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What happens after menopause? (WHAM): A prospective controlled study of depression and anxiety up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy

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HIGHLIGHTS

- Risk of depressive symptoms doubles within 3 months of premenopausal RRBSO.
- Risk of depressive symptoms remains elevated in the 3 to 12 months after RRBSO.
- Prior depression and VMS are risk factors for depressive symptoms after RRBSO.
- Risk of anxiety symptoms triples within 3 months of RRBSO and plateaus by 6 months.
- Depression and anxiety symptoms after RRBSO occur despite use of Hormone Therapy.

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ABSTRACT

Objective. Risk-reducing bilateral salpingo-oophorectomy (RRBSO) substantially reduces ovarian cancer risk in women with pathogenic gene variants and is generally recommended by age 34–45 years. Natural menopause is a vulnerable period for mood disturbance, but the risk of depression and anxiety in the first 12 months after RRBSO and potential modifying effect of hormone therapy are uncertain.

Methods. Prospective controlled observational study of 95 premenopausal women planning RRBSO and a Comparison group of 99 premenopausal women who retained their ovaries,- 95% of whom were at population level risk of ovarian cancer. Clinically significant symptoms of depression and anxiety were measured using standardised instruments at baseline, 3, 6 and 12 months. Chi-square tests and adjusted logistic regression models compared differences between groups.

Results. Baseline symptoms and previous depression or anxiety did not differ between groups. At 3 months after RRBSO clinically significant depressive symptoms were doubled (14.5% vs 27.1%, $p = 0.010$), which persisted at 12 months. Depressive symptoms were stable in comparisons. At 3 months after RRBSO, clinically significant anxiety symptoms almost trebled (6.1% vs 17.7%, $p = 0.014$) before plateauing at 6 months and returning to baseline at 12 months. Compared to comparisons, RRBSO participants were at 3.0-fold increased risk of chronic depressive symptoms (Wald 95% CI 1.27–7.26), 2.3-fold increased risk of incident depression (95% Wald CI 1.08–5.13) and 2.0-fold increase of incident anxiety (Wald 95% CI 0.78–5.00). Depression and anxiety were slightly more common in Hormone Therapy users after RRBSO vs non-users.

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Conclusions. RRBSO leads to a rapid increase in clinically significant depressive and anxiety symptoms despite Hormone Therapy use.

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1. Introduction

Depression is almost twice as common in women compared to men, and natural menopause is a time of heightened vulnerability, particularly for those with previous depressive disorders [1]. Anxiety symptoms may also increase over the natural menopause transition [2]. In premenopausal women with pathogenic gene variants which increase the risk of ovarian cancer, RRBSO will induce surgical menopause with a rapid reduction in endogenous estrogen exposure [3]. In the general population, surgical menopause may increase long-term risk of depression and anxiety [4]. However, two short studies of surgical menopause in the general population have been published with conflicting results. One showed an increased trajectory of depressive symptoms compared to natural menopause [5], and the other showing no change in depressive symptoms following surgical menopause [6]. In high-risk women, the impact of RRBSO on depression and anxiety is also uncertain. Two prospective studies have reported no change in depressive symptoms but neither established premenopausal status prior to oophorectomy and used either non-validated measures for depressive symptoms or indirect measures such as antidepressant use which may underestimate rates of depression since many symptomatic women do not seek medical treatment [7] [8] [9].

Hormone therapy (HT) is recommended after surgical menopause for the prevention and management of vasomotor symptoms, which may contribute to mood disturbance [10] [11]. Whilst HT may reduce the risk of depression and anxiety over the natural menopause transition [12] [13], it is uncertain whether HT affects depression or anxiety following surgical menopause [14] [15].

Patients and clinicians face complex choices around the elective removal of normal ovaries in premenopausal women, even those at elevated risk of ovarian cancer [16,17]. Many of these women are also at elevated risk of breast cancer, and evidence gaps remain about the association between HT and breast cancer risk in this population [18]. The aim of this study was to prospectively measure changes in clinically significant symptoms of depression and anxiety up to 12 months following RRBSO compared to premenopausal comparisons, and the modifying effects of HT on these outcomes.

