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RESEARCH ARTICLE

Menopause

Urinary incontinence more than 15 years after premenopausal risk-reducing salpingo-oophorectomy: a multicentre cross-sectional study

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Abstract

Objective: To study the impact of premenopausal risk-reducing salpingo-oophorectomy (RRSO), compared with postmenopausal RRSO, on urinary incontinence (UI) ≥10 years later.

Design: Cross-sectional study, nested in a nationwide cohort.

Setting: Multicentre in the Netherlands.

Population: 750 women (68% *BRCA1/2* pathogenic variant carriers) who underwent either premenopausal RRSO (≤45 years, $n = 496$) or postmenopausal RRSO (≥54 years, $n = 254$). All participants were ≥55 years at the time of the study.

Methods: Urinary incontinence was assessed by the urinary distress inventory-6 (UDI-6); a score ≥33.3 indicated symptomatic UI. The incontinence impact questionnaire short form (IIQ-SF) was used to assess the impact on women's health-related quality of life (HR-QoL). Differences between groups were analysed using regression analyses adjusting for current age and other confounders.

Main outcome measures: Differences in UDI-6 scores and IIQ-SF scores between women with a premenopausal and a postmenopausal RRSO.

Results: Women in the premenopausal RRSO group had slightly higher UDI-6 scores compared with women in the postmenopausal RRSO group ($P = 0.053$), and their risk of symptomatic UI was non-significantly increased (odds ratio [OR] 2.1, 95% confidence interval [95% CI] 0.93–4.78). A premenopausal RRSO was associated with a higher risk of stress UI (OR 3.5, 95% CI 1.2–10.0) but not with urge UI. The proportions of women with a significant impact of UI on HR-QoL were similar in the premenopausal and postmenopausal RRSO groups (10.4% and 13.0%, respectively; $P = 0.46$).

For affiliations refer to page 107.

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Trial submission: https://clinicaltrials.gov/ct2/show/NCT03835793; Date of registration: 11 February 2019.

Clinical trial identification number: NCT03835793; URL of registration site: https://clinicaltrials.gov/ct2/home

Conclusions: More than 15 years after premenopausal RRSO, there were no significant differences in overall symptomatic UI between women with a premenopausal and those with a postmenopausal RRSO.

KEYWORDS
BRCA pathogenic variant carriers, health-related quality of life, menopause, premenopausal RRSO, preventive bilateral salpingo-oophorectomy, stress incontinence, urge incontinence

1 | INTRODUCTION

Women carrying a *BRCA1/2* germline pathogenic variant (*BRCA1/2*pv) are advised to undergo risk-reducing salpingo-oophorectomy (RRSO) to prevent ovarian cancer. *BRCA1*pv carriers are advised to undergo RRSO at ages 35–40 and *BRCA2*pv carriers at ages 40–45, after completion of childbearing. The consequence of this procedure is an immediate menopause, at a considerably younger age than in women from the general population. This may induce long-term morbidity and reduced health-related quality of life (HR-QoL) due to menopause-related vulvovaginal atrophy and urinary tract symptoms.

Reduced circulating estrogen levels due to menopause result in reduced collagen content, urethral shortening, thinning of urethral mucosa and vaginal epithelium, decreased urinary sphincter contractility and reduced bladder compliance.[1] These postmenopausal changes in the urogenital tissues may result in lower urinary tract symptoms such as urgency, recurrent urinary tract infections and urinary incontinence (UI).[2,3]

The prevalence of UI in postmenopausal women aged >60 years varies between 38% and 55%.[4] Up to 70% of women relate the onset of UI to their final menstrual period,[1] which is consistent with a peak in UI prevalence at ages 45–55, suggesting that menopause-associated anatomical and functional changes of the urogenital tissues are important contributors to UI.[5,6]

Stress urinary incontinence (SUI, involuntary loss of urine due to abdominal pressure, such as during exercise or coughing) shows a peak prevalence around menopause, and declines afterwards. In contrast, urge urinary incontinence (UUI, the sudden need to pass urine that is difficult to postpone), shows an increasing prevalence with a longer duration after menopause, possibly due to progressive atrophy.[4,7,8]

The prevalence of UI increases with age.[9] Therefore, when examining risk factors for UI, it is difficult to discriminate effects of menopause from general ageing effects. Other established risk factors for UI in women include higher body mass index (BMI), parity and vaginal delivery. Besides menopause, other potential risk factors include diabetes and hysterectomy.[1,10,11] Systemic menopausal hormone therapy (MHT) does not appear to reduce UI risk, but may do so when administered vaginally.[12]

While hysterectomy appears to increase the risk of urinary incontinence, studies are inconsistent as to whether a bilateral salpingo-oophorectomy has an additional negative effect on UI.[13–15] The effect of a premenopausal salpingo-oophorectomy has not been examined. Therefore, we aimed to examine the impact of a premenopausal RRSO on the prevalence of UI at least 10 years later. We hypothesised that women with a premenopausal RRSO, compared women of equal age with a postmenopausal RRSO, would more often experience UI due to their longer postmenopausal period.

