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What Happens After Menopause? (WHAM): A prospective controlled study of cardiovascular and metabolic risk 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy

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HIGHLIGHTS

- First prospective controlled study of cardiometabolic risk after RRBSO.
- Waist circumference and waist hip ratio significantly increased after RRBSO.
- Hormone therapy prevented the increase in waist circumference after RRBSO.
- Overweight/obesity and elevated CRP was more common in RRBSO participants.
- BP and circulating cardiometabolic risk factors largely unchanged at 12 months.

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ABSTRACT

Objective. To prospectively measure cardiometabolic risk 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy (RRBSO) compared to a similar age comparison group, and the effects of Hormone Therapy (HT) on cardiometabolic risk.

Methods. Prospective observational study of 95 premenopausal women planning RRBSO and 99 comparisons who retained their ovaries. At baseline and 12 months, blood pressure (BP), Body Mass Index (BMI), waist and hip circumference, fasting total, HDL and LDL cholesterol, triglycerides, high-sensitivity C-reactive protein, glucose and insulin were measured and HOMA-IR was calculated. Chi-square tests, *t*-tests and adjusted logistic regression models were used to compare groups.

Results. Baseline cardiometabolic phenotypes were similar between groups but more RRBSO participants were overweight/obese with higher waist/hip ratios. By 12 months, BP and cardiometabolic phenotypes were largely unchanged. Paired *t*-tests showed statistically significant increases in BMI ($p = 0.037$) and weight ($p = 0.042$) and larger increases in waist circumference ($p < 0.001$) and waist-hip ratio ($p = 0.009$) after RRBSO vs comparisons. However, these were not significant when adjusted for baseline values. After RRBSO 60% initiated Hormone Therapy (HT). Paired *t*-tests demonstrated that non-HT users had a significantly greater mean increase in waist circumference of 4.3 cm (95% CI 2.0–6.5) compared to 1.3 cm in HT users (95% CI -0.2-2.7, $p < 0.001$), which remained significant when adjusted for baseline values ($p = 0.02$). At 12 months, mean waist circumference was 2.94 cm greater in non-HT users compared to HT users.

Conclusions. Cardiometabolic risk markers are largely unchanged 12 months after RRBSO. Hormone Therapy after RRBSO may prevent against an increase in waist circumference.

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1. Introduction

In women with pathogenic gene variants conferring an elevated risk of ovarian cancer, risk-reducing bilateral salpingo-oophorectomy (RRBSO) is the only intervention shown to reduce ovarian cancer deaths and all-cause mortality [1]. RRSBO is generally recommended at around 35–40 years for BRCA1 and at 40–45 years for women with BRCA2 pathogenic variants. Premenopausal RRBSO will induce immediate surgical menopause [2]. Women at elevated risk of ovarian cancer must balance the established benefits of RRBSO for cancer risk reduction against the potential adverse health sequelae of surgical menopause. In clinical practice, concerns about adverse health consequences from surgical menopause and gaps in knowledge are a barrier to this potentially life-saving surgery [3]. The lack of consensus guidelines on follow-up after RRBSO reflects the paucity of prospective studies of non-cancer outcomes in this population. This limits evidence-based, individualized care to prevent the long-term consequences of surgical menopause such as cardiometabolic disease [4].

Cardiovascular disease (CVD) and metabolic disease are leading causes of morbidity and mortality in women worldwide. Burgeoning evidence suggests that timing and type of menopause contribute to cardiovascular risk with surgical menopause potentially conferring a greater risk than spontaneous early menopause [5]. The underlying mechanisms are not fully understood, but the cardioprotective effects of ovarian estrogens may include inhibiting development of atherosclerosis, the main mechanism leading to the development of CVD [6]. Loss of estrogen may also increase metabolic risk, although it is uncertain whether the increase in cardiovascular and metabolic disease in post-menopausal women are attributable to age or changes in the sex steroid milieu [7].

Surgical menopause following premenopausal RRBSO leads to a rapid and premature loss of endogenous estrogen. Several long-term prospective studies in the general population have observed that surgical menopause increases the risk of CVD [5,8–12] and diabetes [13,14] although findings are inconsistent [15]. It remains uncertain whether these findings are generalizable to women with pathogenic BRCA gene variants who may differ from the general population in CVD risk and who are more likely to have been exposed to chemoradiation and/or endocrine therapy which may affect cardiometabolic health [16]. In addition, RRBSO generally does not include hysterectomy and the published data on cardiometabolic outcomes after surgical menopause are derived from oophorectomy at the time of hysterectomy which might independently increase cardiovascular risk [17].