2. Methods

2.1. Study population

Premenopausal women at elevated risk of ovarian cancer planning RRBSO were recruited from familial cancer clinics or via gynaecology oncologists at public and private hospitals (Fig. 1). The Comparison group were premenopausal women not planning oophorectomy or pregnancy within the study period who self-referred to the same recruitment sites in response to advertising promoted via traditional and social media, hospital websites and cancer foundation/research websites (Fig. 1). Women with pathogenic gene variants were eligible to be comparisons provided they met inclusion criteria. Almost 700 potential participants were consecutively screened between 2013 and 2019 at 5 sites in Australia (4 sites) and the USA (1 site). Around one third met inclusion criteria and were willing to participate, resulting in 224 enrolments [19] (Fig. 1). Screening was within the 8 weeks prior to surgery (for the RRBSO group) or baseline (for the Comparison group). The baseline visit was performed prior to RRBSO. Premenopausal status was based on a history of regular menstrual cycles, day 2–6 Follicle Stimulating Hormone ≤15 IU/L and estradiol >100 pmol/L. In those taking hormonal contraception, premenopausal status was based on prior regular menstrual cycles. Exclusion criteria were < 3 months since pregnancy or lactation, irregular bleeding or use of anti-estrogens such as tamoxifen.

2.2. Study assessments

A comprehensive schedule of WHAM study assessments and measures has been previously described [19]. Briefly, measures of vasomotor symptoms, mood, and use of medication including antidepressants and HT were collected at baseline, 3, 6 and 12 months. RRBSO occurred between baseline and 3 months. This study reports the results from prospective measures of depressive and anxiety symptoms.

2.3. Measurements of depression and anxiety

Depressive symptoms were assessed at baseline, 3, 6 and 12 months using the Centre for Epidemiologic Studies Depression (CES–D) Scale, a 20-item measure that asks about frequency of bother due to depressive symptoms during the previous week on a 4-point scale of 0 ("rarely") to 3 ("most or all of the time") [20]. The final CES-D score (range 0–60) is the sum of the 20 items, and a score of ≥16 points is indicative of clinically relevant depression symptoms [21].

Anxiety symptoms were assessed at baseline, 3, 6 and 12 months using the Generalized Anxiety Disorder (GAD-7) Scale [22]. The GAD-7 measures the frequency of anxiety symptoms in the past 2 weeks using 7 items scored from 0 to 3. The final GAD-7 score (0−21) is the sum of the 7 items and scores of ≥10 are indicative of clinically relevant anxiety symptoms [22].

Potential confounders in the associations between RRBSO and the outcomes of interest included age at baseline, previous clinically diagnosed depression or anxiety, body mass index (BMI), smoking status and vasomotor symptoms. BMI was classified using WHO criteria as underweight/normal (≤24.9 kg/m^2), overweight (25.0 to ≤29.9 kg/m^2) and obese (≥30 kg/m^2). Cigarette smoking was categorised as non-smoker (never smoked), ex-smoker (history of smoking but ceased prior to baseline) and current smoker (smoker at any time from baseline to 12 months). Vasomotor symptoms were diagnosed based on responses of "yes" at 3, 6 or 12 months to questions about hot flashes or night sweats in the past week using the intervention version of the Menopause-related Quality of Life questionnaire [23].

2.4. Statistical analysis

Statistical analyses were conducted in SAS (version 9.4). Data screening was conducted to check for cell sizes and missing data. Data were missing for selected measures in $n = 19$ (9.8%) women at baseline, $n = 10$ (5.2%) at 3 months, $n = 6$ (3.1%) at 6 months, and $n = 7$ (3.7%) at 12 months. Baseline missing data were primarily due to participants completing a different measure of anxiety and depression (Hospital Anxiety and Depression Scale, HADS). For sensitivity analysis, missing values were imputed using multiple imputation, specifying 20 datasets and using a fully conditional specification (imputation by chained equations) and discriminant function due to categorical variables. Differences in continuous CES-D scores between baseline and 3 months were tested in the RRBSO group using a paired samples *t*-test. Differences between groups (ie. RRBSO vs Comparison group and RRBSO who initiated HT vs those who did not) were measured using chi-square tests at each time point. Chronic symptoms of depression or

