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

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HIGHLIGHTS

- Sleep disturbance significantly increases after premenopausal RRSO ($p < 0.001$).
- Risk factors include severe vasomotor symptoms, obesity and smoking.
- Hormone therapy reduces but does not resolve sleep disturbance after RRSO.

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ABSTRACT

Objective. Sleep difficulties impair function and increase the risk of depression at menopause and premenopausal oophorectomy may further worsen sleep. However, prospective data are limited, and it remains uncertain whether Hormone Therapy (HT) improves sleep. This prospective observational study measured sleep quality before and up to 12 months after risk-reducing salpingo-oophorectomy (RRSO) compared to a similar age comparison group who retained their ovaries.

Methods. Ninety-five premenopausal women undergoing RRSO and 99 comparisons were evaluated over a 12-month period using the Pittsburgh Sleep Quality Index (PSQI).

Results. Almost half reported poor sleep quality at baseline. Overall sleep quality was not affected by RRSO until 12 months ($p = 0.007$). However, sleep disturbance increased by 3 months and remained significantly elevated at 12 months ($p < 0.001$). Trajectory analysis demonstrated that 41% had increased sleep disturbance after RRSO which persisted in 17.9%. Risk factors for sleep disturbance included severe vasomotor symptoms, obesity and smoking. Around 60% initiated HT after RRSO. Sleep quality was significantly better in HT users vs non users ($p = 0.020$) but HT did not restore sleep quality to baseline levels.

Conclusions. Overall sleep quality is not affected by RRSO, but new onset sleep disturbance is common, particularly in those with severe vasomotor symptoms. Clinicians should be alert to new-onset sleep disturbance and the potential for HT to improve sleep quality.

1. Introduction

Sleep difficulties are more common in women than in men affecting 30–50% over the natural menopause transition. During this period one quarter meet DSM criteria for insomnia with severe symptoms affecting

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daytime function [1]. Sleep disturbance characterized by night-time awakenings is the most common problem [2]. Vasomotor symptoms (VMS, hot flashes and night sweats) may disturb sleep and increase the risk of insomnia [1,2]. Since the median duration of VMS is around 7.4 years [3] sleep disturbance may become a chronic problem. Sleep difficulties largely explain the relationship between VMS and depressed mood over the menopause transition [4].

In women at high inherited risk of ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) is the only intervention shown to reduce ovarian cancer deaths and improve overall survival [5,6]. The National Comprehensive Cancer Network recommends RRSO at age 35–40 years in women with BRCA1 and 40–45 for those with BRCA2 mutations [7]. In high-risk women and in the general population, cross-sectional studies report that surgical menopause doubles the risk of insomnia compared to natural menopause [8–12]. However, baseline data were not collected in these studies, a major limitation since premenopausal sleep patterns are the main predictor of postmenopausal sleep difficulties [13,14].

The primary objective of this study was to measure the impact of RRSO on sleep quality over a 12-month period compared to a premenopausal comparison group who retained their ovaries. Secondary objectives were to measure: (1) the domains of sleep quality affected by RRSO, (2) sleep trajectories over the 12-month study period, and (3) the effects of HT on sleep quality.

2. Methods

2.1. Study population

The WHAM study protocol has been published and describes in detail the ethics approvals, consenting procedures and eligibility criteria [15]. Around 700 women aged 18 to 50 years were screened at four recruitment sites in Australia and one in the USA between 2013 and 2019. Of these, 224 met inclusion criteria and were willing to participate [15] (Fig. 1). The RRSO group consisted of premenopausal women at high-risk of ovarian cancer planning RRSO. Comparisons were premenopausal women not planning oophorectomy or pregnancy over the follow-up period (Fig. 1). Eligibility screening was performed within the 8 weeks prior to RRSO or baseline (for the comparison group). Premenopausal status was confirmed by regular menstrual cycles, days 2 to 6 Follicle Stimulating Hormone ≤15 IU/L and estradiol >100 pmol/L [16]. Exclusions from both groups included women within 3 months of pregnancy or lactation, planning pregnancy, experiencing irregular bleeding or using anti-estrogens such as tamoxifen [15].

2.2. Study assessments

A comprehensive schedule of WHAM study assessments has been published [15]. Briefly, assessments were conducted at baseline, 3, 6 and 12 months, and RRSO occurred between baseline and 3 months. This study reports the results from prospective measures of sleep quality after RRSO.