Cross-sectional studies of cardiovascular and metabolic risk after RRBSO are conflicting, with some suggesting that risks are elevated [18] and others reporting lower risk compared to age matched women from the general population [19]. Only one small prospective study has measured circulating cholesterol and lipids pre- and post-oophorectomy and reported an increase in total cholesterol and LDL-C at 12 months [20]. However, this study was limited to 26 premenopausal women of whom half had previously received chemotherapy for cancer treatment [21].

Hormone therapy (HT) is generally recommended after surgical menopause but uptake is low [22] and the benefits for cardiovascular and metabolic health remain uncertain [23,24]. Many women with pathogenic gene variants which increase ovarian cancer risk are also at increased risk of breast cancer, and the overall risk vs benefits of HT in this population remain unclear. One cross-sectional study suggested that HT reduced cardiovascular risk after RRBSO [25], but no prospective studies have been published.

Clinicians managing patients after RRBSO need to know whether and when cardiovascular and metabolic risk should be assessed and whether to recommend HT to reduce risk. The aim of this study was to prospectively measure biomarkers of cardiovascular and metabolic risk up to 12 months after RRBSO compared to similar age comparisons who retained their ovaries, and the effect of HT on these outcomes.

2. Methods

2.1. Study population

The WHAM study protocol has been published and describes the ethics approvals, consenting procedures and eligibility criteria that facilitated participant recruitment [26]. 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 [26] (Fig. 1).

The RRBSO group consisted of premenopausal women at high-risk of ovarian cancer planning RRBSO. 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 RRBSO or baseline (for the comparison group). Premenopausal status was confirmed by a history of regular menstrual cycles, day 2 to 6 Follicle Stimulating Hormone ≤15 IU/L and estradiol >100 pmol/L [26]. Exclusions were women within 3 months of pregnancy or lactation, planning pregnancy, irregular bleeding or use of anti-estrogens such as tamoxifen [26].

2.2. Study assessments

A comprehensive schedule of WHAM study assessments has been published [26]. Briefly, data for these analyses included measurements of height, weight, waist and hip circumference, BP and fasting cholesterol, lipids, triglycerides, glucose, insulin and high-sensitivity C-Reactive Protein at baseline and 12 months. Homeostatic Model Assessment, Insulin Resistance (HOMA-IR) was calculated [27]. RRBSO occurred between baseline and 3-month study visits. This study reports cardiovascular and metabolic risk outcomes at 12 months.

2.3. Measures of blood pressure, BMI and waist and hip circumference

Blood pressure was measured after 15 min rest in a seated position using an appropriately-sized cuff on the bared right upper arm supported at heart level. Auscultatory readings with an aneroid sphygmomanometer and stethoscope or automated oscillometric readings with a single read per activation device were collected by trained operators. A dedicated and calibrated device was used for all participants and time-points at each recruitment site. If the systolic or diastolic BP was low or elevated, a second reading was obtained at least two minutes later [28]. Hypertension was defined as systolic blood pressure (SBP) ≥130 mmHg and diastolic blood pressure (DBP) ≥80 and was sub-grouped into mild (SBP = 130–139 and DBP = 80–89), moderate (SBP = 140–180 and DBP = 90–120) or severe (SBP ≥180 and DBP >120) [29].

Height was measured to the nearest 0.5 cm accuracy using a vertical ruler in a standing position without shoes. Weight was measured using an electronic digital scale by a trained technician with 0.1 kg accuracy with clothing but without shoes. Body Mass Index (BMI) was calculated by dividing weight in kg by height in meters squared and classified using WHO criteria as underweight /normal (≤ 24.9 kg/m^2), overweight (25.0 to ≤29.9 kg/m^2) or obese (≥ 30 kg/m^2).

Waist and hip circumference measures to the nearest 0.5 cm were collected at baseline and 12 months. Waist circumference was measured parallel to the ground from the narrowest point between the iliac crest and the lowest lateral portion of the rib cage after exhalation. Hip circumference was measured parallel to the ground at the point where the buttocks are most extended when viewed from the side. The waist-hip ratio was derived with an online calculator provided by Bupa Health Services Pty Ltd. Australia (https://www.bupa.com.au/healthlink/health-tools/waist-to-hip-ratio). Cardiometabolic disease risk according to waist-hip ratios was defined as low (0–0.804), moderate (0.805–0.894) and high (≥0.895).