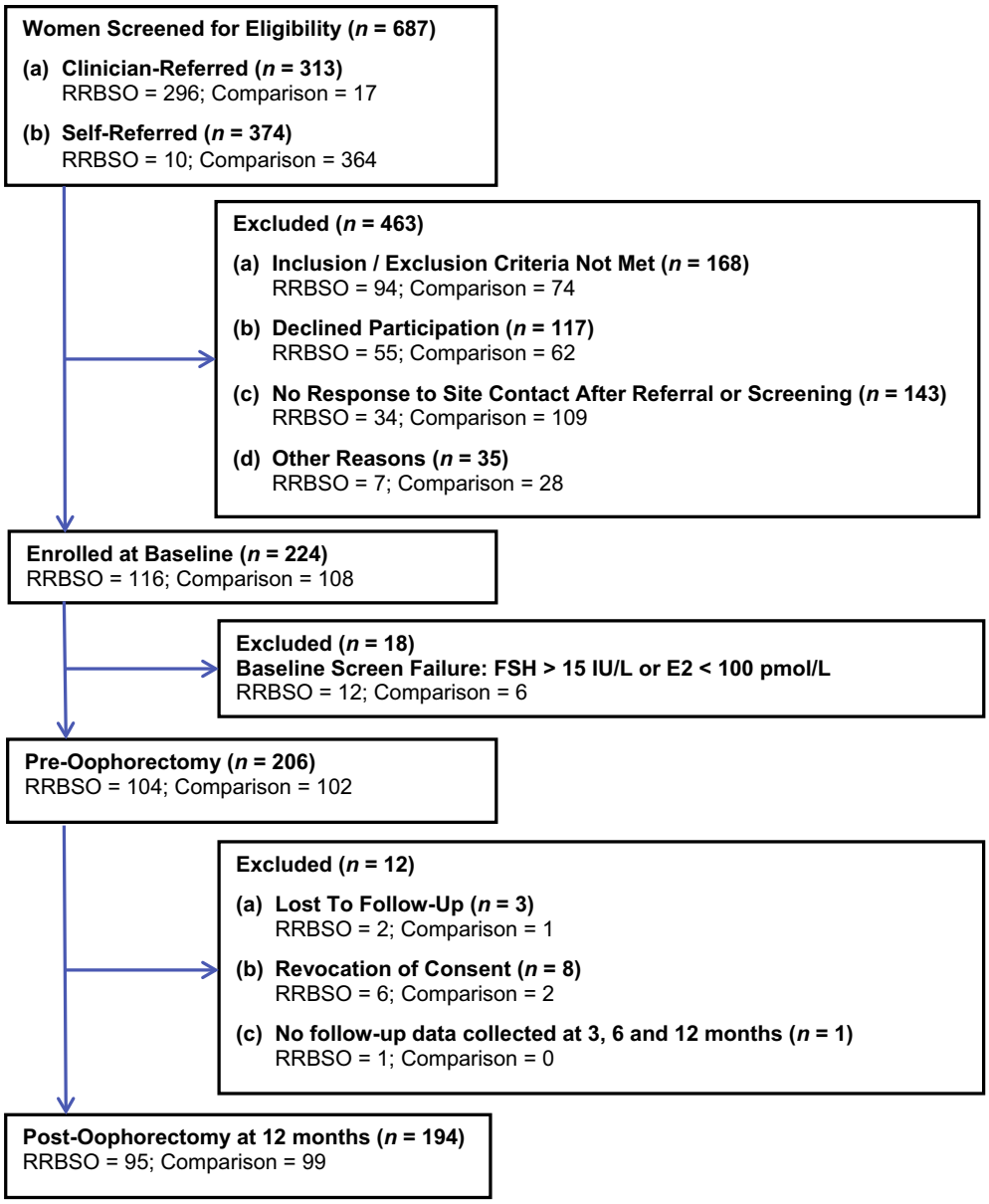

Fig. 1. Participant flowchart. Number of participant screenings, enrolments and withdrawals relevant to the first 12 months of the WHAM study. Women were either clinician- or self-referred to one of five recruitment sites in Australia and the USA during 2013 to 2019. *FSH* = Follicle-Stimulating Hormone; *E2* = Estradiol.

anxiety were defined as scores at or above the clinical cut-off at 2 or 3 time points between 3 and 12 months. Incident cases of depression or anxiety were defined as scores below the clinical cut-off for clinically significant symptoms at baseline but at or above the cut-off at any time point from 3 to 12 months. Logistic regression was used to investigate whether group status was associated with incident cases or with chronicity, controlling for covariates. Covariates included a clinical diagnosis of depression or anxiety prior to baseline, CES-D or GAD-7 scores at or above the clinical cut-off at baseline (not used in the model for incident cases), age and BMI at baseline, smoking status, and vasomotor symptoms at any point from 3 to 12 months. Covariates were dropped from the final model if the effect size was negligible (<0.1). Post-hoc analyses were conducted to ascertain whether high scores on the CES-D sleep question accounted for the increase in clinically significant depressive symptoms [24]. To address this, subscores were created for the CES-D questions limited to negative affect, anhedonia and somatic symptoms and excluding the question on sleep, consistent with previous approaches [25]. Independent sample *t*-tests were used to compare subscore means for the CES-D between RRBSO participants scoring at or above the cut-off for clinically significant depressive symptoms (score ≥ 16) to those scoring below.