2 | METHODS

2.1 | Patient selection and recruitment

Participants were Dutch women participating in the HARMOny study[16] (ClinicalTrials.gov NCT03835793), a multicentre cross-sectional study, nested in a nationwide cohort of women at high familial risk of breast/ovarian cancer.[17,18] Study design and procedures have been described previously.[16] Briefly, between 2018 and 2021, we invited women from this cohort to a study assessing the long-term effects of RRSO on cardiovascular disease, bone health, cognition and HR-QoL. Eligibility criteria included a high familial risk of breast/ovarian cancer, current age of ≥55 years and having undergone RRSO either before age 45 or after age 54. Exclusion criteria were ovarian cancer, metastatic disease and therapy-induced menopause >5 years before RRSO. Breast cancer was not an exclusion criterion. The study has been approved by the Institutional Review Board of the NKI.

2.2 | Study assessments

Women were asked to complete an online questionnaire on general health, cancer-specific outcomes, cardiovascular health, reproductive history and medical treatments, including use of MHT.

2.3 | Assessment of urinary incontinence

We assessed urogenital problems with the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire short-form (IIQ-SF),[19,20] two validated questionnaires designed to assess UI and the impact of UI on HR-QoL. The UDI-6 is a six-item symptom inventory to assess symptoms

associated with lower urinary tract dysfunction. The IIQ-SF is an eight-item instrument to assess impact of UI on physical activity, travel, work, social activities and emotional health. Responses are scored on a four-point Likert scale. Higher scores indicate more symptom distress (UDI-6) or more impact on daily life (IIQ-SF; see Table S1 for detailed information). Based on the literature, a UDI-6 score of 33.3 is the optimal cut-off for distinguishing women with symptomatic and asymptomatic UI. With an IIQ-SF score of 9.5 or higher, UI has a significant impact on a woman's HR-QoL.[21]

2.4 | Statistical analyses

Characteristics between the premenopausal RRSO group (RRSO ≤45 years of age) and the postmenopausal RRSO group (≥55 years of age) were compared using the chi-square test or Fisher's exact test for categorical data, and independent samples *t*-test for continuous data. We created several dichotomous variables; first for symptomatic UI (UDI-6 score ≥33), second for a significant impact of UI on the HR-QoL (IIQ-SF score ≥9.5) and last for substantial UUI and SUI by combining the categories 'moderately' and 'greatly' for scoring complaints of UUI and SUI.

To examine associations between timing of RRSO and various endpoints, we used multivariable linear regression for the UDI-6 score and the IIQ-SF score, and multivariable logistic regression analyses for the presence of symptomatic UI, UI affecting HR-QoL, UUI and SUI, yielding regression coefficients and odds ratios (OR) with accompanying 95% confidence intervals (95% CI). We used a Directed Acyclic Graph (DAG) to visualise confounding factors, mediating factors and competing exposures (Figure S1). In all regression analyses, we explored the confounding effects of age at questionnaire completion, breast cancer history, MHT, BMI, parity, diabetes and hysterectomy. A variable was removed from the model if the association between the exposure (RRSO) and the outcome (UI) did not change significantly (>10%), with the exception of age and breast cancer, which always remained in our model.

Because the question on type of delivery was added later in the study questionnaire, this variable was missing for 54.8% of women. Among 335 women who filled out their delivery mode, 88.1% delivered only vaginally, 5.4% had both a vaginal delivery and a caesarean section, and 6.6% delivered by caesarean section. Among women with known delivery mode we explored whether delivery mode was a confounding variable. As this was not the case, we did not include delivery mode in our models.

We also performed several stratified analyses. Because of the recommendation for *BRCA1*pv carriers to undergo a RRSO between ages 35 and 40, and for *BRCA2*pv carriers to undergo a RRSO between ages 40 and 45, we compared prevalence of UI between women with RRSO before age 41 (the early premenopausal group) and between ages 41 and 45 (the later premenopausal group). Additionally, we examined whether the effect of RRSO on UI differed by MHT use (current, former, never), delivery mode and parity (Results S1, Tables S3–S12). For all statistical analyses, STATA version 15.0 (StataCorp LLC) was used. *P*-values <0.05 were considered statistically significant.

3 | RESULTS

In total, 817 women gave informed consent (response rate 62.3%), of whom 529 were in the premenopausal RRSO group (RRSO ≤45 years of age) and 288 in the postmenopausal RRSO group (RRSO ≥55 years of age; Figure 1).

3.1 | Study participant characteristics

Mean age at questionnaire completion was 60.0 years in the premenopausal group and 70.2 years in the postmenopausal group ($P < 0.001$; Table 1). Because women in the premenopausal RRSO group were substantially younger than women in the postmenopausal RRSO group, we restricted the comparison of UI between these groups to 365 women in the overlapping age range, i.e. 60–70 years old at completion of the questionnaire (premenopausal group, $n = 224$, postmenopausal group, $n = 141$). In all 496 women with a premenopausal RRSO we compared UI between women in the early premenopausal group ($n = 152$) and the later premenopausal group ($n = 344$).