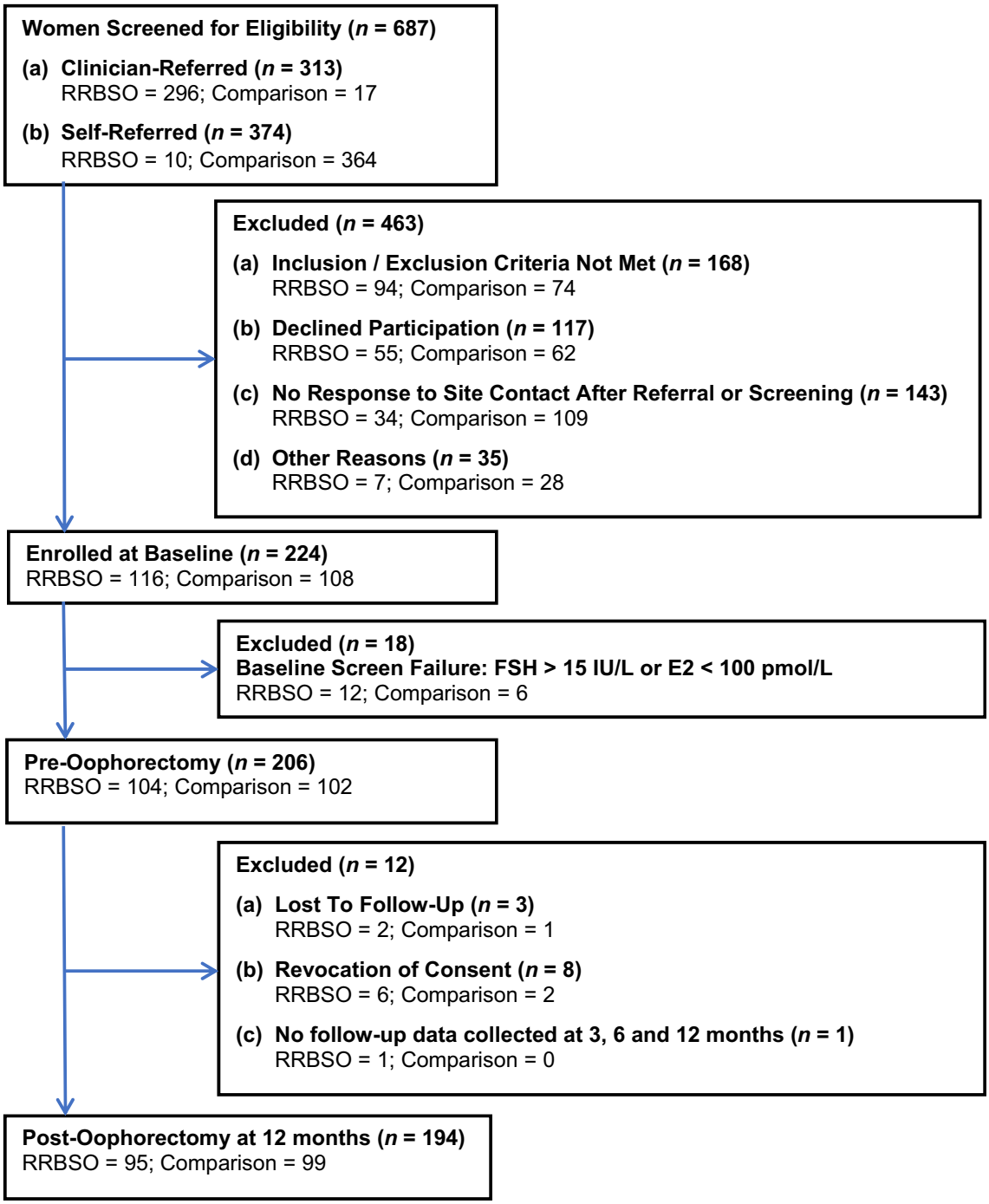

Fig. 1. Participant flowchart. Number of participant screenings, enrolments and withdrawals relevant to the first 12 months of the WHAM study. Women were either clinician- or self-referred to one of five recruitment sites in Australia and the USA during 2013 to 2019. *FSH* = Follicle-Stimulating Hormone;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

2.4. Measurement of circulating biomarkers of cardiovascular and metabolic risk

Blood samples were collected after at least 8 h of overnight fasting for circulating cholesterol, high density lipoprotein (HDL–C), low density lipoprotein (LDL-C), triglycerides (TG), insulin, glucose, and high sensitivity C-Reactive Protein (hs CRP). Australian samples were tested by commercial laboratories accredited by the National Association of Testing Authorities (NATA, Australia) and The Royal College of Pathologists of Australia (RCPA) for compliance with National Pathology Accreditation Advisory Council (NPAAC, Australia) standards and ISO15189. USA samples were tested by commercial laboratories accredited by the Clinical Laboratories Improvement Amendments (CLIA) regulations. Test results were interpreted in accordance with normative reference values and any cohort-specific information (e.g. age, gender) provided by the testing laboratories. Unless otherwise specified, results were defined as follows: (i) Reduced: any result below the lowest

reference value, (ii) Normal: any result equal to or between the lowest and highest reference values, and (iii) Elevated: any result greater than the highest reference value.