2.3. Measurement of sleep quality

Sleep quality was measured at each time-point using the validated Pittsburgh Sleep Quality Index (PSQI) [17]. The PSQI includes 18 items measuring sleep habits over the past month. Responses range from 'not during the past month', 'less than once a week', once or twice a week' or 'three or more times a week'. Total scores range from 0 to 21, with a score of >5 distinguishing poor from good sleep [17]. Seven domain scores can be derived from the PSQI, each scored from 0 (no difficulty) to 3 (severe difficulty): sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use and daytime dysfunction [18]. Sleep disturbance is measured from responses to 9 questions including 'wake up in the middle of the night or early morning', 'have to get up to use the bathroom', 'feel too hot', and 'feel too cold'.

Following RRSO, use of treatments for vasomotor symptoms including hormone therapy (HT, dose and type [estrogen only or combined]) were collected at each time-point. Potential confounders in the associations between RRSO and sleep quality included age at baseline, body mass index (BMI), VMS between 3 and 12 months and smoking status. The presence of VMS was determined from scores >1 on questions about hot flashes and/or night sweats on the Menopause-Specific Quality of Life Intervention Version (MENQOL-I) questionnaire [19]. Symptom severity was categorized as no symptoms (score of 1), mild symptoms (scores of 2 to 5) or severe symptoms (scores of 6 to 8) [20]. BMI was classified using WHO criteria as underweight / normal (≤ 24.9 kg/m2), overweight (25.0 to ≤29.9 kg/m2) and obese (≥ 30 kg/m2). Tobacco smoking was categorized 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).

2.4. Statistical analysis

Data were analyzed using SAS 9.4 (SAS Institute, North Carolina). Initial data screening was conducted to check distributions and outliers. To investigate the primary objective, differences between the RRSO and comparison groups at each time point for the PSQI overall were tested using independent sample *t*-tests and differences in the numbers of women in each group reporting poor sleep (PSQI total score > 5) [17] at each time point were compared using Chi-square tests. In the RRSO group, differences between baseline and 3 months after RRSO and between baseline and 12 months were tested using paired *t*-tests. To investigate secondary aim 2, differences between the RRSO and comparison groups at each time point for each PSQI domain were tested using independent sample t-tests. To investigate secondary aim 2, significant differences in average PSQI scores after RRSO were further investigated using trajectory modelling (proc traj). Models specified a censored normal distribution and were tested with 1 to 5 groups. The optimal number of groups was chosen based on theory, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) values and group size. Risk factors including vasomotor symptoms (yes/no), use of HT, smoking and high BMI (overweight or obese) were used to refine trajectories and group assignment, with risk factors significant at $p < 0.05$ retained in the final model. Characteristics of the groups identified by trajectory analysis were investigated using cross-tabulations and chi-square tests of difference. To investigate secondary aim 3, differences in poor sleep quality at each study time point were investigated in RRSO participants who did and did not use HT using Chi-square tests. HT use was also included as a risk factor in the trajectory modelling.

3. Results

3.1. Participant demographics

Data were collected from 194 women: 95 RRSO and 99 comparisons (Fig. 1). At baseline, the groups were similar in age, smoking status and BMI, although more RRSO participants were obese (28.4% vs 17.2%, Table 1). All RRSO participants were at elevated risk of ovarian cancer and most comparisons were at population risk, based on personal and family cancer history (Table 1). More RRSO participants had previous breast cancer (11 vs 2 women) and one developed breast cancer over the 12-month follow-up period. All RRSO participants underwent RRSO and approximately one third (30/95, 31.6%) had concurrent hysterectomy. None of the comparison group underwent oophorectomy or gonadotoxic treatments during the 12-month follow-up period. No occult ovarian cancers were detected at RRSO but one STIC (serous tubal intraepithelial carcinoma) was identified.