Among women aged 60–70 years at study, mean time since RRSO was 20.6 years in the premenopausal group and 10.6 years in the postmenopausal group (Table 1). In the premenopausal group, mean age at questionnaire completion was 62.7 years, compared with 67.0 years in the postmenopausal group ($P < 0.001$). Mean time since menopause was 20.6 years in the premenopausal group and 16.7 years in the postmenopausal group ($P < 0.001$). In all, 68% of women in the premenopausal-RRSO group carried a *BRCA1/2*pv versus 63.1% in the postmenopausal RRSO group ($P = 0.32$). In the premenopausal RRSO group, 60.3% of women had a history of breast cancer, compared with 58.9% in the postmenopausal group ($P = 0.79$). MHT was more often prescribed to women in the premenopausal RRSO group (29.1% versus 9.2% in the postmenopausal RRSO group; $P < 0.001$). Parity and mode of delivery were comparable between the two groups. In the premenopausal RRSO group, 18.6% of women had no children compared with 23.0% of women in the postmenopausal RRSO group ($P = 0.31$).

3.2 | Urinary incontinence and its impact on HR-QoL at ages 60–70 years in women with a premenopausal or postmenopausal RRSO

Unadjusted mean UDI-6 scores were 20.4 (SD 17.7) and 18.8 (SD 16.2; $P = 0.39$) in the premenopausal RRSO group and in the postmenopausal RRSO group, respectively (Figure 2). After adjustment for confounders in a linear regression

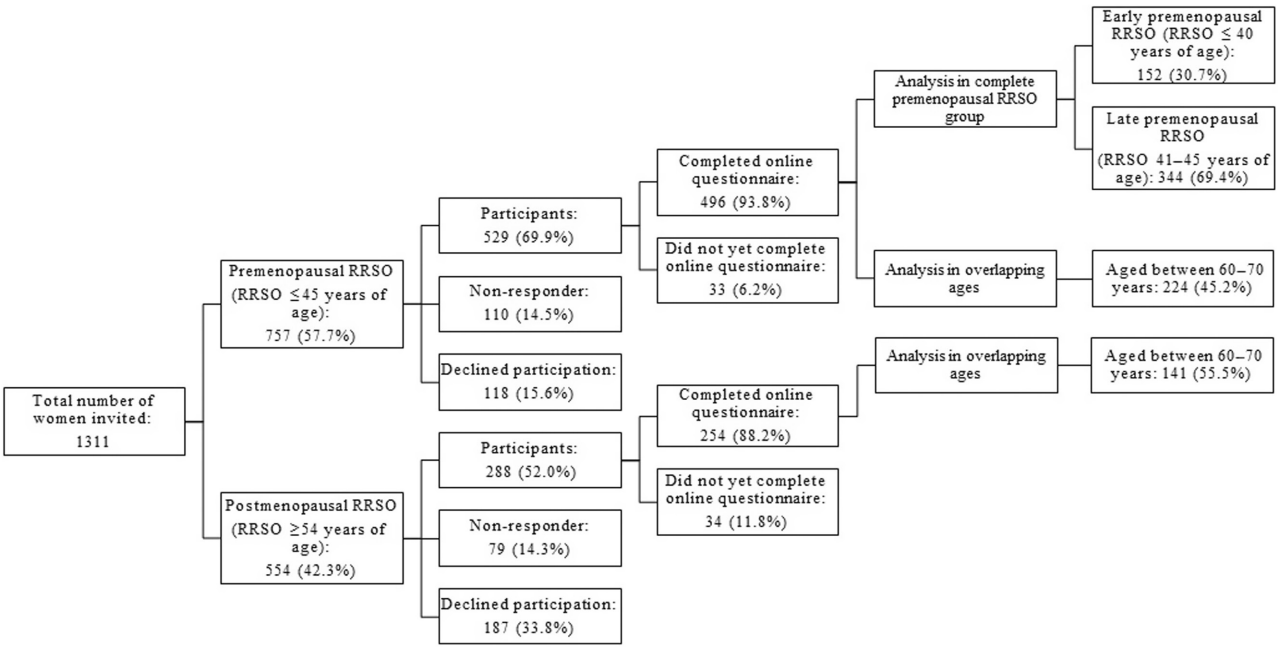

FIGURE 1 Participant flowchart. Number of participants enrolled, non-responders and number of women who declined participation. We have sent out regular reminders to women to complete the online questionnaire.

analysis, a premenopausal RRSO was associated with a slightly higher UDI-6 score, but this difference was not statistically significant (β-coefficient 5.0, 95% CI −0.1 to 10.1). The proportion of women with a premenopausal RRSO who had symptomatic UI according to the cut-off of 33.33 points was 23.6%, compared with 18.9% of women with a postmenopausal RRSO (P = 0.31). After adjustment for confounders in a logistic regression analysis, an association between premenopausal RRSO and symptomatic urinary incontinence (UDI-6 score ≥33.33) was borderline statistically significant (OR 2.1, 95% CI 0.93–4.78).