2.5. Diagnosis of insulin resistance

Homeostasis Model Assessment (HOMA-IR) values were calculated by the equation [fasting insulin (μU/ml) x fasting glucose (mM)]/22.5. Insulin resistance was defined by a HOMA value >4 [27]. The presence of prediabetes or diabetes was defined from fasting blood glucose and HbA1c using American Diabetes Association criteria. Fasting glucose of 100 to 125 mg/dL was defined as prediabetes, fasting glucose ≥126 mg/dL and HbA1c results of >6.5% were defined as type 2 diabetes (www.diabetes.org).

2.6. Diagnosis of metabolic syndrome

Metabolic syndrome was defined according to the 2005 NCEP ATP III criteria for women described in the AHA/NHLBI Scientific Statement [30] as the presence of any 3 or more of the following 5 risk factors: (i) waist circumference ≥ 88 cm, (ii) fasting plasma glucose ≥100 mg/dL or drug treatment for hyperglycemia, 3) fasting triglycerides ≥150 mg/dL or drug treatment for dyslipidemia, 4) fasting HDL-C < 50 mg/dL or drug treatment for dyslipidemia, or 5) hypertension defined as SBP ≥130 mmHg and DBP ≥85 mmHg or treatment for hypertension [31].

2.7. Statistical analysis

An a priori power calculation for WHAM was conducted. This found that a sample size of 89 women per group (RRBSO, comparison) would provide 80% power at a two-sided 5% level of significance to detect a 21% difference between groups [26].

Differences at baseline and at 12 months between the RRBSO and comparison groups were investigated using chi-square tests of differences for categorical variables and independent sample *t*-tests for continuous variables. Change between baseline and 12 months within groups was investigated using paired-sample t-tests. Differences at 12 months between the comparison and RRBSO groups in weight-related measures were investigated using linear regression. Adjusted models included baseline values, height (for BMI), smoking and vasomotor symptoms if statistically significant.

3. Results

3.1. Participant demographics

Data were collected from 194 women: 95 RRBSO and 99 comparisons (Fig. 1). At baseline, the groups were similar in mean age, diabetes history, smoking status and BMI (Table 1). Three RRBSO participants had diabetes at baseline and none developed diabetes during the study. More RRBSO participants (11 vs 2) had previous breast cancer and one developed breast cancer during the 12-month follow-up period (Table 1). All RRBSO participants underwent RRBSO, 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 RRBSO but one STIC (serous tubal intraepithelial carcinoma) was identified.

3.2. Use of Systemic Hormone Therapy

No participants were taking HT at baseline. After RRBSO, 60% (57/95) commenced HT. Most (47/57, 82.5%) initiated HT within 3 months of RRBSO and continued until 12 months. Only 10 (17.5%) delayed initiating HT beyond 3 months after RRBSO. A range of different HT

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

Characteristic (*n*, %)	Overall *n* = 194	By study group		
		Comparison *n* = 99	RRBSO *n* = 95	*p*[a]
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)	
Waist Circumference at baseline				
<88 cm	116 (59.8)	63 (63.6)	53 (55.8)	0.265
≥88 cm	78 (40.2)	36 (36.4)	42 (44.2)	
Waist-Hip ratio at baseline				
Low	99 (51.0)	59 (59.6)	40 (42.1)	0.051
Moderate	69 (35.6)	29 (29.3)	40 (42.1)	
High	26 (13.4)	11 (11.1)	15 (15.8)	
Previous diabetes diagnosis[b]				
No	192 (99.0)	99 (100.0)	93 (97.9)	–
Yes	2 (1.0)	0 (0.0)	2 (2.1)	
Glycemic drug use at baseline				
No	192 (99.0)	99 (100.0)	93 (97.9)	–
Yes	2 (1.0)	0 (0.0)	2 (2.1)	
Previous hypertension diagnosis[c]				
No	181 (93.3)	94 (94.9)	87 (91.6)	0.348
Yes	13 (6.7)	5 (5.1)	8 (8.4)	
Anti-hypertensive drug use at baseline				
No	184 (94.8)	96 (97.0)	88 (92.6)	–
Yes	10 (5.2)	3 (3.0)	7 (7.4)	
Previous dyslipidemia diagnosis[d]				
No	188 (96.9)	98 (99.0)	90 (94.7)	–
Yes	6 (3.1)	1 (1.0)	5 (5.3)	
Dyslipidemia drug use at baseline				
No	191 (98.5)	98 (99.0)	93 (97.9)	–
Yes	3 (1.5)	1 (1.0)	2 (2.1)	
Hysterectomy[e]				
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[f]				
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[g]				
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)	
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[h]				
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)	