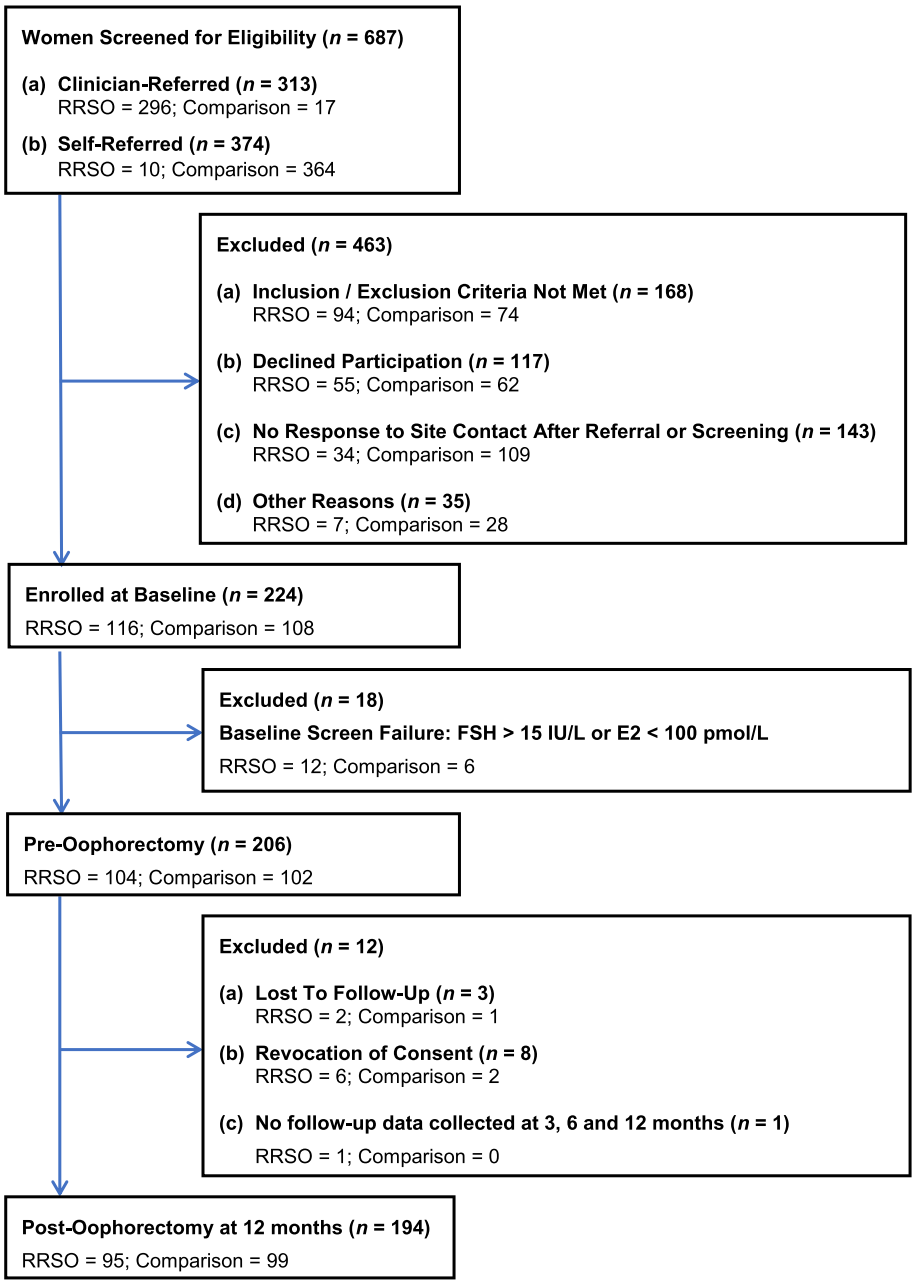

Fig. 1. Participant Flowchart. Number of participant screenings, enrolments and withdrawals relevant to the first 12 months of the WHAM study. Women were either clinician- or self-referred to one of five recruitment sites in Australia and the USA during 2013 to 2019. *FSH* = Follicle-Stimulating Hormone;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

3.2. Use of systemic hormone therapy

No participants were taking HT at baseline. Most of the RRSO group (57/95, 60%) initiated HT, most within 3 months (47/57, 82.5%) and continuing for 12 months. Ten women (10/57, 17.5%) delayed initiation of HT until 3 to 12 months after RRSO. Twenty participants took estrogen-only HT (due to previous hysterectomy) and 37 took combined (estrogen plus progestin) HT. Estrogen dose was determined clinically but most (45/57, 78.9%) took doses equivalent to or greater than 50 μg/day of transdermal estradiol. Only 3 (5.3%) took doses <50 μg/day of estradiol, and for one participant the dose was unknown. Over the follow-up period, 7 women increased their estrogen dose, and one reduced her dose. None of the comparison group started HT within the 12-month study period.