Assessing the impact of UI using the IIQ-SF, mean scores in the premenopausal and postmenopausal RRSO groups were 3.2 (SD 8.4) and 3.8 (SD 8.9), respectively (P = 0.53; Figure 3). After adjustment for confounders, linear regression analysis also did not show a difference between the groups (β-coefficient −1.0, 95% CI −3.6 to 1.5). The proportion of women with an IIQ-SF score ≥9.5 was 10.4% in women with a premenopausal RRSO and 13.0% in women with a postmenopausal RRSO (P = 0.46). After adjustment for confounders in a logistic regression analysis, a premenopausal RRSO was also not associated with a significant impact of UI on the HR-QoL (OR 0.7, 95% CI 0.3–2.0).

3.3 | Urge and stress urinary incontinence at ages 60–70 years in women with a premenopausal or postmenopausal RRSO

Substantial UUI was reported by 19.6% of women with a premenopausal RRSO (Figure 4), compared with 22.7% in the postmenopausal RRSO group (P = 0.48). After adjustment for age, breast cancer and BMI, a premenopausal RRSO was not associated with substantial UUI (OR 1.1, 95% CI 0.5–2.4). Substantial complaints with regard to SUI were experienced by 13% of women with a premenopausal RRSO, compared with 8% in the postmenopausal RRSO group (P = 0.15, Figure 4). After adjustment for age, breast cancer history and BMI, a premenopausal RRSO was associated with a higher risk of substantial SUI complaints (OR 3.5, 95% CI 1.2–10.0). In a regression analysis with 'time since RRSO' as continuous variable, the risk of having substantial SUI complaints increased by 10% for every year since RRSO (OR 1.1, 95% CI 1.01–1.2).

3.4 | Urinary incontinence by age at RRSO among women with a premenopausal RRSO, comparing an early premenopausal RRSO (RRSO ≤40 years of age) with later premenopausal RRSO (RRSO at 41–45 years of age)

Mean UDI-6 scores in the early and later premenopausal RRSO groups were 18.2 (SD 17.1) and 18.8 (SD 17.3), respectively (P = 0.74; Figure 5). After adjustment for confounders in a linear regression analysis, an early premenopausal RRSO was not associated with a higher UDI-6 score (95% CI −4.2 to 2.9). The proportions of women with symptomatic UI were 22.6% and 20.5% in the early and later premenopausal RRSO groups, respectively (P = 0.61). Multivariable logistic regression analysis also showed that an early premenopausal RRSO was not associated with symptomatic UI (OR1.0, 95% CI 0.95–1.04).

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TABLE 1 Baseline socio-demographic and clinical characteristics of study participants.

	Entire study population		Women aged 60–70 years	
	Premenopausal RRSO (RRSO ≤45 years, *n* = 496)	Postmenopausal RRSO (RRSO ≥54 years, *n* = 254)	Premenopausal RRSO (RRSO ≤45 years, *n* = 224)	Postmenopausal RRSO (RRSO ≥54 years, *n* = 141)
Age at questionnaire completion, mean (SD)	60.0 (3.5)	70.2 (4.3)*	62.7 (2.5)	67.0 (2.1)*
Age at RRSO, mean (SD)	41.7 (2.8)	58.4 (3.6)*	42.1 (2.5)	56.5 (1.9)*
Time since RRSO, mean (SD)	18.3 (4.1)	11.9 (3.0)*	20.6 (3.3)	10.6 (1.9)*
Time since menopause, mean (SD)	18.3 (4.2)	19.9 (6.5)*	20.6 (3.4)	16.7 (5.5)*
Pathogenic genetic variants[a]				
BRCA1 germline mutation	243 (49.0%)	74 (29.1%)*	109 (48.9%)	39 (27.7%)*
BRCA2 germline mutation	97 (19.6%)	94 (37.0%)	43 (19.3%)	50 (35.5%)
Established non-carrier	156 (31.5%)	86 (33.9%)	71 (31.8%)	52 (36.9%)
Breast cancer (yes)	293 (59.0%)	164 (64.6%)	135 (60.3%)	83 (58.9%)
Breast cancer before RRSO	237 (84.3%)	148 (91.4%)*	105 (80.8%)	73 (91.3%)*
Breast cancer after RRSO	44 (15.7%)	14 (8.6%)*	25 (19.3%)	7 (8.8%)*
Treatment of breast cancer				
Surgery	284 (97.6%)	159 (98.8%)	132 (97.1%)	80 (98.8%)
Chemotherapy	222 (76.3%)	86 (52.4%)*	97 (48.7%)	51 (42.9%)
Radiotherapy	182 (62.5%)	95 (59.0%)	86 (63.2%)	54 (66.7%)
Endocrine therapy	106 (36.4%)	53 (32.9%)	41 (30.2%)	29 (35.8%)
Prophylactic mastectomy: yes[b]	300 (62.1%)	84 (34.6%)*	140 (61.9%)	48 (33.8%)*
MHT use				
Current user	26 (5.2%)	2 (0.8%)*	14 (6.3%)	1 (0.7%)*
Past user	101 (20.4%)	28 (11.0%)*	46 (20.5%)	11 (7.8%)*
Never user	337 (67.9%)	213 (83.9%)*	147 (65.6%)	119 (84.4%)*
Unknown	32 (6.5%)	11 (4.3%)	17 (7.6%)	10 (7.1%)
MHT duration in years, mean (SD)	2.2 (4.5)	1.4 (3.3)	2.1 (4.4)	1.6 (3.9)
BMI, mean (SD)	26.5 (5.0)	25.8 (4.5)	26.6 (5.2)	26.2 (5.0)
Hysterectomy: yes[c]	69 (16.2%)	53 (28.5%)*	43 (19.3%)	28 (19.7%)
Mode of delivery				
Vaginal delivery	202 (85.2%)	94 (95.0%)*	101 (90.2%)	52 (96.3%)
Vaginal delivery and caesarean section	14 (5.9%)	4 (4.0%)*	6 (6.4%)	1 (1.9%)
Caesarean section	21 (8.9%)	1 (1.0%)*	5 (4.5%)	1 (1.9%)
Missing	259 (52.2%)	156 (61.4%)	112 (50.0%)	88 (62.4%)
Parity				
0	93 (18.8%)	40 (15.7%)	44 (19.6%)	21 (14.9%)
1–2	278 (56.0%)	151 (59.4%)	134 (59.8%)	79 (56.0%)
3–4	113 (22.8%)	57 (22.4%)	45 (20.1%)	36 (25.5%)
≥5	7 (1.4%)	3 (1.2%)	1 (0.5%)	2 (14.9%)