RRBSO = risk-reducing salpingo-oophorectomy; *BMI* = body mass index.
[a] Chi-square test was not performed in cases where the cell sizes were too small.
[b] Diabetes Mellitus Type 1 (RRBSO: n = 1) and Type 2 (Comparison: n = 1). One additional RRBSO participant developed Type 2 diabetes in the follow-up period and used glycemic-modulating drugs for treatment.
[c] Hypertension as diagnosed by a clinician prior to baseline. No participants from either group developed hypertension in the follow-up period.
[d] Dyslipidemia as diagnosed by a clinician prior to baseline. One additional RRBSO participant developed dyslipidemia in the follow-up period and used cholesterol-modulating drugs for treatment.
[e] N = 3 comparison and *n* = 1 RRBSO participants had a hysterectomy prior to baseline. *N* = 30 RRBSO participants had concurrent hysterectomy with RRBSO and n = 1 comparison participant (Lynch Syndrome) had hysterectomy with ovarian preservation between baseline and 3 months.
[f] Both comparison particpants were BRCA1 carriers. One RRBSO participant developed breast cancer during the follow-up period.
[g] Pathogenic genetic variants known to increase ovarian cancer risk.
[h] *Non-smoker* = never smoked; *ex-smoker* = history of smoking but ceased prior to baseline; *current smoker* = smoker at any time from baseline to 12 months.

preparations were used. Those who underwent concurrent hysterectomy ($n = 20$) took estrogen-only HT. Of those who retained their uterus ($n = 37$), 5 took oral progestins, 1 used transdermal progestin, 28 used intrauterine progestin (Mirena), and 3 took tibolone. Estrogen dose was determined clinically but most (45/57, 79%) took doses equivalent to ≥50 μg/day of transdermal estradiol and 3 (5.3%) 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 estrogen dose was unknown. None of the comparison group initiated HT during the study period.

3.3. Blood pressure

At baseline the prevalence of diagnosed hypertension was low and there was no significant difference between the RRBSO and comparison groups (Table 1). Baseline systolic and diastolic BP were similar between the groups (Table 2). Between baseline and 12 months there was no significant change in BP in either group. Of the 20 RRBSO participants with mild hypertension at baseline, only 11 had mild hypertension at 12 months (Table 2). Following RRBSO there were no significant differences in blood pressure measures between HT users and non-HT users over the study follow-up period (data not shown).

3.4. Weight and BMI

More RRBSO participants (60.6%) were overweight/obese (BMI ≥25 kg/m^2) at baseline compared to comparisons (46.5%) (Table 1) and the RRBSO group was on average 3.5 kg heavier at baseline than comparisons (Table 3). At 12 months this pattern continued with no

Table 2
Comparison of circulating biomarkers and anthropomorphic measures of CVD risk at baseline and 12 months by study group (n, %).

Measure	Baseline			12 months		
	Comparison	RRBSO	p[a]	Comparison	RRBSO	p[a]
Total Cholesterol[b]						
Normal	11 (11.3)	34 (35.8)	**<0.001**	10 (10.4)	36 (40.5)	**<0.001**
Elevated	86 (88.7)	61 (64.2)		86 (89.6)	53 (59.5)	
Triglycerides[b]						
Normal	91 (93.8)	84 (88.4)	0.189	87 (90.6)	78 (87.6)	0.514
Elevated	6 (6.2)	1 (11.6)		9 (9.4)	1 (12.4)	
HDL-C[b]						
Normal	93 (95.9)	90 (94.7)	0.134	95 (99.0)	85 (95.5)	–
Reduced	4 (4.1)	5 (5.3)		1 (1.0)	4 (4.5)	
LDL-C[b]						
Normal	17 (17.5)	43 (45.7)	**<0.001**	15 (15.6)	38 (43.2)	**<0.001**
Elevated	80 (82.5)	51 (54.3)		81 (84.4)	50 (56.8)	
hs CRP[b]						
Reduced	0 (0.0)	1 (1.1)	0.024	0 (0.0)	0 (0.0)	–
Normal	83 (87.4)	66 (71.7)		78 (83.0)	62 (69.7)	
Elevated	12 (12.6)	25 (27.2)		16 (17.0)	27 (30.3)	
Glucose[b,c]						
Normal	93 (98.9)	90 (96.8)	–	89 (96.7)	87 (96.7)	–
Pre-diabetes	1 (1.1)	2 (2.1)		3 (3.3)	2 (2.2)	
Type 2	0 (0.0)	1 (1.1)		0 (0.0)	1 (1.1)	
Insulin[b]						
Normal	96 (100)	87 (97.8)	–	95 (100)	89 (100)	–
Elevate	0 (0.0)	2 (2.2)		0 (0)	0 (0)	
Waist-Hip Ratio						
Low	59 (59.6)	40 (42.1)	0.051	53 (54.6)	26 (29.2)	**0.002**
Moderate	29 (29.3)	40 (42.1)		28 (28.9)	43 (48.3)	
High	11 (11.1)	15 (15.8)		16 (16.5)	20 (22.5)	
HOMA IR						
Normal	90 (96.8)	83 (95.4)	–	90 (98.9)	83 (94.3)	–
Elevated	3 (3.2)	4 (4.6)		1 (1.1)	5 (5.7)	
Metabolic syndrome						
Yes	5 (5.1)	10 (10.5)	–	2 (2.0)	11 (11.6)	**0.020**
No	92 (92.9)	85 (89.5)		92 (54.4)	77 (81.1)	
Unknown	2 (2.0)	0 (0.0)		5 (5.1)	7 (7.4)	
Systolic BP[d]						
Normal/Reduced	91 (91.9)	80 (87.0)		86 (91.5)	77 (96.3)	
Mild Hypertension	5 (5.1)	8 (8.7)		7 (7.4)	1 (1.2)	
Mod Hypertension	3 (3.0)	4 (4.3)		1 (1.1)	2 (2.5)	
Diastolic BP[e]						
Normal/Reduced	82 (82.8)	68 (73.9)		78 (83.0)	64 (80.0)	
Mild Hypertension	13 (13.1)	20 (21.7)		13 (13.8)	11 (13.8)	
Mod Hypertension	4 (4.1)	4 (4.4)		3 (3.2)	5 (6.2)	

