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What happens after menopause? (WHAM): A prospective controlled study of symptom profiles up to 12 months after pre-menopausal risk-reducing salpingo-oophorectomy

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HIGHLIGHTS

- This study contributed unique information on the symptoms women can expect in the 12 months after RRSO.
- Symptoms clustered into three distinct profiles: most symptoms, few symptoms and sexual symptoms.
- 81% of women who did not take HT reported most symptoms by 3 months and had almost no chance of improvement by 12 months.
- 64% of women who took HT reported fewer symptoms and they had the most chance of improvement by 12 months.
- HT use made a difference but the diversity of symptoms highlights the need for more effective treatments.

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ABSTRACT

Objective. Understanding how symptoms cluster after premenopausal risk-reducing salpingo-oophorectomy (RRSO) can inform patient expectations but information is lacking. We aimed to identify symptom profiles after RRSO, changes over time, and the effect of hormone therapy (HT).

Method. Participants were premenopausal women from a longitudinal controlled study (What Happens After Menopause? (WHAM)). Menopausal symptoms were prospectively measured in three groups: pre-menopausal comparisons who retained their ovaries ($n = 99$), RRSO HT users ($n = 57$) and RRSO non-HT users ($n = 38$). Symptoms (hot flashes, night sweats, low desire, vaginal dryness, poor sleep, anxiety/depression) were measured at baseline (pre-surgery) and at 3, 6 and 12 months using standardised questionnaires. Latent transition analysis was used to identify symptom profiles post-RRSO, and the probability of changing profiles over time.

Results. Three symptom profiles were identified: Most Symptoms (81–87% non-HT; 36–41% HT; 7–9% comparisons), Few Symptoms (7–13% non-HT; 36–42% HT; 77–80% comparisons), and Sexual Symptoms (0–10% non-HT; 17–27% HT; 14–15% comparisons). Most of the non-HT group reported Most Symptoms at 3 months with only a 2% chance of improvement by 12 months. The HT group were split between profiles at 3 months with a 5–13% chance of improvement by 6 months (14% chance of worsening), and a 12–32% chance of improvement by 12 months (4–25% chance of worsening).

Conclusions. Symptoms cluster into distinct profiles after premenopausal RRSO. Most non-HT users are highly symptomatic with little chance of improvement by 12 months. In contrast, two-thirds of HT users have fewer symptoms and a much higher chance of improvement. These findings can inform patient decision-making and expectations.

1. Introduction

Bilateral salpingo-oophorectomy by age 40 years is recommended for women at high inherited risk of ovarian cancer due to BRCA1/2 pathogenic variants and will generally induce surgical menopause [15]. Bilateral oophorectomy may also be performed at the time of hysterectomy or for chronic pelvic pain [14]. Whilst it is commonly stated that surgical menopause may lead to more severe symptoms [10,16,17], this group is typically excluded from studies of symptom profiles [7,8,11,17]. Understanding the nature, severity and patterns of symptoms following surgical menopause is important because it is almost always an elective procedure and concerns about managing

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menopausal symptoms is a leading barrier to risk-reducing salpingo-oophorectomy (RRSO) [18]. Women considering RRSO want to know what symptoms to expect and how best to manage them [19], and this information is currently lacking [19,20].

Vasomotor complaints (hot flashes and night sweats) are the cardinal symptom of menopause and the leading patient priority for treatment [4]. Other symptoms may include sleep disturbance, mood symptoms, and vaginal dryness [1,3]. However, there is a great deal of heterogeneity between women and within the same women over time. Few studies have explored changes in symptom profiles over time, even though key symptoms such as hot flashes [11] and sleep disturbance [12] follow distinct trajectories. In addition, most studies have excluded women taking hormone therapy (HT) or did not distinguish between HT users and non-users [7,10,11,13]. Finally, menopausal symptoms tend to cluster together [7–10]. Understanding symptom profiles or clusters after RRSO might provide more nuanced information on what to expect and could lead to more personalized treatments that match symptom profiles with optimal treatment options [10].

To support women and their healthcare providers making decisions about RRSO, the aims of this study were to: 1) identify distinct profiles of symptoms following RRSO; 2) identify changes in symptom profiles over time; 3) examine whether symptom profiles and changes over time differ for women who do and do not use HT.

