women with and without HRT use (Table S5).

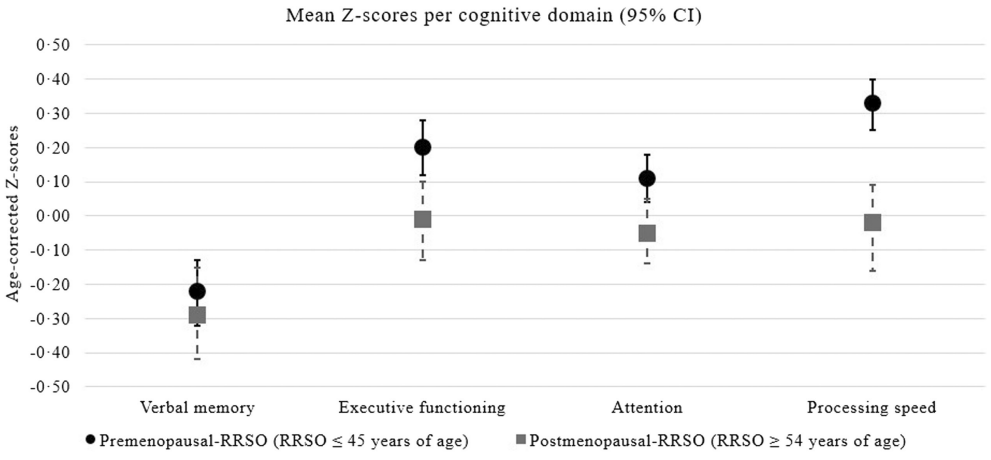

FIGURE 1 Differences in age-corrected *z*-scores per cognitive domain and the corresponding 95% confidence interval between the premenopausal and postmenopausal RRSO groups. The *z*-scores are age-corrected and describe the score's relation to the mean in a group of scores, with 0 being the mean of the group and 1 or −1 being 1 standard deviation above or below the mean, respectively. CI, confidence interval; RRSO, risk-reducing salpingo-oophorectomy.

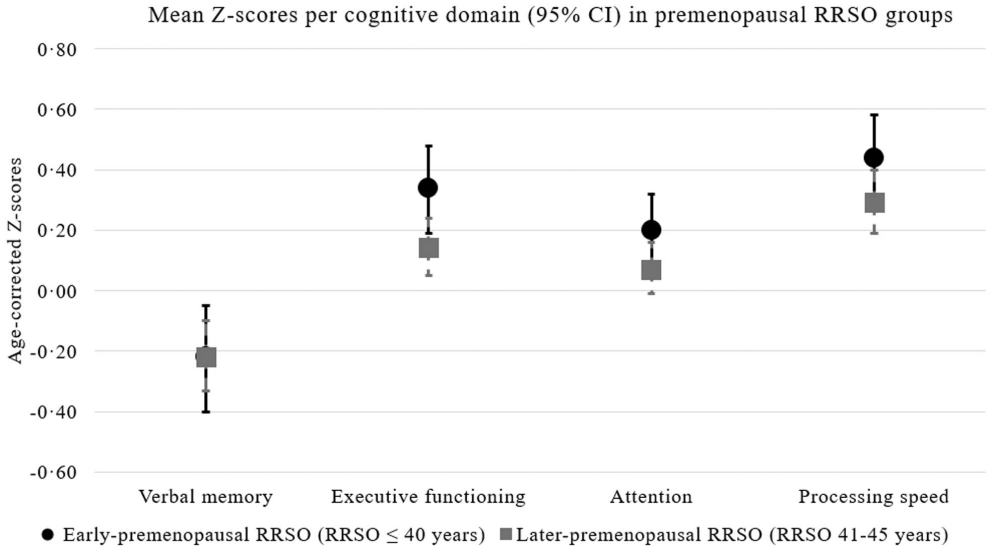

FIGURE 2 Comparison performance cognitive domains between early-premenopausal RRSO (RRSO ≤40 years) versus later-premenopausal RRSO (RRSO 41–45 years). The *z*-scores are age-corrected and describe the score's relation to the mean in a group of scores, with 0 being the mean of the group and 1 or –1 being 1 standard deviation above or below the mean, respectively. CI, confidence interval; RRSO, risk-reducing salpingo-oophorectomy.