HDL-C = high density lipoprotein; *LDL-C* = low density lipoprotein; *hs CRP* = high sensitivity C-Reactive Protein; *HOMA IR* = Homeostasis Model Assessment for Insulin Resistance; *BP* = blood pressure; mod = moderate.

[a] Chi-square test was not performed in cases where the cell sizes were too small.

[b] Fasting venous blood tests.

[c] *Pre-diabetes* = 100–125 mg/dL; *Type 2* = ≥126 mg/dL.

[d] SBP: *Normal/Reduced* ≤130 mmHg; *mild hypertension* = 130–139 mmHg; *moderate hypertension* = 140–180 mmHg. None of the participants had severe systolic blood pressure (>180 mmHg) at baseline.

[e] DBP: *Normal/Reduced* ≤80 mmHg; *mild hypertension* = 80–89 mmHg; *moderate hypertension* = 90–120 mmHg. None of the participants had severe diastolic blood pressure (>120 mmHg) at baseline.

Table 3
Comparison of continuous anthropomorphic measurements (M, SD) at baseline and 12 months by study group.

Measure	Baseline			12 months		
	Comparison	RRBSO	*p*	Comparison	RRBSO	*p*
Body Mass Index (BMI)	25.81 (4.86)	27.38 (6.31)	0.057	26.06 (4.77)	27.60 (4.77)	0.063
Weight (kg)	70.47 (14.45)	73.99 (17.22)	0.124	71.28 (14.19)	74.79 (17.04)	0.128
Waist circumference (cm)	84.40 (12.55)	87.38 (13.90)	0.118	85.44 (12.64)	89.54 (14.02)	0.037
Hip circumference (cm)	105.7 (12.63)	106.2 (13.46)	0.787	106.2 (11.15)	106.6 (13.57)	0.812
Waist-hip ratio	0.80 (0.07)	0.82 (0.07)	0.018	0.80 (0.08)	0.84 (0.07)	0.003

significant difference in weight or BMI between the groups and no significant change from baseline values (Table 4).

3.5. Waist and hip circumference and waist-hip ratio

At baseline, the average waist-hip ratio was slightly higher in the RRBSO group compared to the comparisons (Table 3). The differences between groups in waist or hip circumference were not statistically significant, (Table 3) but mean waist circumference at baseline was 3 cm greater in the RRBSO group compared to comparisons (Table 3). At 12 months, waist circumference and waist-hip ratio were higher in the RRBSO group compared to comparisons (Table 3), but these differences reduced in magnitude after adjustment for baseline values and only the difference in waist-hip ratio remained statistically significant (Table 5). Between baseline and 12 months, waist circumference and waist-hip ratio increased in the RRBSO group but not in comparisons. The mean increase in waist circumference after RRBSO was 2.5 cm compared to 1.1 cm in comparisons (Table 4). Hip circumference did not significantly increase in either group.

3.6. Effect of Hormone Therapy on weight, BMI, waist, and hip circumference

At baseline there were no differences in RRBSO participants who subsequently initiated HT and those who did not initiate HT in mean weight, BMI, waist circumference, hip circumference, or waist-hip ratio (Table S1). Twelve months after RRBSO, those who initiated HT (60%) had less weight gain (0.8 kg vs 1.5 kg), less increase in BMI (0.31 vs 0.56), less increase in waist circumference (1.3 cm vs 4.3 cm), smaller hip circumference (0.1 cm decrease vs 1.6 cm gain) and less increase in waist-hip ratio (0.01 vs 0.03) compared to those who did not initiate HT (Table S2). At 12 months, after adjusting for baseline values, mean waist circumference was 2.94 cm greater in non-HT users compared to HT users (Table S3).