3. Results

3.1. Participant demographics

Data from 194 premenopausal women were included for analysis: 95 women planning RRBSO and 99 Comparison women (Fig. 1). At baseline, mean age (41 years, range of 24–52 years), smoking status and BMI did not differ between the groups (Table 1). More RRBSO participants had a previous history of breast cancer ($n = 11$) compared to comparisons ($n = 2$). All RRBSO participants were at elevated risk of ovarian cancer, and 94% of comparisons were at population risk (Table 1). "At baseline, $n = 17$ participants ($n = 5$ from the RRBSO group) reported hot flashes and $n = 43$ participants ($n = 19$ from the RRBSO group) reported night sweats. Overall, $n = 50$ ($n = 20$ from

Table 1
Demographic characteristics (n, %) of the overall sample and by study group.

Characteristic	Overall $n = 194$	By study group		p
		Comparison $n = 99$	RRBSO $n = 95$	
Age at baseline (M, SD)	41.45 (5.08)	40.81 (5.78)	42.11 (4.15)	0.074
Age Range at baseline	24.1–52.5	24.1–50.4	32.0–52.5	
BMI at baseline				
Under/normal	90 (46.4)	53 (53.5)	37 (39.0)	0.078
Overweight	60 (30.9)	29 (29.3)	31 (32.6)	
Obese	44 (22.7)	17 (17.2)	27 (28.4)	
Has had hysterectomy[a]				
No	159 (82.0)	95 (96.0)	64 (67.4)	<0.001
Yes	35 (18.0)	4 (4.0)	31 (32.6)	
Has had breast cancer[b]				
No	181 (93.3)	97 (98.0)	84 (88.4)	0.008
Yes	13 (6.7)	2 (2.0)	11 (11.6)	
BRCA mutation[c]				
No *BRCA* pathogenic variant	117 (60.3)	94 (95.0)	23 (24.2)	–
Has *BRCA1* pathogenic variant	38 (16.6)	2 (2.0)	36 (37.9)	
Has *BRCA2* pathogenic variant	35 (18.0)	3 (3.0)	32 (33.7)	
Has *BRCA1* & *2* pathogenic variants	4 (2.1)	0 (0)	4 (4.2)	
Lynch syndrome[c]				
No/unknown	189 (97.4)	98 (99.0)	91 (95.8)	–
Yes	5 (2.6)	1 (1.0)	4 (4.2)	
Hormonal contraception at baseline				
No	115 (59.3)	53 (53.5)	62 (65.3)	0.097
Yes	79 (40.7)	46 (46.5)	33 (34.7)	
Smoking status				
Non-smoker	117 (60.3)	60 (60.6)	57 (0.0)	0.719
Ex-smoker	62 (32.0)	30 (30.3)	32 (33.7)	
Smoked during the study period	15 (7.7)	9 (9.1)	6 (6.3)	
Previous depressive disorder				
No	163 (84.0)	82 (82.8)	81 (85.3)	0.644
Yes	31 (16.0)	17 (17.2)	14 (14.7)	
Taking antidepressants at baseline				
No	180 (93.8)	94 (95.0)	86 (90.5)	0.234
Yes	14 (7.2)	5 (5.1)	9 (9.5)	
Previous anxiety disorder				
No	164 (85.5)	79 (79.8)	85 (89.5)	0.062
Yes	30 (15.5)	20 (20.2)	10 (10.5)	
Taking anxiolytics at baseline				
No	182 (93.8)	92 (92.9)	90 (94.7)	0.601
Yes	12 (6.2)	7 (7.1)	5 (5.3)	

[a] $N = 3$ comparison participants and $n = 1$ RRBSO participant had a hysterectomy prior to baseline. $N = 1$ comparison had a hysterectomy during baseline and 3 months.
[b] All participants had breast cancer prior to baseline except for one RRBSO participant who developed breast cancer during the study follow-up period.
[c] Chi-square test not performed as some cell sizes were too small.

RRBSO group) reported either night sweats or hot flushes at baseline. Of the $n = 13$ women with a prior history of breast cancer, only one reported vasomotor symptoms at baseline.

All RRBSO were performed between Baseline and 3 months and one third (30/95, 31%) had concurrent hysterectomy. No comparisons underwent oophorectomy over the study period but 4 had a hysterectomy – 3 population risk comparisons prior to Baseline for gynaecological conditions and one high risk comparison between Baseline and 3 months for cancer risk-reduction (related to her carriage of a Lynch Syndrome mutation). Study retention was high in both groups (94% overall at 12 months).