Note: Additional characteristics of the study population are provided in Table S2.

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

[a]All participants had a high familial risk of ovarian cancer. All women were tested for pathogenic variants; not all had a *BRCA1/2* mutation. Established non-carriers include women from *BRCA1/2* families who tested negative as well as women from a breast/ovarian cancer family who tested negative for the pathogenic variants tested in the Netherlands.

[b]Prophylactic mastectomy: bilateral or contralateral.

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

*$P < 0.05$. Groups compared using independent samples *t*-test, Chi-square test or Fisher's exact test.

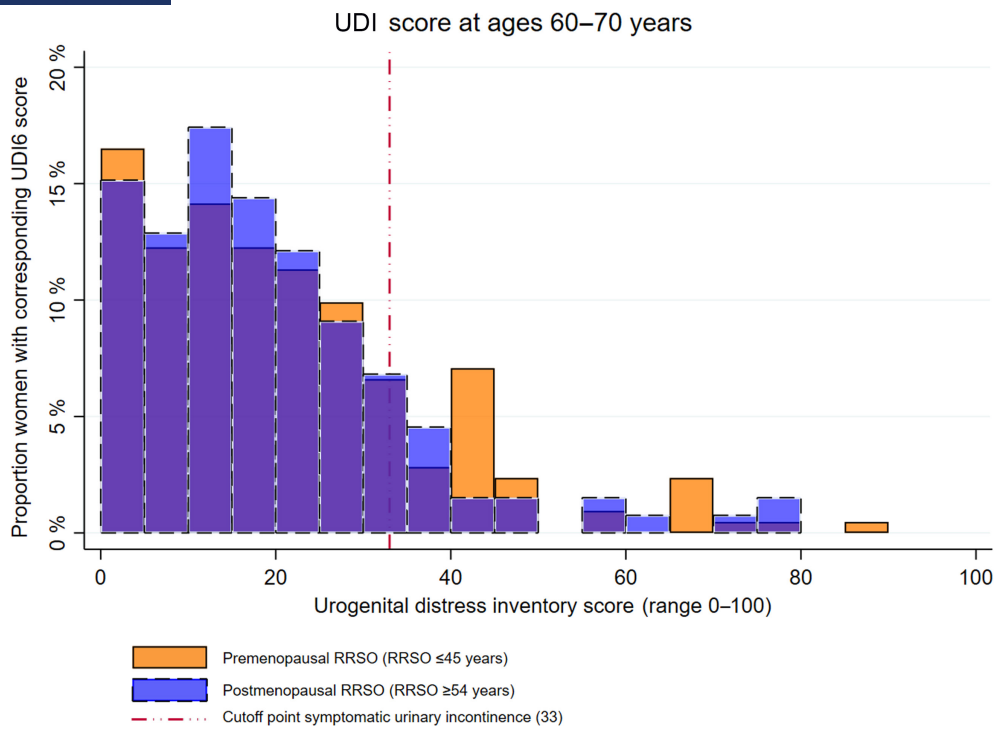

FIGURE 2 Distribution of Urogenital Distress Inventory (UDI-6) scores of women in the premenopausal risk-reducing salpingo-oophorectomy (RRSO) group and the postmenopausal RRSO group. In all, 24% of women with a premenopausal RRSO experienced symptomatic urinary incontinence (UDI-6 score ≥33.33) compared with 19% in the postmenopausal RRSO group.