3.3. Sleep quality

Almost half the participants (50% RRSO and 43.4% comparisons) reported poor sleep quality at baseline, defined as PSQI scores >5 [17], with no significant difference between the groups ($p = 0.363$) (Fig. 2). At both 3 and 6 months, there were no significant differences in sleep quality between RRSO participants and controls (chi-square test, $p = 0.076$, $p = 0.095$, respectively) (Fig. 2). By 12 months, rates of poor sleep quality were significantly higher in the RRSO group than the comparisons (62.5% vs 42.9%, $p = 0.007$). Sleep quality in the comparison group remained stable over the follow-up period.

In the RRSO group, reduced sleep quality was largely explained by increased sleep disturbance (secondary objective 1). At baseline there were no differences between the groups in sleep disturbance or any

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

Characteristic (n, %)	Overall $n = 194$	Study Group		p
		Comparison $n = 99$	RRSO $n = 95$	
Age at baseline (M, SD)	41.45 (5.08)	40.81 (5.78)	42.11 (4.15)	0.074
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)	
Had VMS at baseline[a]				
No	143 (74.1)	69 (69.7)	74 (78.7)	0.152
Yes	50 (25.9)	30 (30.3)	20 (21.3)	
Has had hysterectomy[b]				
No	159 (82.0)	95 (96.0)	64 (67.4)	<0.001
Yes	35 (18.0)	4 (4.0)	31 (32.6)	
Previous breast cancer at baseline[c]				
No	181 (93.3)	97 (98.0)	84 (88.4)	0.008
Yes	13 (6.7)	2 (2.0)	11 (11.6)	
Pathogenic genetic variants[d]				
BRCA				
No/unknown	117 (60.3)	94 (95.0)	23 (24.2)	–
BRCA1	38 (19.6)	2 (2.0)	36 (37.9)	
BRCA2	35 (18.0)	3 (3.0)	32 (33.7)	
BRCA1 & 2	4 (2.1)	0 (0)	4 (4.2)	
Lynch syndrome (*MLH1, MSH6, PMS2*)				
No/unknown	189 (97.4)	98 (99.0)	91 (95.8)	–
Yes	5 (2.6)	1 (1.0)	4 (4.2)	
Other pathogenic variants (*STK11, BRIP1*)				
No/unknown	192 (99.0)	99 (100)	93 (97.9)	–
Yes	2 (1.0)	0 (0)	2 (2.1)	
Smoking status				
Non-smoker	117 (60.3)	60 (60.6)	57 (60.0)	0.719
Ex-smoker	62 (32.0)	30 (30.3)	32 (33.7)	
Smoked during WHAM	15 (7.7)	9 (9.1)	6 (6.3)	

[a] Data on vasomotor symptoms at baseline was missing for one RRSO participant.
[b] N = 3 comparison and $n = 1$ RRSO participant had prior hysterectomy. $N = 30$ RRSO had concurrent hysterectomy and $n = 1$ comparisons (Lynch Syndrome) had hysterectomy with ovarian preservation between baseline and 3 months.
[c] Both comparisons carried BRCA1 pathogenic variants. Only one RRSO participant (who had used HT) developed breast cancer during the WHAM follow-up period.
[d] Pathogenic genetic variants known to increase ovarian cancer risk. Chi-square test not performed as some cell sizes were too small.

other PSQI subscales (Table S1). Following RRSO, scores for the sleep disturbance subscale were significantly increased ($p < 0.001$ at 3 months) which persisted at 12 months ($p = 0.001$) (Fig. S1). Post-hoc examinations of individual questions from the PSQI sleep disturbance domain indicated that new onset sleep disturbance after RRSO was mainly due to "feeling too hot", and to a lesser extent "waking during the night or early morning" (Table S2), suggesting that vasomotor symptoms were causing sleep disturbance after RRSO.