3.7. Cholesterol, lipids, triglycerides and high sensitivity CRP

At baseline, fasting total cholesterol was above the normative laboratory range in most participants from both groups, but significantly more comparisons had elevated fasting cholesterol (88.7%) compared to the RRBSO group (64.2%, $p < 0.001$) (Table 2). Similarly, more comparisons had elevated Low-density lipoproteins at baseline (82.5%) vs RRBSO (54.3%, $p < 0.001$) (Table 2). High-density lipoproteins did not differ between the groups at baseline (Table 2). Most participants in both groups had normal triglycerides at baseline. At 12 months these differences between the groups persisted (Table 2). Significantly more RRBSO participants vs comparisons had an elevated high-sensitivity CRP (hs CRP) at baseline (27.2% vs 12.6%, $p = 0.024$) with no significant change at 12 months (Table 2). Of those with elevated hs CRP at baseline, high BMI (overweight/obese, BMI ≥25 kg/m^2) was slightly more common in the RRBSO group compared to the comparison group (88% vs 66.7%). However, in those with an elevated BMI at baseline, significantly more RRBSO participants vs comparisons had elevated hs CRP (40% vs 18.2%). Changes in fasting cholesterol, lipids and hs CRP were not analyzed by HT use due to small cell sizes.

3.8. Fasting glucose, HbA1c, fasting insulin and HOMA-IR

Almost all participants had normal levels of fasting glucose and fasting insulin at baseline and HOMA-IR was normal (Table 2). There were no significant changes in these measures over the 12-month study period (Table 2). The effects of HT were not measured due to small cell sizes.

4. Discussion

This is the first prospective controlled study of cardiovascular and metabolic risk factors in the first 12 months after RRBSO and the first to measure how modifiable factors such as HT use affect these outcomes. The most striking finding was the increase in waist circumference after RRBSO which was more than double that seen in the premenopausal comparison group. Whilst this increase was relatively small, central accumulation of fat as determined by waist circumference is highly predictive of later life cardiometabolic risk in women including hypertension, diabetes and coronary artery disease [32]. A large prospective cohort study showed that waist circumference as an isolated measure predicted coronary heart disease risk in women [33]. Our findings are consistent with a retrospective case control study from Norway which reported greater waist circumference after RRBSO compared to naturally postmenopausal women, despite other markers of cardiovascular and metabolic risk being similar or less than age-matched controls [19]. Similarly, we observed small but statistically significant increases in waist-hip ratio after RRBSO compared to the comparison group. Waist-hip ratio also predicts CVD risk in postmenopausal women independent of BMI and weight alone [32]. Although CVD is a leading cause of morbidity and mortality in women, there are few evidence-based

Table 4
Comparison of anthropomorphic measurements by study group using paired samples *t*-tests (baseline minus 12 months).

Measure	Comparison Group			RRBSO Group		
	n	Avg Diff (95% CI)	*p*	*n*	Avg Diff (95% CI)	*p*
Body Mass Index (BMI)	96	−0.26 (−0.53, 0.02)	0.064	85	−0.41 (−0.80, −0.02)	**0.037**
Weight (kg)	96	−0.75 (−1.46, −0.05)	0.037	89	−1.07 (−2.10, −0.04)	0.042
Waist circumference (cm)	96	−1.07 (−2.47, 0.33)	0.132	89	−2.48 (−3.74, −1.23)	**<0.001**
Hip circumference (cm)	97	−0.44 (−2.24, 1.35)	0.626	89	−0.57 (−2.05, 0.92)	0.448
Waist-hip ratio	97	−0.01 (−0.02, 0.01)	0.424	89	−0.02 (−0.03, −0.00)	0.**009**

Table 5
Unadjusted and adjusted linear regression results for weight-related measures at 12 months, by study group.

Measure	Group	Unadjusted			Adjusted		
		n	Estimate (95% CI)	R^2	*n*	Estimate (95% CI)	R^2
Body Mass Index (BMI)[a]	Intercept	183	26.06 (25.95, 27.16)	2.0%	181	1.58 (0.48, 2.68)	92.3%
	Comparison		0 (Reference)			0 (Reference)	
	RRBSO		1.54 (−0.06, 3.15)			0.22 (−0.23, 0.68)	
Weight (cm)[b]	Intercept	185	71.28 (68.13, 74.42)	1.3%	184	−0.17 (−15.36, 15.00)	93.1%
	Comparison		0 (Reference)			0 (Reference)	
	RRBSO		3.51 (−1.02, 8.04)			0.54 (−0.68, 1.77)	
Waist Circumference (cm)[a]	Intercept	186	85.44 (82.77, 88.11)	2.3%	186	10.62 (4.60 (16.63)	78.0%
	Comparison		0 (Reference)			0 (Reference)	
	RRBSO		**4.11 (0.25, 7.96)**			1.72 (−0.13, 3.56)	
Hip Circumference (cm)[c]	Intercept	186	106.16 (103.69, 108.64)	0.0%	186	28.81 (20.14, 37.47)	66.3%
	Comparison		0 (Reference)			0 (Reference)	
	RRBSO		0.43 (−3.14, 4.01)			1.06 (−1.14, 3.27)	
Waist-Hip Ratio[a]	Intercept	186	0.01 (0.79, 0.82)	4.7%	186	0.36 (0.24, 0.47)	28.6%
	Comparison		0 (Reference)			0 (Reference)	
	RRBSO		**0.04 (0.01, 0.06)**			**0.02 (0.002, 0.03)**	