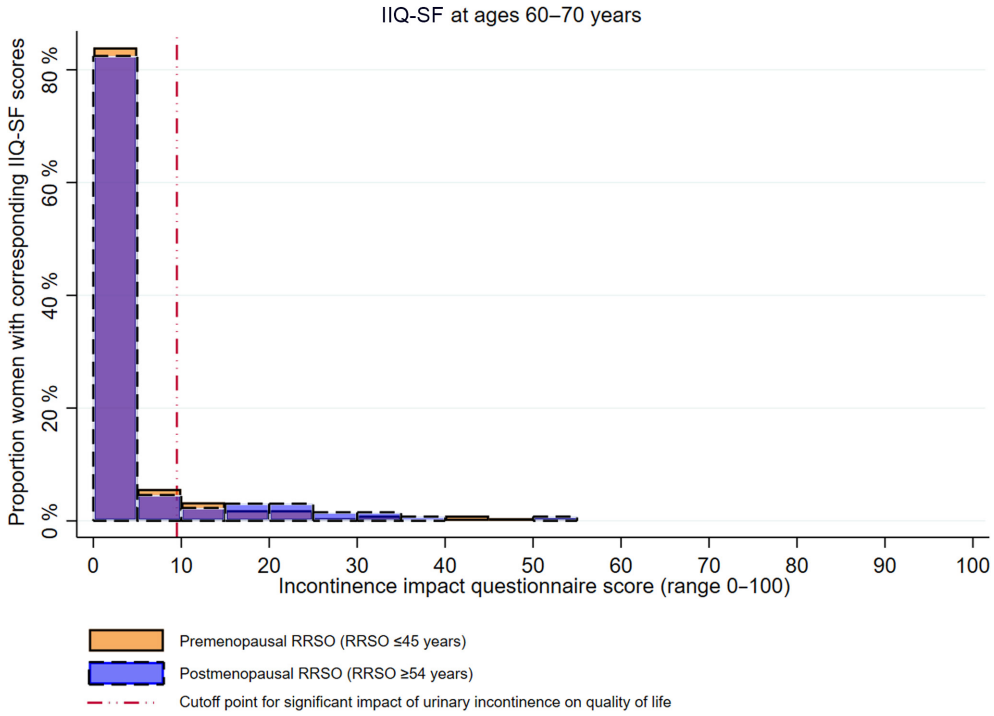

FIGURE 3 Distribution of Incontinence Impact Questionnaire Short Form (IIQ-SF) scores of women in the premenopausal risk-reducing salpingo-oophorectomy (RRSO) group and the postmenopausal RRSO group. In all, 10% of women in the premenopausal RRSO group experienced a significant influence of urinary incontinence on the quality of life (IIQ-SF score ≥9.5) compared with 13% in the postmenopausal RRSO group.

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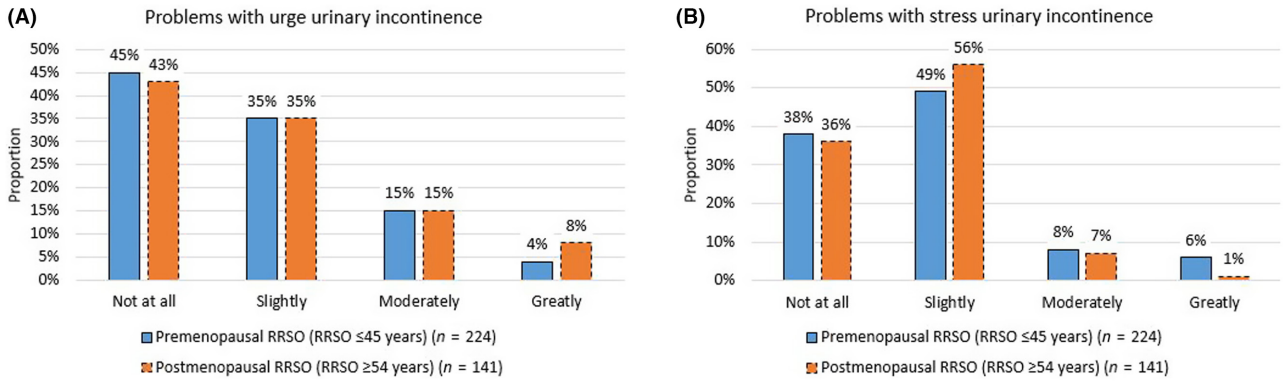

FIGURE 4 Prevalence of problems with (A) urge urinary incontinence and (B) stress urinary incontinence per risk-reducing salpingo-oophorectomy (RRSO) group for women aged 60–70 years.