2. Method

2.1. Participants and procedure

What Happens After Menopause (WHAM) is a prospective observational controlled cohort study, details of which have been previously published [12,21–23]. Briefly, premenopausal women at high risk of ovarian cancer planning to undergo RRSO were recruited at five sites (4 in Australia and 1 in the USA), along with premenopausal women with or without high risk of ovarian cancer not planning RRSO or pregnancy within the next two years (comparison group). Data for this study were collected via questionnaires at baseline, 3, 6 and 12 months. Ethics approval was obtained from each of the recruitment sites and all participants provided written informed consent.

2.2. Measures

Six dichotomous variables were included as indicators of menopausal symptoms, based on our previous work in this cohort [12,22,23]. Decreased sexual desire, vaginal dryness, hot flashes and night sweats were measured with the intervention version of the Menopause-related Quality of Life Questionnaire (MENQOL-I) [24]. The MENQOL-I is a valid measure of menopause-related quality of life and has good test-retest reliability [24]. Participants indicate whether they have experienced each problem in the past week (no, yes), and if so, they rate their level of bother. A score of 1 ('no') for the relevant question was coded as 'no' and a score of 2 ('yes') or an indication of bother (score > 1) was coded as 'yes'.

Poor sleep was measured with the Pittsburgh Sleep Quality Index (PSQI) [25]. The PSQI is the most commonly-used sleep measure in clinical and community settings [26], and is a valid measure of sleep quality [25]. The PSQI contains 18 items assessing sleep quality, latency, duration, efficiency, disturbance, medications and daytime dysfunction. Participants rate their sleep over the past month, with higher scores indicating poorer quality sleep. Scores of ≤5 were coded as 'no' and scores >5 were coded as 'yes' [25].

Depression was measured with the Centre for Epidemiological Studies Depression Scale (CES-D) [27]. The CES-D is a valid and reliable measure of depressive symptoms [27] and is the most frequently-used measure of depression in perimenopause [28]. It contains 20 items and participants rate their symptoms over the past week on a 4-point Likert scale ranging from 0 (rarely) to 3 (most or all of the time). Higher scores indicate higher depressive symptoms. Scores <16 were coded as 'no' and scores ≥16 were coded as 'yes' [27].

Anxiety was measured with the Generalized Anxiety Disorder scale (GAD-7) [29]. The GAD-7 is a valid and reliable measure of generalized anxiety [29]. It contains 7 items and participants rate their symptoms over the past two weeks on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). Higher scores indicate higher anxiety symptoms. Scores <10 were coded as 'no' and scores ≥10 coded as 'yes' [29]. Anxiety and depression were combined into one variable to avoid small cell sizes, and the final variable indicates reports of anxiety and/or depression.

2.3. Statistical analysis

Frequencies of each symptom at each time point were calculated and chi-square tests of association used to test differences between study groups (comparison; RRSO: HT users, non-HT users). Data on symptoms were missing for up to 6% of participants at 3 months, up to 3% of participants at 6 months and up to 4% of participants at 12 months. Participants with missing data were excluded from cross-sectional frequencies and chi-squares, however all participants were included in the longitudinal Latent Transition Analysis.

Latent transition analysis (LTA) was used to answer the research questions. LTA is a multivariate longitudinal statistical model that aims to identify underlying (latent) grouping variables (Aim 1), so that individuals in each latent status share a common profile of symptoms [30]. It also estimates the probability that a person will report the same profile of symptoms at two consecutive measurement points – in other words, whether their symptom profile is likely to change or stay the same over time (Aim 2), and to examine this for different groups of people (Aim 3) [30]. LTA is person-centred rather than data-centred, is free of distributional assumptions such as normality because it uses categorical indicators, considers symptoms from different questionnaires simultaneously, retains participants with some missing data, and provides a nuanced picture of symptom profiles and how these may change over time [30]. We used study group (comparison, non-HT users, HT users) as a grouping variable, and values of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to judge model fit. As a first step, cross-sectional multiple-group Latent Class Analysis (LCA) was run for 3, 6, and 12 months [31]. These suggested 2–3 latent classes (patterns) at each time for each group. Note that we did not include baseline data as there were no significant differences between the study groups on any variable (Table 1) and because we would only expect the symptom patterns to be evident in the RRSO participants post-surgery (i.e. after baseline). As a second step, we compared the fit of freely-estimated and constrained models [31] and established that the assumption of measurement invariance across study groups at 3, 6 and 12 months was reasonable (Supplementary Table 1). As a third step, we conducted multiple-group LTA [31], testing models with 2–6 latent statuses (profiles). We compared the fit of models with item response probabilities free to vary across times with models where item response probabilities were constrained to be equal [31] and established that the assumption of measurement invariance across times was reasonable (Supplementary Table 2). Steps two and three suggested the underlying structure of the symptom profiles was similar for each study group, and that it did not change over time, and so all further modelling was conducted with measurement invariance imposed across groups and times. As a last step, we used AIC values, BIC values and interpretability to choose the best number of symptom patterns [31]. Posthoc, we allocated women to symptom profiles based on their highest posterior probability.