3.2. Depressive symptoms (CES–D)

The groups did not differ in previous history of depression (Table 1). Overall, 7.2% were taking antidepressant medication at baseline (5.1% Comparison vs 9.5% RRBSO) (Table 1). The baseline prevalence of clinically significant depressive symptoms (CES-D score ≥ 16) was similar between groups (Fig. 2). The increase in mean CES-D scores between baseline and 3 months in the RRBSO group was not statistically significant

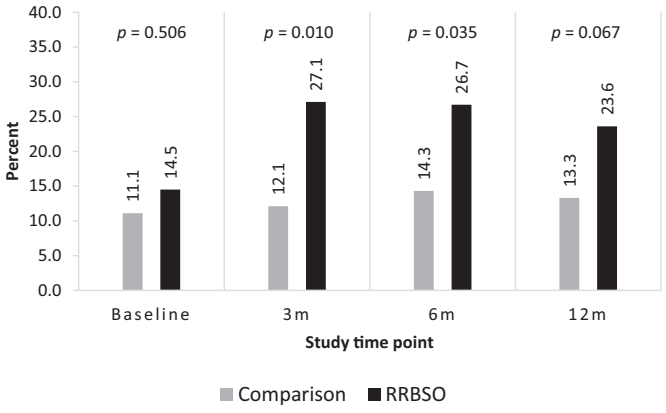

Fig. 2. Prevalence (%) of clinically relevant depressive symptoms (CES-D scores ≥16) for Comparison and RRBSO groups at baseline, 3, 6, and 12 months. *Note*. *RRBS* = risk-reducing bilateral salpingo oophorectomy; *CES-D* = Centre for Epidemiological Studies Depression Scale. Scores of ≥16 indicate clinically relevant symptoms. In the RRBSO group surgery occurred between baseline and 3 months.

(t(71) = −1.54, $p = 0.127$). However, by 3 months the percentage of RRBSO participants with clinically significant depressive symptoms had almost doubled (from 14.5% at baseline to 27.1%, $p = 0.010$) and was essentially unchanged in Comparison participants (11.1% vs 12.1%). The prevalence of clinically significant depressive symptoms remained significantly greater after RRBSO compared to Comparison participants at 6 months ($p = 0.035$) but was reduced slightly by 12 months ($p = 0.067$) (Fig. 2). Around one-third of RRBSO participants (26/76, 34.2%) reported new-onset (incident) clinically significant depressive symptoms (CES-D score < 16 at baseline and ≥ 16 at least once during follow-up) compared to only 15.2% (15/99) of Comparisons.

Logistic regression showed that RRBSO participants were 2.3 times (Wald 95% CI 1.08–5.13) more likely than comparisons to develop incident depression, controlling for prior depression diagnosis (OR = 2.8, Wald 95% CI 1.06–7.26) and vasomotor symptoms between 3 and 12 months (OR = 3.90, Wald 95% CI 1.55–9.80).

Chronic depressive symptoms (CESD ≥16 on 2–3 occasions from 3 to 12 months) were more common after RRBSO compared to Comparison participants (Fig. 3). Around one quarter of the RRBSO group (22/95, 23.2%) reported emergence of chronic depressive symptoms after surgery, during the 3 to 12 month study period, compared to 10.1% (10/99) of Comparisons (Fig. 3). Logistic regression showed that RRBSO participants were 3.0 times (Wald 95% CI 1.27–7.26) more likely than Comparison participants to report chronic depressive symptoms, controlling for clinically significant depressive symptoms at baseline (OR = 7.3, 95% CI 2.71–19.69), previous depression (OR = 2.4, Wald 95% CI 0.88–6.31), and vasomotor symptoms between 3 and 12 months (OR = 1.8, Wald 95% CI 0.67–4.66). Sensitivity analysis using multiple imputations for missing data did not change these associations (data not shown). Participants with clinically significant symptoms of depression and anxiety were informed of these findings and offered additional support including GP referral. Overall, only 8 of 41 participants with clinically significant depressive symptoms sought mental health care, of whom 3 were prescribed psychotropic medication.