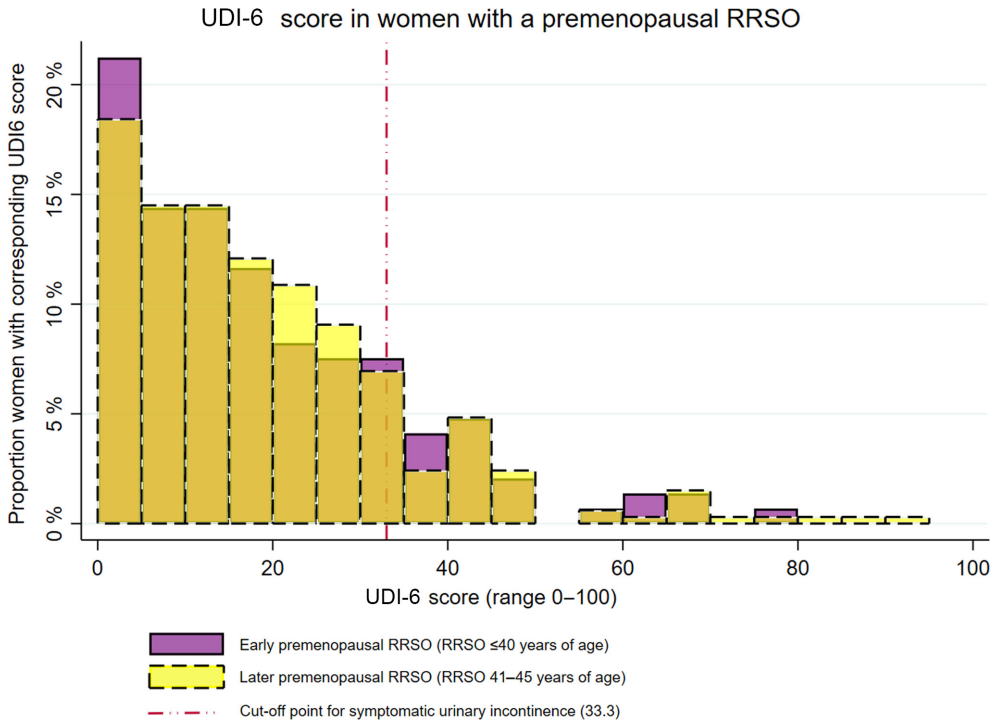

FIGURE 5 Distribution of Urogenital Distress Inventory (UDI-6) scores of women in the early premenopausal risk-reducing salpingo-oophorectomy (RRSO) group and the later premenopausal RRSO group.

When we stratified the premenopausal RRSO group according to MHT use, mean UDI-6 scores in women who still used MHT ($n=25$), had previously used MHT ($n=97$) and had never used MHT ($n=320$) were 18.9 (SD 20.2), 20.2 (SD 18.3) and 17.6 (16.2) ($P = 0.40$), respectively. In women who had ever used MHT or who still used MHT at the time of the study, 28.1% had symptomatic UI, compared with 18.1% in women who had never used MHT ($P=0.02$). After adjustment for age, breast cancer and BMI, former MHT use was significantly associated with symptomatic UI (OR1.9, 95% CI 1.1–3.3) but current MHT use was not (OR1.9, 95% CI 0.7–5.2).

Results from the IIQ-SF score by age at RRSO show no clear differences in UI impact between the early and later premenopausal RRSO groups (Results S2).

3.5 | Urge and stress urinary incontinence in women with a premenopausal RRSO, comparing an early premenopausal RRSO with later premenopausal RRSO

Substantial UUI was reported by 12.5% of women with an early premenopausal RRSO, compared with 16.6% in the later premenopausal RRSO group ($P = 0.25$; Figure S3a). After adjustment for age, breast cancer and BMI, an early premenopausal RRSO was not associated with substantial UUI (OR 0.54, 95% CI 0.28–1.04). Regarding SUI, 11.8% of women with an early premenopausal RRSO experienced substantial complaints, compared with 12.5% of women in the later premenopausal RRSO group ($P = 0.84$; Figure S3b).

After adjustment for age, breast cancer history and BMI, an early premenopausal RRSO was not associated with a higher risk of substantial SUI complaints (OR 0.998, 95% CI 0.52–1.92).

4 | DISCUSSION

4.1 | Main findings

Our study is the first one to assess UI more than 15 years after a premenopausal RRSO (age ≤45) compared with women with a postmenopausal RRSO (age ≥54). At the age of 60–70 years, women with a premenopausal RRSO had a slightly higher UDI-6 score but the difference with the postmenopausal group was not statistically significant. The risk of symptomatic UI associated with a premenopausal RRSO was also somewhat increased, but not statistically significantly so. There was no difference between the two groups regarding impact of UI on HR-QoL. However, a premenopausal RRSO was associated with substantial complaints of SUI; women with a premenopausal RRSO had a 3.5-fold increased risk of substantial SUI compared with women with a postmenopausal RRSO. Regarding UUI we found no difference between the two RRSO groups. When we examined UI within the premenopausal group and compared women with a very early RRSO (before age 41) and a later premenopausal RRSO (age 41–45), we found no differences in symptoms of UI and the impact of UI on HR-QoL. We did find that women who had ever used MHT (current and former users) more often experienced symptomatic UI according to the UDI-6, and their incontinence more often influenced the HR-QoL.