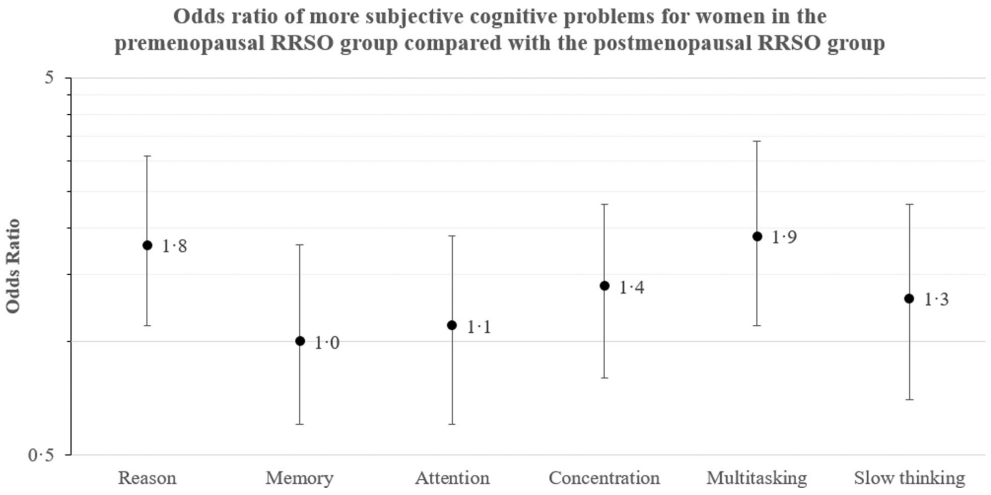

FIGURE 3 Odds ratios and their 95% confidence interval for more subjective cognitive complaints in women with a premenopausal RRSO as compared with women with a postmenopausal RRSO. Corrected for age, breast cancer, HRT, education, depression and cardiovascular risk factors.

3.7 | Subjective cognition

After adjustment for confounders, the premenopausal RRSO group more frequently reported problems with reasoning (OR 1.8, 95% CI 1.1–3.1) and with multitasking (OR 1.9, 95% CI 1.1–3.4), both borderline significant ($p = 0.03$) (Figure 3). For all six questions on subjective cognition, a depression diagnosis was associated with a higher frequency of complaints (OR 1.7–3.1). A sensitivity analysis showed that time since RRSO did not change the results (Table S6). In the overlapping age category (ages 60–70 years), we did not find differences in subjective cognition.

3.8 | Subgroup analysis subjective cognition

After adjusting for confounders, a premenopausal RRSO at ages 41–45 was associated with a higher frequency of problems with reasoning (OR 1.66, 95% CI 1.07–2.57) and slow thinking (OR 1.79, 95% CI 1.13–2.82) compared with a premenopausal RRSO before 41 years of age. Sensitivity analyses showed that longer time since RRSO was associated with less frequent cognitive complaints on all six questions (ORs varied between 0.90 and 0.93, 95% CI between 0.83 and 0.99) (Table S6).

In women with a history of breast cancer, no differences were found between the premenopausal and postmenopausal

RRSO groups. In women without a history of breast cancer, the premenopausal RRSO group more frequently reported problems with reasoning ($p = 0.031$; OR 2.5, 95% CI 1.1–5.7). In women with a premenopausal RRSO, HRT users more frequently reported forgetfulness compared with non-users ($p = 0.03$; OR 1.2, 95% CI 1.1–2.8).

4 | DISCUSSION

After adjusting for age, education, breast cancer, HRT, depression and cardiovascular risk factors among women at high familial risk of breast/ovarian cancer who have had a RRSO, we found no association between timing of RRSO (i.e. premenopausal or postmenopausal) and long-term objective cognition. Women with a premenopausal RRSO before age 46 did not perform worse on cognitive tests compared with women with a postmenopausal RRSO after age 54. Moreover, women with a premenopausal RRSO before age 41 did not perform worse on cognitive tests than did women with a premenopausal RRSO at ages 41–45 years. We found no protective effect of HRT (mean duration, 1.6 years) on cognitive functioning. We showed that the differences in objective cognition between the premenopausal and postmenopausal RRSO groups in univariate analyses could be explained by confounding factors. Regarding subjective cognition, after confounder adjustment, we observed that women with a premenopausal RRSO more frequently reported cognitive complaints about reasoning and multitasking compared with women with a postmenopausal RRSO. Unexpectedly, women with an RRSO at ages 41–45 years more frequently reported cognitive complaints about reasoning and thinking speed compared with women with a premenopausal RRSO before age 41.

In general, our results showed no association between premenopausal RRSO and long-term cognitive functioning. This observation is consistent with one recent study[11] in which women with a *BRCA1/2pv* and a mean age at oophorectomy of 46 years completed an online cognitive screening instrument at a mean age of 54. The authors found no differences in test performance between women with a RRSO before and after age 45, or between women with a RRSO and women without a RRSO. Our study confirms and adds to these results by examining the cognitive effects of a premenopausal RRSO, measured by a more extensive cognitive test battery as well as a self-report questionnaire, with substantially longer time since premenopausal RRSO.

However, our results are in contrast to several earlier studies on the effects of RRSO on cognition.[7–10] A possible explanation for the inconsistent findings lies in the adjustment for confounding factors. We showed that adjusting for these factors influenced the results. Previous studies did not account for cancer, HRT, hypertension or depression. It is therefore possible that the previously observed relation between RRSO and long-term cognition was due to confounding. Also, previous studies included women who underwent bilateral oophorectomy for different indications, i.e. an oophorectomy for cancer treatment, and usually compared with a non-oophorectomy group. This may have caused confounding by indication. The association between RRSO and cognition might have been caused by shared genetic (e.g. pathogenic variant in estrogen receptor) and/or non-genetic factors (e.g. education) that (directly and/or indirectly) increase the likelihood to undergo oophorectomy as well as the risk of developing cognitive impairment.[27,28] In contrast, in our study, all women underwent RRSO because of a high familial risk of ovarian cancer.