3. Results

3.1. Participants

The final sample contained 99 premenopausal comparison participants who retained their ovaries and 95 participants who underwent

Table 1
Sample characteristics and symptoms, by study group.

	Comparison $n = 99$	RRSO: No HT $n = 38$	RRSO: Had HT $n = 57$	p
Age at baseline (M, SD)	40.81 (5.78)	43.02 (4.53)	41.50 (3.79)	0.080
BMI at baseline				
Under/normal	53 (53.5)	17 (44.7)	20 (35.1)	0.202
Overweight	29 (29.3)	11 (29.0)	20 (35.1)	
Obese	17 (17.2)	10 (26.3)	17 (29.8)	
Has had hysterectomy [a]				
No	95 (96.0)	26 (68.4)	38 (66.7)	<0.001
Yes	4 (4.0)	12 (31.6)	19 (33.3)	
Has had breast cancer				
No	97 (98.0)	33 (86.8)	51 (89.5)	0.026
Yes	2 (2.0)	5 (13.2)	6 (10.5)	
Genetic risk of ovarian cancer				
No/unknown	93 (93.9)	7 (18.4)	12 (21.1)	<0.001
Yes	6 (6.1)	31 (81.6)	45 (79.0)	
Smoking status				
Non-smoker	60 (60.6)	17 (44.7)	40 (70.2)	–
Ex-smoker	30 (30.3)	18 (47.4)	14 (24.6)	
Current smoker	9 (9.1)	3 (7.9)	3 (5.3)	
Symptoms at baseline				
Low desire	31 (31.3)	8 (21.6)	17 (29.8)	0.534
Vaginal dryness	17 (17.2)	2 (5.4)	10 (17.5)	0.190
Hot flashes	12 (12.1)	2 (5.4)	3 (5.3)	0.249
Night sweats	24 (24.2)	8 (21.6)	11 (19.3)	0.770
Poor sleep	43 (43.4)	22 (61.1)	24 (42.9)	0.152
Anxiety &/or depression	13 (13.1)	5 (18.5)	10 (20.4)	0.486

Note. "RRSO" = risk-reducing salpingo-oophorectomy. "HT" = Hormone Therapy.
[a] One RRSO and three comparison participants had hysterectomy prior to Baseline.

RRSO. Of the RRSO group, 57 elected to take HT and 38 did not (Table 1). All RRSO participants had their procedure between baseline and 3 months, and 30/95 had concurrent hysterectomy. Most (76/95, 80.0%) of the RRSO participants had a high genetic risk of ovarian cancer, compared to 6.1% (6/99) of the comparison group. Pathogenic variants included BRCA1 (38/194, 19.6%), BRCA2 (35/194, 18.0%), both (4/194, 2.1%) and Lynch Syndrome (5/194, 3%). The three groups were not significantly different in age or BMI at baseline. The non-HT group had a higher percentage of smokers. There were no significant differences on menopause symptoms at baseline (Table 1), although the non-HT group had slightly lower prevalence of vaginal dryness and higher prevalence of poor sleep.

Of the 57 RRSO women in the HT group, 47 (82.5%) initiated HT between baseline and 3 months and 10 initiated HT after 3 months. The majority reported using HT at all three study periods ($n = 45$, 78.9%). Only 8 women (14%) changed their HT dose between 3 and 12 months.