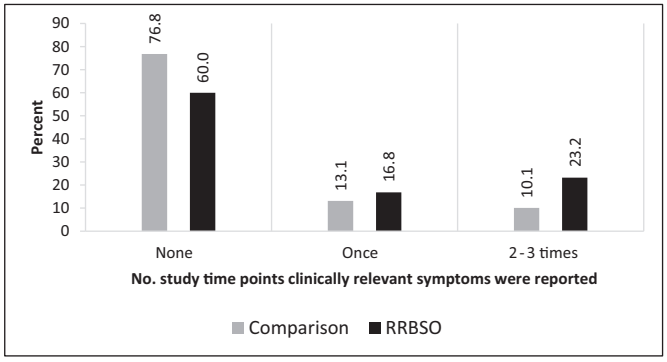

Fig. 3. Number of study time points (3, 6 and/or 12 months) that clinically relevant depressive symptoms (CES-D scores ≥16) were reported for Comparison and RRBSO groups ($p = 0.024$). *Note. RRBSO* = risk-reducing bilateral salpingo oophorectomy; *CES-D* = Centre for Epidemiological Studies Depression Scale. Scores of ≥16 indicate clinically relevant symptoms. Chronicity is indicated by clinically relevant symptoms in 2 or 3 study periods.

3.3. Anxiety (GAD-7)

At baseline, more Comparison participants reported clinician-diagnosed anxiety episodes (20.2%) vs RRBSO (10.5%) (Table 1). Overall, 6.2% were taking anxiolytic medication at baseline (7.1% Comparison vs 5.3% RRBSO) (Table 1). The baseline prevalence of clinically significant anxiety (GAD-7 ≥ 10) was similar between the groups (Fig. S1). However, by 3 months the prevalence of clinically significant anxiety was 2.9 fold greater in the RRBSO group vs the Comparison group (17.7% vs 6.1%, $p = 0.014$), but at 6 and 12 months there were no significant differences between the groups (Fig. S1). Overall, 23 new-onset incident anxiety cases were identified over the follow-up period, representing 18.7% of the RRBSO group and 9.1% of the Comparison group. Of the 41 women with incident depression, 13 (31.7%) also had incident anxiety. Logistic regression showed that RRBSO participants were 2.0 times (Wald 95%CI 0.78–5.00) more likely than the Comparison group to develop clinically significant anxiety symptoms between 3 and 12 months, controlling for vasomotor symptoms occurring between 3 and 12 months (OR = 1.8, Wald 95% CI 0.68–5.43, whereby multi- and univariate results were consistent). There were no differences in chronic anxiety symptoms between the groups ($p = 0.121$) (Fig. S2). Sensitivity analysis using multiple imputation did not change these associations (data not shown). Overall, only 6 of the 23 participants with clinically significant anxiety sought mental health care of whom 2 were prescribed psychotropic medication.

3.4. Sleep disturbance and depressive symptoms

To explore whether menopause-related sleep disturbances were driving the increases in incident depression, depressive symptoms were re-analysed using CES-D subscores which more precisely reflect DSM-V criteria for the diagnosis of major depressive disorder (negative affect, anhedonia and somatic symptoms) having excluded the question on "restless sleep" from the somatic symptom subscore [25]. After RRBSO, participants who scored at or above the clinical cut-off on the CES-D (≥16 overall) had significantly higher mean scores on all three CES-D subscores at 3, 6 and 12 months, compared with the RRBSO group who scored below the clinical cut-off (Table 2). This suggests that RRBSO is associated with worsening (higher scores) across all domains of the CES–D.

Table 2
Mean (95% CI) scores on CES-D subscales at 3, 6 and 12 months for RRBSO participants below and above the cut-off for clinically relevant depressive symptoms.

	3 months			6 months			12 months		
	CES-D < 16 $n = 62$	CES-D ≥ 16 $n = 23$	p	CES-D < 16 $n = 66$	CES-D ≥ 16 $n = 24$	p	CES-D < 16 $n = 68$	CES-D ≥ 16 $n = 21$	p
Total score[a]	6.05 (4.95, 7.14)	23.81 (19.39, 28.23)	<0.001	4.97 (4.05, 5.89)	24.94 (20.99, 20.89)	<0.001	6.21 (5.26, 7.15)	23.97 (19.67, 28.26)	<0.001
Negative affect[b]	0.79 (0.50, 1.08)	4.30 (2.91, 5.70)	<0.001	0.64 (0.35, 0.92)	5.04 (3.76, 6.32)	<0.001	0.72 (0.41, 1.04)	4.90 (3.42, 6.39)	<0.001
Somatic symptoms[c]	1.73 (1.30, 2.12)	7.09 (5.86, 8.31)	<0.001	1.64 (1.23, 2.04)	6.75 (5.61, 7.89)	<0.001	1.84 (1.43, 2.25)	6.86 (5.37, 8.35)	<0.001
Anhedonia[d]	1.52 (0.90, 2.13)	5.09 (3.86, 6.32)	<0.001	1.15 (0.70, 1.60)	5.42 (4.29, 6.54)	<0.001	1.62 (1.08, 2.16)	4.86 (3.88, 5.84)	<0.001

Note: CES-D = Centre for Epidemiological Studies Depression Scale with subscores [25]. A score of 16 or higher indicates clinically relevant symptoms. Higher subscale and total scores equate to a greater frequency of symptoms being experienced by the participant.