Trajectory modelling was performed in the RRSO group to explore sleep disturbance between 3 and 12 months (secondary objective 2). There was little difference in model fit between the 3-group (BIC = −335.04; AIC = −315.89) and 4-group (BIC = −340.64; AIC = −315.10) models. A 4-group model was selected because all group sizes were adequate, and trajectories were all statistically significant. One third of the RRSO group demonstrated a stable low trajectory of sleep disturbance ($n = 34/95$, 35.8%), one quarter showed a stable high trajectory ($n = 22/95$, 23.2%) and around one fifth showed a sharp increase in sleep disturbance that was apparent by 3 months ($n = 17/95$, 17.9%). For the remaining participants sleep disturbance varied over the follow-up period (n = 22/95, 23.1%) (Fig. 3). The stable low group had the highest percentage of HT users, the highest percentage with normal /underweight BMI, the lowest percentage of smokers and the lowest percentage of women with vasomotor symptoms (Table S3). In the "up and down" group, 59% were taking HT, and all but one reported vasomotor symptoms between 3 and 12 months. This group had the highest percentage of overweight participants.

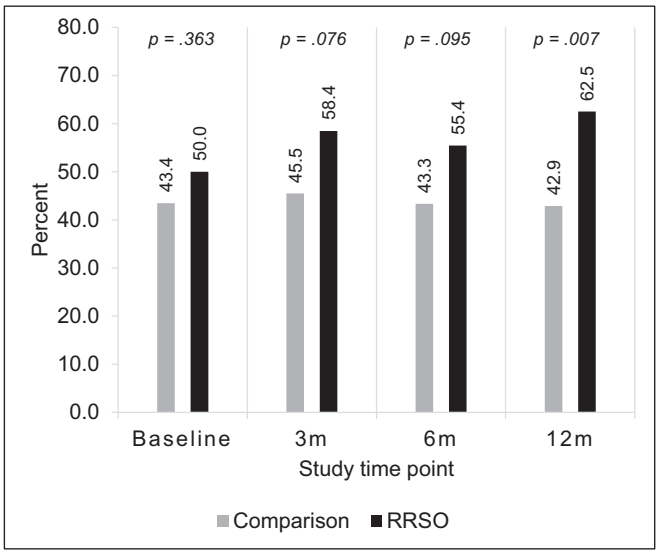

Fig. 2. Prevalence of poor sleep quality (% with PSQI score > 5) from baseline to 12 months by study group.

Almost all (16/17) of the "sharp increase" group reported vasomotor symptoms with severe hot flashes in 58.8% (10/17) and severe night sweats in 35.3% (6/17) (Table S3). Fewer than half the sharp increase group took HT. This group also had the highest percentages of obese women (7/17, 41.2%) and smokers (9/17, 52.9%). In the stable high group, fewer than half were taking HT and all but 2 reported vasomotor symptoms. This group had the second-highest percentage of participants with severe hot flashes (11/22, 50.0%) and night sweats (7/22, 31.8%) and the second-highest percentage of overweight (7/22 31.8%) and obese (8/22, 36.4%) women. A previous history of depression was more common in this group (Table S3).

3.4. Effect of hormone therapy on sleep quality

In the RRSO group, those who initiated HT experienced significantly better sleep quality compared to non-HT users (secondary objective 3). Between 3 and 6 months, sleep quality in HT users was similar to comparisons, but at 12 months sleep quality was worse in HT users vs comparisons (Fig. 4). In non-HT users, the prevalence of poor sleep increased after RRSO and remained elevated above baseline levels throughout the 12-month follow up period (Fig. 4). In the trajectory

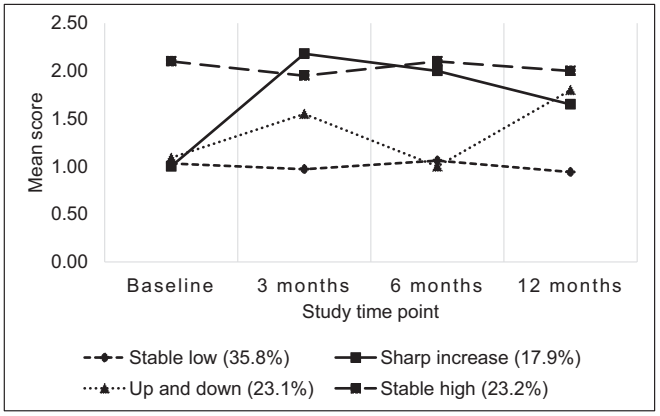

Fig. 3. Trajectories of PSQI sleep disturbance domain mean scores from baseline to 12 months in the RRSO group ($n = 95$), including the percentage of participants in each of four trajectory groups.