3.2. Prevalence of individual symptoms

There were differences between the groups in the prevalence of every individual menopause symptom at 3, 6 and 12 months (Table 2). In the comparison group, the prevalence of each symptom was low (with the exception of poor sleep), and relatively stable over time. In contrast, the prevalence of every symptom was higher in the RRSO groups and tended to be highest in the non-HT group. Symptom prevalence varied over time, suggesting that menopause-related symptoms may not be stable.

3.3. Prevalence of symptom profiles

To investigate symptom profiles, the fit of a series of LTAs with 2–6 latent patterns was compared to determine the number of symptom profiles that provided the best balance between fit and parsimony (Supplementary Table 3). The 5-pattern model had the lowest AIC value, however BIC values started to increase at 3 profiles. Prevalences were too small in the 5-profile model and so the 3-profile model was chosen. In other words, we identified 3 distinct profiles of symptoms in our sample.

We named the three symptom profiles based on the symptoms that the participants in each profile were most likely to experience (see item response probabilities, top half of Table 3) Participants in the Few Symptoms profile were unlikely to report any symptoms, with most probabilities close to 0. Poor sleep had the highest probability at 0.40. In contrast, participants in the Most Symptoms profile were likely to report almost all symptoms, with about a 50% chance of sexual symptoms, about a 75% chance of poor sleep and night sweats, and a 95% chance of hot flashes. The probability of reporting anxiety/depression was highest in this profile, even though the item response probability was below 0.50. Finally, participants in the Sexual Symptoms profile had a similar likelihood of reporting vasomotor, mood and sleep symptoms to participants in the Few Symptoms profile. However, what set the Sexual Symptoms profile apart was the much higher likelihood of reporting vaginal dryness (78% chance) and decreased desire (51% chance).

The prevalence of each symptom profile varied by study group (Table 3). The majority of the comparison group (77–80%) reported Few Symptoms. In contrast, the majority of the non-HT group (81–87%) reported Most Symptoms. The HT group showed the most diversity in symptom profiles, with 36–41% reporting Most Symptoms, 36–42% reporting Few Symptoms, and 17–27% reporting Sexual Symptoms.

3.4. Transitions between symptom profiles over time

Comparison group. There was a high degree of symptom stability in the comparison group. At 3 months, 80% of comparison participants

Table 2
Prevalence of symptoms (N, %) at 3, 6 and 12 months, by study group.

	3 months[a]				6 months[b]				12 months[c]			
	Comparisons	No HT	Had HT	p	Comparison	No HT	Had HT	p	Comparison	No HT	Had HT	p
Low desire	22 (22.2)	15 (41.7)	28 (52.8)	0.001	32 (32.7)	20 (58.8)	26 (45.6)	0.021	24 (24.5)	20 (60.6)	25 (46.3)	<0.001
Vaginal Dryness	15 (15.2)	16 (44.4)	23 (43.4)	<0.001	14 (14.3)	16 (47.1)	26 (45.6)	<0.001	14 (14.3)	16 (48.5)	14 (25.9)	<0.001
Hot flashes	9 (9.1)	29 (80.6)	21 (39.6)	<0.001	11 (11.2)	29 (85.3)	21 (36.8)	<0.001	12 (12.2)	28 (84.9)	22 (40.0)	<0.001
Night sweats	18 (18.2)	20 (55.6)	22 (41.5)	<0.001	22 (22.5)	23 (67.7)	20 (35.1)	<0.001	25 (25.5)	19 (57.6)	23 (41.8)	0.002
Poor sleep	45 (45.5)	27 (75.0)	25 (47.2)	0.007	42 (43.3)	24 (70.6)	27 (47.4)	0.022	42 (42.9)	24 (72.7)	31 (57.4)	0.008
Anxiety/depression	12 (12.1)	13 (39.4)	17 (32.7)	0.001	16 (16.3)	7 (21.9)	19 (33.3)	0.050	15 (15.3)	8 (23.5)	17 (30.9)	0.074

Note. "HT" = hormone therapy.
[a] Missing data at 3 m: low desire, vaginal dryness, hot flashes, night sweats, poor sleep = 5; anx/dep = 9.
[b] Missing data at 6 m: low desire, vaginal dryness, hot flashes, night sweats = 4; poor sleep = 5; anx/dep = 6.
[c] Missing data at 12: low desire, vaginal dryness, poor sleep = 8; hot flashes, night sweats = 7; anx/dep = 6.