[a] Total Score: Questions 1 to 20, score range of 0–60.

[b] Negative affect: Questions 3, 6, 14, 18 (blues, depressed, lonely, sad), score range of 0–12.

[c] Somatic symptoms: Questions 1, 2, 5, 7, 20 (bothered, appetite, mind, effort, get going), score range 0–15. Note: We excluded the question on sleep.

[d] Anhedonia: Questions 4, 8, 12, 16 (as good, hopeful, happy, enjoy), score range of 0–12. Original items were reverse scored.

3.5. Use of systemic hormone therapy

No study participants were taking HT at baseline. Following RRBSO, just over half of the RRBSO group (57/95, 60%) initiated HT. Of these, almost all (47/57, 82.5%) initiated HT within 3 months of RRBSO and continued for 12 months. A range of different HT preparations were used. Those who underwent concurrent hysterectomy ($n = 20$) took estrogen-only HT. Of those who retained their uterus ($n = 37$), $n = 5$ took oral progestins, 1 used transdermal progestin, $n = 28$ used intrauterine progestin (Mirena), and n = 3 took tibolone. None of the Comparison group initiated HT over the study period. Estrogen dose in HT was determined clinically, but most (45/57, 79%) took doses equivalent to ≥50 μg/day of transdermal estradiol and only 3 took doses equivalent to <50 μg/day. Over the follow-up period, 7 women increased their estrogen dose, and one reduced her dose. For one participant the dose was unknown.

3.6. Systemic hormone therapy, depressive and anxiety symptoms

There were no differences at baseline in clinically relevant symptoms of depression or anxiety between those who initiated HT after RRBSO and those who did not (Figs. S3 and S4). At 6 months, the prevalence of clinically relevant depressive symptoms was greater in HT users compared to non-HT users (31.6% vs 18.2%) but was broadly similar at 3 and 12 months (Fig. S3). Rates of incident depression were similar between HT users (18/49, 36.3%) and non-HT users (8/27, 29.6%). More HT users reported chronically elevated depressive symptoms over the 12-month follow-up period compared to non-HT users, (28.1% vs 15.8%) (Fig. S5). At 3 months after RRBSO, the prevalence of clinically significant anxiety symptoms was similar between HT users and non-HT users (15.4% vs 21.2% respectively), but at 6 and 12 months the prevalence of anxiety was slightly higher in HT users (17.9% and 14.8% respectively) compared to non-HT users (9.1% and 8.6% respectively) (Fig. S4). Incident anxiety was slightly higher in HT users (10/48, 20.8%) compared to non-HT users (4/27, 14.8%), and there was no difference in chronically elevated anxiety symptoms by HT status (both 10.5%).

4. Discussion

This is the first prospective study of depression and anxiety in the first 12 months following RRBSO, taking into consideration risk factors such as previous mood disturbance and baseline depression and anxiety symptoms. We observed a doubling in clinically significant depressive symptoms at 3 months which persisted over the 12-month follow-up period and a tripling in clinically significant anxiety symptoms at 3 months which plateaued at 6 months and returned to baseline by 12 months. In total around one-third of RRBSO participants (26/76, 34.2%) reported incident clinically significant depressive symptoms compared to only 15.2% (15/99) of the Comparison group where these symptoms were stable over the 12 months period. Over the natural menopause transition, severe and prolonged vasomotor symptoms are associated with depressive symptoms [10] [12]. We observed an almost 4-fold increased risk of depressive symptoms in women who reported vasomotor symptoms after RRBSO. However, we also observed clinically meaningful and statistically significant increases in depressive symptoms after adjustment for vasomotor symptoms, suggesting that vasomotor symptoms alone did not explain this increase in depressive symptoms. Disturbed sleep due to VMS may potentially explain the increase in depressive symptoms after RRBSO [26]. However, post-hoc analyses demonstrated that anhedonia, negative mood and somatic symptoms of depression persisted even when the question about "restless sleep" was excluded from the CES–D. Our findings differ from previous reports that surgical menopause for benign conditions [6] or as RRBSO [8] does not increase depression. However, these studies did not measure depressive symptoms in the initial months after RRBSO and included women who were already peri- or postmenopausal at the time of oophorectomy [7] [8] or for whom pre-operative menopause status was unknown [6]. Together, our data suggest that the initial 12 months after RRBSO may be a period of vulnerability to depression, potentially due to the rapid and profound endocrine changes following surgical menopause.