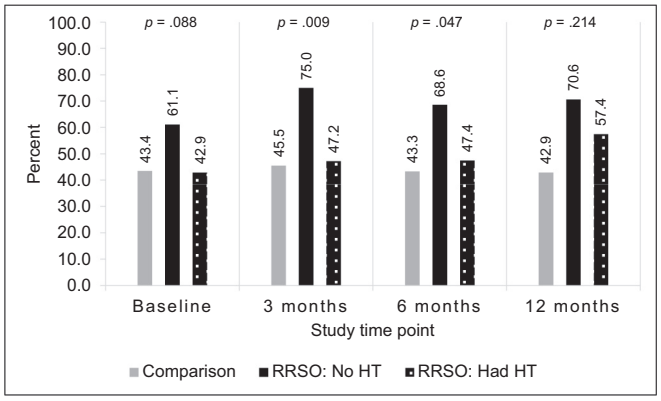

Fig. 4. Prevalence of poor sleep quality (% with PSQI score > 5) from baseline to 12 months by study group and hormone therapy (HT) use. A total of 57/95 (60%) RRSO participants used HT at some stage over the 12-month follow up period.

analysis of sleep disturbance, almost half (27/57, 47.4%) of HT users were in the "stable low" trajectory and only 12.3% (7/57) were in the sharp increase group.

4. Discussion

This is the first prospective study of sleep after RRSO or surgical menopause for any indication to use a valid instrument to measure sleep (the PSQI) and to confirm premenopausal status prior to oophorectomy. Overall, sleep quality did not change after RRSO, but there was a significant increase in new-onset sleep disturbance. This was apparent by three months and persisted for 12 months. These findings are consistent with data from The Study of Women's Health Across the Nation (the SWAN study) showing that surgical menopause disrupts sleep maintenance [21]. Trajectory analysis showed that 41% experienced new onset sleep disturbance with 17.9% reporting a sharp elevation at 3 months that persisted for at least 12 months. This proportion is almost identical to that reported in the SWAN study over the natural menopause transition [14] and following surgical menopause [21]. Our data add to these findings suggesting that VMS are the principal cause of sleep disturbance after RRSO since "feeling too hot" was the main reason for new onset sleep disturbance. Women with steep or variable increasing patterns of sleep disturbance were more likely to report VMS and not be taking HT. Additional risk factors for this "sharp increase" in sleep disturbance were obesity and current smoking. Together, our data suggest that women and clinicians should be aware that RRSO may cause new-onset sleep disturbance and be aware of risk factors in order to prevent adverse sequelae of chronically disturbed sleep such as depression and CVD [22,23].

There are few prospective studies of surgical menopause and sleep in the general population and none in high-risk women. Based on a single question, the SWAN study reported worsened sleep maintenance in around 20% ($n = 17$) after surgical menopause [21], similar to that observed over the natural menopause transition [14]. However, the SWAN study did not use a validated measure of sleep and the mean age at surgical menopause was 51.2 years, when most women are already *peri* or postmenopausal [10]. Two cohort studies reported that "trouble sleeping" is increased after hysterectomy plus oophorectomy compared to natural menopause [24], even when adjusted for baseline psychological, vasomotor, somatic and sleep symptoms [10]. No previous studies have prospectively measured sleep difficulties before and after RRSO or surgical menopause using validated scales.

Anxiety is an established cause of sleep disturbance [25]. Although generalized anxiety did not differ between the groups at baseline, at 3 and 6 months anxiety levels were significantly elevated in the RRSO group but had normalized by 12 months [26]. Elevated anxiety may have contributed to the observed increase in sleep disturbance after RRSO.

Obesity also increases the risk of sleep disorders in postmenopausal women [27]. In trajectory analysis, obese women were more likely to report poor sleep at baseline or a sharp increase in new-onset sleep disturbance after RRSO. Clinicians should be aware that obese women may be at greater risk of sleep disturbance and sleep disorders, like obstructive sleep apnea, and offer proactive management including investigation for sleep disordered breathing when indicated [22].

In this study population of premenopausal women with mean age of 41 years, almost half reported poor sleep quality at baseline, emphasizing the importance of prospective data collection. Our data suggest that the high prevalence of sleep difficulties reported in cross-sectional studies of surgical menopause may over-estimate sleep difficulties by failing to account for baseline symptoms or include premenopausal comparisons.