Table 3
Item response probabilities for each symptom profile, and prevalence of each symptom profile at 3, 6, and 12 months by study group.

	Symptom profiles		
	Few symptoms	Most symptoms	Sexual symptoms
Item response probabilities (all groups)			
Low desire	0.22	**0.58**	**0.51**
Vag. dryness	0.01	0.48	**0.78**
Hot flashes	0.04	**0.95**	0.06
Night sweats	0.15	**0.74**	0.20
Poor sleep	0.40	**0.76**	0.40
Anx/dep	0.13	0.41	0.19
Symptom profile prevalence by group			
Comparison (n = 99)			
3 months	0.80	0.07	0.14
6 months	0.77	0.08	0.15
12 months	0.77	0.09	0.14
RRSO: No HT (n = 38)			
3 months	0.09	0.81	0.10
6 months	0.07	0.87	0.07
12 months	0.13	0.87	0.00
RRSO: Had HT (n = 57)			
3 months	0.36	0.36	0.27
6 months	0.39	0.36	0.25
12 months	0.42	0.41	0.17

Note. "RRSO" = risk-reducing salpingo-oophorectomy. "HT" = Hormone Therapy.

reported Few Symptoms (Table 3). We can see by looking at probabilities on the diagonal matrix in Table 4 that comparison group participants who reported Few Symptoms at 3 months had a 97% chance of reporting Few Symptoms again at 6 months (i.e. no change). Comparison group participants who reported Few Symptoms at 6 months had a 97% chance of reporting Few Symptoms again at 12 months. Overall, the majority of the participants in the comparison group reported Few Symptoms, and there was very little chance of their symptom profile changing across the study.

Non-HT group. Non-HT participants had some chance of moving to a different symptom profile between 3 and 6 months. However, symptom profiles were largely stable in this group between 6 and 12 months. Between 3 and 6 months, there was a 2% chance of symptoms decreasing (i.e. from Most to Few symptoms), and a 31–49% chance of symptoms increasing (Table 4). Between 6 and 12 months, only participants with Sexual Symptoms were likely to improve (Table 4).

At 3 months, 81% of non-HT participants reported Most Symptoms (Table 3). Tracing the pathway through Fig. 1, we can see these participants had a 98% chance of reporting Most Symptoms again at 6 months, and a 100% chance of reporting Most Symptoms again at 12 months (Table 4, Fig. 1). In other words, if non-HT participants reported Most Symptoms at 3 months there was very little chance of this changing.

Non-HT participants who reported Few Symptoms at 3 months (9%; Table 3) had a 51% chance of reporting Few Symptoms again at 6 months, but they also had a 49% chance of symptoms increasing to Most Symptoms (Table 4, Fig. 1). There was no chance of changing to a different symptom profile between 6 and 12 months (Table 4, Fig. 1). In other words, if non-HT participants reported Few Symptoms at 3 months, they had an almost 50/50 chance of symptoms staying the same or increasing, and there was no chance of change from 6 months.

Non-HT participants who reported Sexual Symptoms at 3 months (10%, Table 3) had a 69% chance of reporting them again at 6 months, but then a 100% chance of symptoms decreasing to Few Symptoms by 12 months (Table 4, Fig. 1). Non-HT participants who reported Sexual Symptoms at 3 months also had a 31% chance of symptoms increasing to Most Symptoms at 6 months, and then no chance of symptoms decreasing between 6 and 12 months. In other words, there was a chance of symptoms staying the same or increasing.

HT group. The HT group showed the highest chance of changing to different symptom profiles over time (Table 4, Fig. 2). Between 3 and 6 months, there was a 5–15% chance that symptoms would decrease and a 14% chance that they would increase (Table 4). Between 6 and 12 months, there was a 12–32% chance that symptoms would decrease and a 4–25% chance that symptoms would increase (Table 4).

HT participants who reported Most Symptoms at 3 months (36%; Table 3) had an 84% chance of reporting Most Symptoms again at 6 months, and then a 74% chance of reporting Most Symptoms again at 12 months (Table 4, Fig. 2). However, there was also a chance of symptoms reducing to Sexual Symptoms (13% chance) or Few Symptoms (12% chance) at 12 months (Table 4, Fig. 2). In other words, HT participants with Most Symptoms at 3 months only had a 16% chance of symptoms reducing by 6 months.