Women with a premenopausal RRSO reported more cognitive complaints than did women with a postmenopausal RRSO, also after adjustment for age and education. An explanation could be that the age adjustment we applied in the regression analyses was insufficient, due to the large age differences between the two groups, as among women aged 60–70, we found no differences in subjective cognition between women with a pre- or postmenopausal RRSO. Another explanation might be that subjective cognition reflects not only cognitive ability but also psychosocial factors such as expectations and coping style. Women in the premenopausal RRSO group were more often employed than were women in the postmenopausal RRSO group, and possibly had higher expectations of their own functioning. In addition, women with a premenopausal RRSO may have been more alert to their cognitive problems because they were aware of possible cognitive consequences of premature menopause.

Unexpectedly, within the premenopausal RRSO group, women with RRSO between ages 41 and 45 reported somewhat more cognitive complaints compared with women with a premenopausal RRSO ≤ age 40 despite similar stage of life, education and cognitive test performance. The difference was small and was not in line with our other findings. Future studies could focus on cognitive complaints after a premenopausal RRSO in relation to stage of life and whether they progress over time.

It is noteworthy that, in our study, verbal memory was the only domain where both groups scored lower than the normative population. Verbal memory has frequently been shown to be affected after oophorectomy[9] and is associated with brain regions that are rich in estrogen receptors (i.e. hippocampus and frontal lobe).[29] On other domains, the premenopausal RRSO group performed better than the normative population. Participants visiting clinical geneticists are generally higher educated, have greater awareness of health issues and genetic risk factors for cancer, and are less socially deprived and more affluent than the general population.[28,30] All these characteristics have been associated with better cognition.[31] Moreover, women from *BRCA1/2pv* families tend to have healthier lifestyles than their peers, especially after RRSO.[32] This healthy lifestyle may protect against cognitive impairment.[33]

A limitation of this study is the difference in inclusion rate between the premenopausal and postmenopausal RRSO groups. The inclusion rate in the postmenopausal RRSO group was relatively low, possibly because the HARMOny study was focused on long-term effects after a premenopausal

RRSO. This could mean that we overestimated the cognitive ability in the postmenopausal RRSO group, as women with lower functioning may not have participated. However, if this were the case, the premenopausal group would have performed even better than the postmenopausal RRSO group, providing even more evidence against the earlier hypothesis. Another limitation is possible misclassification bias; 10.1% of the women in our study could not remember if they had ever used HRT. However, we performed sensitivity analyses with patients with missing values included and the results did not differ from the complete case analyses. A last limitation was that we did not correct our analyses for computer use due to multicollinearity between computer use and age, and timing of RRSO. An earlier study of our group showed that more frequent computer use was associated with better performance on the online cognitive tests.[34] Therefore, we may have overestimated the test performance of the premenopausal RRSO group, who more often used the computer than the postmenopausal RRSO group.

5 | CONCLUSION

After adjustment for confounders (age, education, breast cancer, HRT, depression and cardiovascular risk factors), timing of RRSO was not associated with long-term objective cognition. We found no difference in cognitive test performance between women with a premenopausal or postmenopausal RRSO. Women with a premenopausal RRSO did report more complaints, but this may have been due to the large age difference between the groups and/or awareness of potential cognitive consequences of premature menopause in the premenopausal RRSO group. Future studies should longitudinally examine objective and subjective cognition to see whether cognitive changes arise at later ages in women with a premenopausal RRSO. If our results are confirmed by other studies, a clinical implication could be that the age at which women undergo RRSO does not make a difference in long-term cognitive effects. In view of the clinical guidelines for *BRCA1/2* mutation carriers recommending a premenopausal RRSO to reduce ovarian cancer risk and the high uptake of RRSO, our findings regarding cognition are reassuring.

AUTHOR CONTRIBUTIONS

FvL, SS, AM and MJH were involved in the conception and design of the study. LT, PL and JAvR assessed and verified the data. LT, PL, JAvR, SS and FvL drafted the paper. MB, MvB JRvL, HvD, JdH, EvD, CM, BS, KG, MM, LvdK, MC, MW, MA, KvE, IvdB, LB, CvA, EG, AM, MH, BHK and EvdW were involved in the final version of the article. All authors have read and approved the article.

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CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

With publication, de-identified data collected for the study, including participant data, will be made available to others upon reasonable request. Data can be requested with a proposal by sending an e-mail to the corresponding author. Study protocol and statistical analysis plan are available on clinicaltrials.gov, file number NCT03835793.

ETHICS APPROVAL

This study was conducted according to the standards of Good Clinical Practice, in agreement with the principles of the Declaration of Helsinki and with Dutch law as stated in the Medical Research Involving Human Subjects Act (WMO). The study has been approved in writing by the Institutional Review Board of the AVL/NKI to be conducted in all University Medical Centres and the Antoni van Leeuwenhoek, and has been registered at 'CCMO Toetsingonline' from the Dutch Central Committee on Research involving Human Subjects (file number NL63554.031.17) and on clinicaltrials.gov, M18HAR.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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