Within the premenopausal RRSO group we performed stratified analysis according to age at RRSO and MHT use. Based on our hypothesis and the results in the 60–70 year group, we would have expected more UI in the early premenopausal group. However, we did not find an association between timing of premenopausal RRSO and UI. This might be explained by the rather small difference in time since RRSO between the two groups; on average 21.1 years since oophorectomy in women with an early premenopausal RRSO and 17.0 years since oophorectomy in women with a later premenopausal RRSO. Remarkably, both past users of MHT and women who currently used MHT more often experienced symptomatic UI and UI impacting HR-QoL. This association might be explained by confounding by indication, considering that women with more substantial complaints of UI may more often have been prescribed MHT.

4.2 | Strengths and limitations

One of the limitations of our study is the difference in age distributions of the premenopausal and postmenopausal RRSO groups at time of study participation. This age difference was largely due to the strongly increasing prevalence of premenopausal RRSO after 2007.[22] To overcome this limitation, we compared UI between women with a premenopausal and a postmenopausal RRSO in the overlapping age range, 60–70 years at questionnaire completion, and corrected for age in all analyses.

Furthermore, as this is a cross-sectional study >15 years after RRSO, we do not have data on UI shortly after RRSO. As we are the first to assess UI after a premenopausal bilateral oophorectomy, there are no available data on UI prevalence directly after RRSO. Future research should focus more on the development of UI in the years after RRSO to see how many women experience SUI and UUI.

Strengths of our study include the large sample size, providing sufficient power to perform subgroup analyses. Additionally, by excluding women with RRSO between the ages of 46 and 54, we were able to make a more distinct evaluation of the differences in UI between women who had undergone RRSO prior to the onset of natural menopause and women with a postmenopausal RRSO. The participation rate was good (62.3%) and we employed validated questionnaires that are widely used.

4.3 | Interpretation

We can compare our results with UDI-6 and IIQ-SF scores reported for the Dutch general population.[19] The mean UDI-6 scores in our study (20.4 and 18.8 in the premenopausal and postmenopausal RRSO groups, respectively) were higher than the mean UDI-6 score of 12.2 (SD 12.7) in the Dutch reference data, but this difference may not be clinically relevant.[19] The mean IIQ-SF scores in our study (3.2 and 3.8 for the pre- and postmenopausal groups, respectively) are comparable with the Dutch reference data,[19] which show a mean IIQ-SF score of 4.2 (SD 11.2). Comparing our results on UI prevalence with the prevalence in the general population of other western countries is difficult, as the questionnaires and definitions of UI used in the literature differ substantially. The prevalence of substantial UUI (19.6% and 22.7% in the premenopausal and postmenopausal RRSO groups, respectively) in our study was higher than reported by Linde et al. (7.9%), whereas the prevalence of substantial SUI in our population was lower (13.4% and 8.5% in the premenopausal and postmenopausal RRSO groups, respectively) compared with the prevalence found by Linde et al. (25.4%).[10]

We calculated that, based on a two-sided α of 0.05 and 350 women in the study, we had 80% power to detect a difference in UDI-6 score of 3.8 between the two groups. We observed a nonsignificant difference of 1.6 in women aged 60–70 years. Based on our effect size calculations, we cannot exclude the possibility that the number of women included in this analysis was not large enough to identify this difference as statistically significant. However, one could also argue that this difference is not clinically relevant.

Our findings are generally reassuring for women who underwent a premenopausal. RRSO. Our results regarding SUI are remarkable, as the peak prevalence of SUI in general occurs postpartum and around menopause, and the

prevalence of UUI increases after menopause. As our study participants had been postmenopausal for a substantial period, we had expected a higher prevalence of UUI rather than SUI in women with a premenopausal RRSO. It is possible that the peak prevalence of SUI is higher after surgical menopause than after natural menopause. Unfortunately, we could not find any literature regarding the prevalence of SUI after early surgical menopause.

Future studies should focus on the short- and long-term consequences of a RRSO on urinary incontinence, as RRSO can have a significant impact on the HR-QoL. Future researchers should specifically take into account use of MHT, as the low proportion of MHT users in our study precluded subgroup analyses in MHT users.

5 | CONCLUSIONS

At the age of 60–70 years, more than 15 years after premenopausal RRSO, women reported slightly higher UI scores and slightly more symptomatic UI than women of similar age with a RRSO after natural menopause. However, these differences were not statistically significant and did not to lead to a lower HR-QOL in women with a premenopausal RRSO. Unexpectedly, we found an association between a premenopausal RRSO and SUI, which deserves further study. This study highlights the importance of addressing UI when counselling this special population of BRCA pathogenic variant carriers, as many women do not bring this subject up spontaneously.[23]

AUTHOR CONTRIBUTIONS

FEvL, MJH, AHEMM and LT were involved in the conception and design of the study. LT, FEvL, MJB, EE, MJEM, MJH and BAMH-G drafted the paper. MJB, JERvL, HCvanD, JAdH, EBLvD, CHM, BFMS, KNG, LEvdK, JMC, MRW, MGEMA, KvE, IvdB, LPVB, CJvA, EBGG, ABS and AHEMM were involved in the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

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SUPPORTING INFORMATION

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

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