HT users who reported Few Symptoms at 3 months (36%; Table 3) had an 86% chance of reporting Few Symptoms again at 6 months, and then a 76% chance of reporting Few Symptoms again at 12 months, although there was also a chance of symptoms increasing to Sexual Symptoms (4% chance) or Most Symptoms (21% chance) at 12 months (Table 4, Fig. 2). In other words, HT participants with Few Symptoms at 3 months had a high chance (76–86%) of symptoms continuing to be Few.

HT users who reported Sexual Symptoms at 3 months (27%; Table 3) had an 87% chance of reporting Sexual Symptoms again at 6 months, and then a 25% chance of symptoms increasing to Most Symptoms by 12 months and a 32% chance of symptoms decreasing to Few Symptoms by 12 months (Table 4, Fig. 2). In other words, HT users who reported sexual symptoms at 3 months were the most likely group to see a change in their symptom profiles (for better or worse) between 6 and 12 months.

4. Discussion

Compared to a group of premenopausal women who retained their ovaries, we identified three distinct symptom profiles in the 12 months

Table 4
Probabilities of stability or change in symptom profiles across time, by study group.

	Comparison group (n = 99)			No HT group (*n* = 38)			HT group (n = 57)		
	Few symptoms	Most symptoms	Sexual symptoms	Few symptoms	Most symptoms	Sexual symptoms	Few symptoms	Most symptoms	Sexual symptoms
Profile at 3 m	***Profile at 6 months***			***Profile at 6 months***			***Profile at 6 months***		
Few symp.	**0.97**	0.01	0.02	**0.51**	0.49	0.00	**0.86**	0.14	0.00
Most symp.	0.00	**0.31**	0.69	0.02	**0.98**	0.00	0.11	**0.84**	0.05
Sex symp.	0.00	0.38	**0.62**	0.00	0.31	**0.69**	0.13	0.00	**0.87**
Profile at 6 m	***Profile at 12 months***			***Profile at 12 months***			***Profile at 12 months***		
Few symp.	**0.97**	0.00	0.03	**1.00**	0.00	0.00	**0.76**	0.21	0.04
Most symp.	0.00	**0.47**	0.53	0.00	**1.00**	0.00	0.12	**0.74**	0.13
Sex symp.	0.11	0.39	**0.51**	1.00	0.00	**0.00**	0.32	0.25	**0.43**

Note. Note. "RRSO" = risk-reducing salpingo-oophorectomy. "HT" = Hormone Therapy. Bolded values on the diagonal indicate stability in symptom profile (i.e. the probability that a participant will remain in the same symptom profile at two consecutive measurement points: 3 and 6 months, and 6 and 12 months).

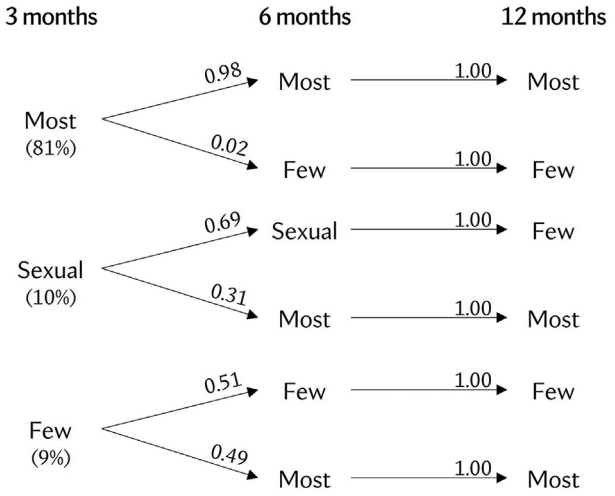

Fig. 1. Prevalence of symptom profiles at 3 months in RRSO participants who did not take hormone therapy (HT; $n = 38$), and the probability of transitioning to the same or different symptom profiles between 3 and 6 months and between 6 and 12 months post-RRSO ($n = 38$). Symptoms were low desire, vaginal dryness, hot flashes, night sweats, poor sleep and symptoms of anxiety/depression. Note: there were no significant differences in symptoms at baseline and so these were not included in the latent transition analysis and are not represented in the figure.