Women with previous depression are at increased risk of recurrence over the natural menopause transition [12] [27] [28]. We observed that those with elevated depressive symptoms at baseline or a previous history of depression were at almost 3-fold risk of incident depression after RRBSO. Together, our data suggest that clinicians should enquire about both previous and current depressive symptoms prior to RRBSO and be alert for new-onset symptoms.

The increase in clinically significant anxiety symptoms was confined to the initial months following RRBSO and had resolved by 6 months. These findings are similar to those reported over the natural menopause transition [30]. Depression and anxiety are highly comorbid, so it is uncertain as to why anxiety symptoms were less persistent than depressive symptoms after RRBSO.

Despite being informed of their elevated scores for depressive and/or anxiety symptoms most participants did not seek medical attention. This suggests that studies reporting rates of depression based on clinical diagnoses or antidepressant use may underestimate the true prevalence of depression and anxiety after RRBSO [8].

Previous studies report that earlier age at menopause and higher BMI increase the risk of depression at menopause [31] [32] [33]. However, we did not find an independent effect for age or BMI on the incidence or persistence of mood disturbance after RRBSO. This may reflect the relatively narrow age range in our sample with most women aged 35–45 years at the time of RRBSO.

International guidelines recommend HT after surgical menopause until around age 50 years in women without contraindications such a previous breast cancer [34]. Previous studies have suggested that HT may reduce the risk of depression over the natural menopause transition [13] although findings are conflicting [33]. We observed a higher incidence of depressive symptoms in HT users. The reasons for this are uncertain and women with depressive symptoms may have been more likely to take HT to manage mood symptoms that appear to be hormonally related. Together these data suggest that women presenting after RRBSO with clinically significant symptoms of anxiety and/or depression should be assessed and managed using established effective psychopharmacologic and psychotherapeutic treatments for these conditions, and that HT alone should not be used to prevent or treat mood disorders [12].

Strengths of the WHAM study include a prospective design and sample size, powered for the outcomes of interest over a 12-month period. Premenopausal women undergoing RRBSO were compared with premenopausal comparisons of a similar age, providing a meaningful comparison group. Our detailed prospective data collection included validated questionnaires for clinically significant depressive and anxiety symptoms and vasomotor symptoms and prospective data on HT use.

Limitations include lack of data on financial problems and employment status and psychosocial factors such as stressful life events, physical activity, attitudes towards aging and menopause and cancer-related worry, which may have affected depression and anxiety symptoms [12] [29]. We were also unable to analyze by type of HT due to small numbers. The comparison group included a small number of women who were at elevated risk of ovarian cancer. A more suitable comparison group may have been high-risk women who opted for screening or interval salpingectomy rather than RRBSO. However, these interventions have not been proven to reduce ovarian cancer risk in women with pathogenic gene variants. More RRBSO participants had a personal history of cancer, which is likely to have increased stress that may precipitate anxiety and depression [35], but numbers were too small to make meaningful comparisons.

We did not measure sex steroids or Follicle Stimulating Hormone after baseline, although levels of these hormones do not reliably predict or reflect mood disturbances at menopause [12]. Whilst the comparison group were similar in age, previous history of depression, use of hormonal contraception at baseline, smoking and BMI, more comparisons had a prior history of anxiety disorders, which may have increased their vulnerability to subsequent anxiety symptoms. However, comparisons showed little change in measures of depression or anxiety over the 12-month follow-up period, suggesting that the mood changes observed in the RRBSO group were attributable to the surgery or factors associated with their high-risk condition. Depression and anxiety symptoms were derived from self-report data, which may be subject to social desirability bias [33]. Use of hormonal contraception also limited our ability to establish premenopausal status at baseline in all participants. Almost all participants (84%) were White and the findings may not be generalisable to women of other races.

In summary, this large prospective controlled study of depression and anxiety following premenopausal RRBSO demonstrated a high incidence of new onset, clinically significant depressive symptoms which were not prevented by use of HT. These findings will inform clinical decision-making and evidence-based care for women considering RRBSO, particularly in the first 12 months after surgery. Depression and anxiety are common, particularly in women. Our findings emphasise the importance of clinical awareness of these symptoms, particularly in those at elevated risk due to depressive symptoms at baseline, vasomotor symptoms, or a previous history of mood disturbances, and the importance of intervening with effective treatments where indicated. Longer-term follow-up is needed to define the trajectories of these symptoms over time.

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Appendix A. Supplementary data

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