This is the first study to prospectively measure the efficacy of HT for sleep after RRSO or surgical menopause for any indication. We found that HT prevented the decline in sleep quality after RRSO for up to 12 months, at which point sleep quality worsened despite HT use. It is unclear why sleep quality declined at 12 months in HT users. There is no reason to believe that the beneficial effects of HT on sleep wane by 12 months [28].

Hormone therapy (HT) is recommended following RRSO for women without contraindications such as breast cancer [29]. However, whether HT improves sleep after natural [30] or surgical [22] menopause is uncertain. Two systematic reviews of cross-sectional [31] and longitudinal studies [32] reported mixed results with some showing that HT improves sleep and others that HT may worsen sleep [10]. A recent meta-analysis concluded that HT modestly improves sleep quality after surgical menopause, potentially by reducing vasomotor symptoms [33]. Decision making about using HT can be complex in high-risk women who are also at elevated risk of breast cancer [29]. The uptake of HT of 60% in our study is similar to that reported in other studies of high-risk women [34,35]. Our data suggest that HT should be considered to preserve sleep quality after RRSO with potential benefits for mood [4]. However, HT did not restore sleep to baseline levels and sleep quality worsened at 12 months despite HT use. Continued follow-up in WHAM will determine long-term sleep trajectories after RRSO.

The mechanisms underlying sleep disturbance after RRSO may include changes in hypothalamic-pituitary-ovarian axis affecting the secretion of melatonin and other circadian hormones [22], direct effects on sleep circuitry [36], age-related changes, vasomotor symptoms disturbing sleep, mood disturbance, use of alcohol or tobacco and sleep disordered breathing [32]. Endocrine therapy for breast cancer [22] and hysterectomy [10,24] may also impair sleep. However, we did not find any differences in sleep quality in women with previous breast cancer or hysterectomy in WHAM (independent sample *t*-tests non-significant at every time point for the sleep disturbance domain score, data not shown) and women taking endocrine therapy were excluded from the study.

Strengths of WHAM include a large sample size, powered for the outcomes of interest and a premenopausal Comparison group. Our detailed data collection includes validated questionnaires to measure sleep quality with demonstrated test-retest reliability [17] and detailed prospective data on HT use. Limitations include the inclusion of hormonal contraception users at baseline (40.1% overall) which may have affected sleep. However, use of hormonal contraception did not affect PSQI measures (data not shown). Follow-up was limited to 12 months and long-term sleep trajectories may differ. However, 10-year follow-up after surgical menopause in the SWAN study did not detect any further increase in sleep difficulties after the first year [21]. Racial and ethnic differences are known to contribute to sleep patterns over the natural menopause transition [37]. Almost all WHAM participants

were White, and our findings may not apply to women from other racial groups. We used self-reported measures of sleep which may carry a risk of information bias. However, these are the clinical criterion standard for management of sleep problems and the primary driver of treatment [21]. We did not screen participants for other sleep disorders and recognize that the numbers of participants in each sleep trajectory was relatively small.

RRSO is now a leading cause of surgical menopause [38]. For high-risk women considering RRSO, concerns about menopausal symptoms including sleep disturbance are a potential barrier to life-saving surgery [39].

Women facing RRSO want to know what symptoms to expect and how troublesome symptoms can be effectively managed [40]. Our findings demonstrate that new onset sleep disturbance is common and persistent in around 18%, and is associated with untreated VMS, obesity and smoking. HT improves sleep but did not fully prevent the decline in sleep quality after RRSO. There are currently no consensus management guidelines following RRSO. WHAM will provide new evidence on which evidence-based care for these women can be developed.

Declaration of Competing Interest

MH is an editor for the Cochrane Collaboration Group and has received pharmaceutical funding from QUE Oncology P/L, Madorra P/L and Ovoca Bio (Australia) P/L for clinical trials outside of the submitted work. CDW is the Deputy Chair (Honorary) of VCS Foundation P/L and has received sponsorship and honoraria from Biogen and Seqirus outside of the submitted work. SMD has received personal fees from AstraZeneca outside of the submitted work. KMM, EOK, JK, AB, AT, GDM and FCB have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.05.036.

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