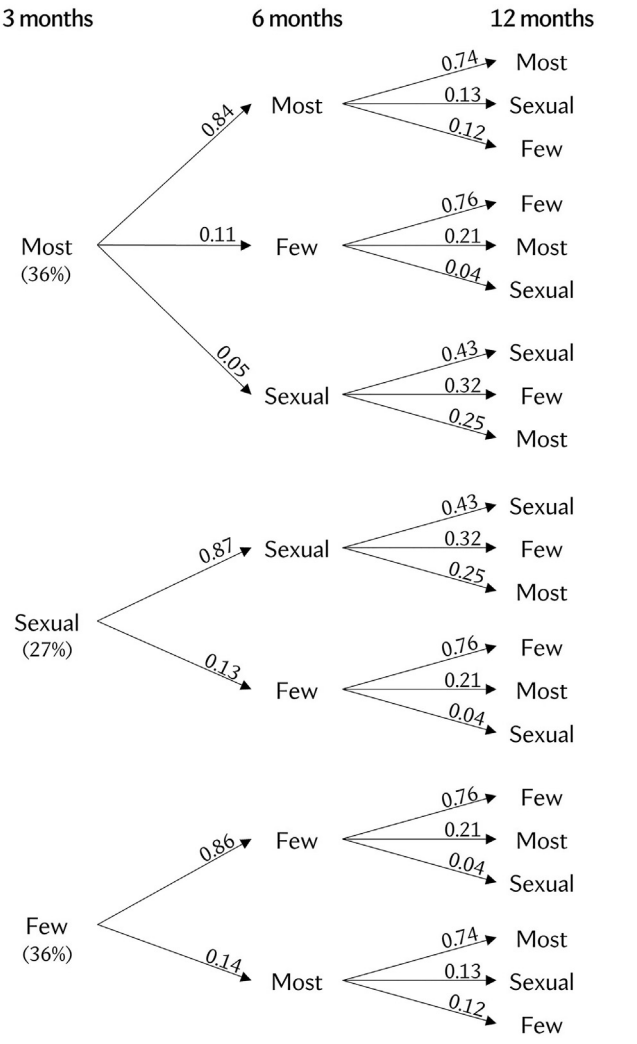

Fig. 2. Prevalence of symptom profiles at 3 months in RRSO participants who had hormone therapy (HT; $n = 57$), and the probability of transitioning to the same or different symptom profiles between 3 and 6 months and between 6 and 12 months post-RRSO. Symptoms were low desire, vaginal dryness, hot flashes, night sweats, poor sleep and anxiety/depression. Note: there were no significant differences in symptoms at baseline and so these were not included in the latent transition analysis and are not represented in the figure.

following RRSO. The percentage of women in these profiles differed between HT users and non-HT users, as did the probability of symptom profiles changing over time. These findings have important clinical implications, as understanding the interrelationships between symptoms can give women considering RRSO or surgical menopause for other indications a better idea of what to expect and may inform clinical care [7,10,11,17]. In the case of RRSO, more information about likely symptoms and their management may remove or reduce a barrier to potentially life-saving surgery [19].

This study contributed unique information on the symptoms women can expect to experience after RRSO and how they are likely to change (or not change) over time. Most women who do not take HT can expect to experience most symptoms measured here by 3 months and these are unlikely to improve by 12 months. Approximately one third of women who take HT will also experience most of the symptoms measured here by 3 months, but they have a higher chance of improvement over time. Two-thirds of the women who take HT will experience far fewer symptoms than women who do not take HT, and despite some variation over time, there is a high probability that their symptom patterns will be stable between 3 and 12 months.

Two of our symptom patterns were similar to those identified in other studies of clusters of menopausal symptoms, although prevalence differed. The first was Few Symptoms, where poor sleep was the only likely symptom. This pattern is found in 20–70% of women in other studies over the menopause transition [7,9,10], and in our study prevalence differed by group. As expected, 77–80% of the comparison group were likely to report this pattern, which is in line with findings that only a small percentage of premenopausal women report these symptoms [8,11]. After RRSO, more HT users (36–42%) than non-HT users (9–13%) reported Few Symptoms, consistent with evidence that HT is effective but does not fully resolve menopausal symptoms and may not work for everyone [12,20,22,23,32–34].