[a] Adjusted for baseline value.
[b] Adjusted for baseline value and height.
[c] Adjusted for baseline value, smoking status and vasomotor symptoms.

strategies for early detection and prevention and sex-specific risk factors are incompletely understood. Understanding and identifying early changes in cardiovascular and metabolic risk is particularly important for women facing early menopause who may accrue the greatest benefit from early detection and prevention of long-term cardiometabolic disease [9].

Consistent with retrospective and cross-sectional studies of RRBSO, we found no overall change in weight, cholesterol, lipids or inflammatory markers over 12 months [34]. However, more than twice as many women in the RRBSO group had an elevated CRP at baseline compared to the comparison group. This is the first report of elevated CRP in this population. Further studies are needed to determine whether BRCA1/2 pathogenic variants are associated with a pro-inflammatory state.

Together, our data suggest that measurement of blood pressure and circulating cardiometabolic risk factors is not routinely indicated in the first 12 months after RRBSO since these markers are unlikely to change. However, metabolic changes manifesting as increases in waist circumference which may herald adverse cardiovascular and metabolic risk may be detectable within 12 months and should be included in follow-up protocols. We found that overweight and obesity were more common the RRBSO group compared to comparisons, suggesting that high-risk women are not generally "healthier" than women in the general population, as previously reported in cross-sectional studies [19]. Our data suggest that clinical care for high-risk women should include instigation of preventive measures such as diet and weight-bearing exercise which may confer health benefits including reducing long-term cardiovascular and metabolic risk [35].

The risks vs benefits of HT in women at elevated risk of breast and ovarian cancer remain poorly defined. Our study provides new evidence to support a potential benefit of HT for cardiovascular and metabolic health by demonstrating that HT use was associated with significantly less increase in waist circumference after RRBSO compared to non-HT users. Changes in average waist circumference at 12 months in HT users were close to those seen in the comparison group (+1.3 cm vs +1 cm), substantially less than the 3.9 cm observed in non-HT users. Our finding are consistent with a retrospective study which reported a lower mean waist circumference in HT users after RRBSO compared to non-HT users and age-matched premenopausal comparisons [25]. In addition to increasing cardiometabolic risk, women may be concerned about changes in their physical appearance after RRBSO [3]. Our data suggest that following RRBSO women should be aware that HT may be protective against increasing waist circumference with possible benefits for longer-term risk of cardiovascular and metabolic disease.

Strengths of this study include the prospective design with baseline data on cardiovascular and metabolic risk, confirmed premenopausal status at baseline, prospective collection of circulating biomarkers and anthropometry at 12 months. Dates of initiation, dose and duration of HT use were collected. Limitations include the relatively small sample size and baseline differences between the RRBSO group and comparisons related to fasting cholesterol and lipids, BMI and BP. The comparison group were predominantly at population risk of ovarian cancer but included a small number of pathogenic gene variant carriers which may have affected our findings. Follow-up was limited to 12 months which may be too early to detect clinically significant changes in cardiovascular and metabolic risk. The mean age at RRBSO was around 41 years and the adverse effects of surgical menopause may be greater in younger women [10]. The study was not randomized and use of HT was clinically determined. Women with more vasomotor symptoms may have been more likely to choose HT and vasomotor symptoms have been associated with elevated CVD risk [36]. We did not collect information about family history of cardiovascular or metabolic disease or physical activity. Blood pressure was measured manually. Study participants were almost all Caucasian and the findings may not be generalizable to women from other races where reproductive factors may have differential effects on cardiovascular and metabolic risk.

In conclusion, this prospective controlled study of cardiovascular and metabolic risk after premenopausal RRBSO demonstrated that waist circumference at 12 months was greater than in similar age comparisons who retained their ovaries and that HT users gained almost 3 cm less in waist circumference compared to non-HT users.

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. SMD has received personal fees from AstraZeneca outside of the submitted work. KMM, GDM, EOK, AT and RAW have no conflicts of interest to declare.

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Appendix A. Supplementary data

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