The second symptom pattern was Most Symptoms, with women likely to report hot flashes, night sweats, poor sleep and low desire. This group also had the highest likelihood of reporting anxiety/depression. This pattern was reported in 13–17% of women over the natural menopause transition [7,9,10]. In our study, 7–9% of the comparison group, 36–41% of the HT group and 81–87% of the non-HT group reported Most Symptoms. These percentages are higher than in other studies, which may reflect differences in menopausal stage, as some studies included participants in several stages of menopause [8,9], whereas WHAM participants were within 12 months post-RRSO, when menopause is acute [32]. Following RRSO or surgical menopause for other indications, HT is recommended until around age 50 years [3,33,35]. However, uptake is low due to contraindications or fears about risk [3,16,33,36]. Uptake of HT following RRSO ranges from 5–60% [3,20,32], similar to that reported in WHAM (60%).

The third symptom pattern was unique to this study: it comprised the sexual symptoms of vaginal dryness and reduced desire. This pattern was reported by 14–15% of comparisons, 0–10% of non-HT users, and 17–27% of HT users. This symptom pattern was not reported in women during the natural menopause transition when surgical menopause was excluded [8]. Following RRSO, several cross sectional and prospective studies have reported sexual difficulties, suggesting that these may be more common after premenopausal RRSO compared to natural menopause [1,37–39]. Consistent with recent reports from prospective studies of RRSO, our data suggest that HT may alleviate but not resolve sexual difficulties [34,40]. Despite similar sexual function at baseline, sexual symptoms remained elevated after RRSO compared with comparisons despite use of HT. [32] In addition, sexual symptoms

are often under-reported [1]. Clinicians should advise women considering RRSO that they may develop sexual problems which are not necessarily resolved by HT.

4.1. Strengths and limitations

This study had several strengths. It measured symptoms prospectively over time, reducing potential recall bias. It included a comparison group, which provided a clear comparison with symptoms experienced by premenopausal women of a similar age. We included HT users and specifically explored the difference in symptom experience compared to non-users, which is a gap in the literature. Lastly, it focused on symptoms identified as part of surgical menopause in this cohort using standardised measures [12,22,23].

This study also had several limitations. We were unable to analyse by level of vasomotor symptom severity, since almost all participants reported that their vasomotor symptoms were mild after RRSO [23]. Small cell sizes would have resulted in sparseness and created convergence problems. We recognise that vasomotor symptom severity is important [2] and future studies should consider how this contributes to symptom profiles. Similarly, we could not investigate how different doses of estrogen in HT affected symptoms because most participants took doses equivalent to 50 μg estradiol/day [23]. Also, our study was not randomised and those with more severe symptoms may have been more likely to take HT. For HT users, higher estrogen doses may have reduced symptoms and changed symptom patterns. More information is needed about the optimal dose of estrogen after RRSO. Previous studies of symptom profiles have generally excluded HT users [7,10,11,13] or not provided HT doses [17,32]. Similarly, menopausal symptoms may change in the years following RRSO [20] and we cannot comment on the trajectory of symptoms beyond 12 months.

5. Conclusions

Menopausal symptoms cluster into profiles after RRSO. Symptom profiles and likely changes over time can inform clinical management and help women to better understand what to expect after RRSO. Women who do not take HT are likely to experience a high symptom burden that does not improve by 12 months. Those who take HT experience fewer symptoms, with a greater chance of improvement by 12 months. Amongst HT users there are substantial variations in symptom profiles over time. This highlights the gap in effective treatments for these women and the importance of matching treatments to symptom profiles.

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CRediT authorship contribution statement

Katrina M. Moss: Methodology, Software, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Gita D. Mishra:** Resources, Data curation, Writing – review & editing, Visualization, Supervision. **Efrosinia O. Krejany:** Software, Validation, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration. **Martha Hickey:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

None of the funding agencies had a role in the design or conduct of the study, nor the collection, management, analyses or interpretation of the data, nor the preparation or approval of this manuscript. 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. KM, EOK and GM do not have any conflict 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.2022.07.029.

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