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Associations between modifiable lifestyle factors and health-related quality of life among endometrial carcinoma survivors - A cross-sectional study

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HIGHLIGHTS

- Meeting WHO lifestyle recommendations is associated with improved HRQoL in endometrial carcinoma survivors.
- Survivors who are physically active or have a BMI <25 report better HRQoL than those who are sedentary or have BMI ≥25.
- Sufficient physical activity has the strongest association with improved HRQoL assessed by EORTC QLQ-C30.
- Physical activity should be a priority for endometrial carcinoma survivors and survivorship programs.
- Prospective studies are needed to assess the impact of modifiable life-style factors on HRQoL in cancer survivors.

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ABSTRACT

Objective. To explore possible associations between modifiable lifestyle factors and health-related quality of life (HRQoL) in endometrial carcinoma survivors by assessing differences in HRQoL between survivors meeting and not meeting the World Health Organization's (WHO) recommendations regarding physical activity, BMI, and smoking.

Methods. This was a cross-sectional population-based study in women having undergone surgery for assumed early-stage endometrial carcinoma. Thresholds for clinical importance based on the EORTC QoL working group were used to interpret scores. Effect size (ES) was interpreted as small (d = 0.2–0.49), medium (d = 0.5–0.8), and large (d > 0.8).

Results. In total, 1200 evaluable women were included. Meeting physical activity recommendations and BMI <25 kg/m2 was associated with significantly better global health status, (ES) = 0.18 and ES = −0.11, respectively. On multivariate analysis, women meeting physical activity recommendations had significantly higher scores on physical- (ES = 0.31), role- (ES = 0.15), and social functioning (ES = 0.15), and lower levels of fatigue (ES = −0.16), pain (ES = −0.10), and appetite loss (ES = −0.15) (all $p < 0.05$) compared to non-meeting survivors. Participants with BMI ≥25 kg/m2 had lower scores for social functioning (ES = −0.10), and higher levels of pain (ES = 0.13) and dyspnea (ES = 0.12) (all $p < 0.05$) compared to those with BMI <25 kg/m2. Smokers had lower scores for emotional functioning (ES = −0.09) and higher levels of diarrhea (ES = 0.10) (all p < 0.05) compared to non-smokers.

Conclusion. Meeting WHO recommendations for modifiable life-style factors is associated with better HRQoL among endometrial carcinoma survivors: Being sufficiently physical active and having a BMI <25 kg/m2 are

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significantly associated with better self-reported global health status. All modifiable factors are associated with better functioning, and reduced symptom-burden.

1. Introduction

Endometrial carcinoma is the most common gynecological malignancy in high-income countries. The incidence has increased over the past 30 years mainly due to women living longer, and an obesity pandemic [1]. Although there are substantial racial disparities in mortality for women with endometrial carcinoma [2], mortality rates have and may further decrease due to improved diagnostics and treatment options [3]. With a favorable prognosis, many patients can expect to live for several years after treatment [1]. Although the population of endometrial carcinoma survivors is rapidly increasing, little is known regarding health-related quality of life (HRQoL) [4].

Previous research shows that endometrial carcinoma survivors report lower HRQoL than the general population, mostly due to the disease and its treatment but also due to lifestyle behaviors [4]. Compliance with dietary and exercise recommendations has been shown to be positively related to HRQoL [5]. HRQoL dimensions are important indicators of cancer survivorship since they provide prognostic and predictive information as well as survivor experiences with cancer-related treatment and lifestyle changes [6]. Long-term survival and HRQoL can be improved by having an active lifestyle and maintaining a healthy weight [1,7]. Previous studies have shown that compared to more recent survivors, long-term cancer survivors are less likely to adhere to a variety of lifestyle recommendations [8]. There is insufficient high-quality evidence to determine the effect of lifestyle interventions on HRQoL in endometrial carcinoma survivors. The association between modifiable lifestyle factors and patient reported outcomes should be further investigated [4,5].

Previous efforts in HRQoL studies have focused on defining minimal important differences between various scores, attempting to offer a reference for interpreting differences in scores between groups or changes over time. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group recently provided novel thresholds for clinical importance to improve interpretation of the EORTC Quality of Life questionnaire version C30 (EORTC QLQ-C30) [9]. These new thresholds provide absolute scores based on; patient reported limitations of daily living, perceived need for help or care, and disease- or treatment-related worries by the patient or family/partner. In the current study, we explore the association between modifiable lifestyle factors and HRQoL among endometrial carcinoma survivors in a national health care system. We aimed to compare HRQoL between survivors who adhered to World Health Organization (WHO) recommendations regarding physical activity, body mass index (BMI), and smoking and those who did not.

2. Materials and methods

This study is part of the SENSOR-study [10], a population based cross-sectional study conducted at two tertiary referral centers, serving 66% of the Norwegian population. Regional Committees for Medical Research Ethics [11] approval and patient consent was obtained (reference 149,597 and 7193/2019). The CHERRIES checklist and STROBE recommendations were followed [12,13].

2.1. Data collection

Women treated for assumed early-stage endometrial carcinoma between 2006 and 2021 participated in the study. The study recruitment process has been previously described [10]. Demographics, comorbidities, tumor- and treatment-related factors at time of diagnosis was extracted from electronic medical records. Demographics and the following self-reported comorbidities were collected in the survey: heart disease, hypertension, lung disease, diabetes mellitus, ulcer/stomach disease, kidney disease, liver disease, anemia/blood disease, other cancer, depression, osteoarthritis, back pain, rheumatoid arthritis, thrombosis/pulmonary embolism, and other disease/health complaint. Responders were grouped according to WHO's definition of multimorbidity: coexistence of two or more chronic conditions [14]. Complete and incomplete questionnaires were analyzed, non-answered questions were treated as missing data.

2.1.1. Lifestyle factors

2.1.1.1. Physical activity. Levels of physical activity was assessed by the Nord-Trondelag Health Study Physical Activity Questionnaire (HUNT 4 PA-Q) [15], including three questions covering frequency, duration, and intensity of their physical activity. Each response was scored according to the index created by Kurtze et al. [16] ranging from 0 to 15. Scores <2.5 indicate insufficient activity, scores ≥2.5 indicate sufficient activity according to WHO recommendations on physical activity [17,18].

2.1.1.2. Body Mass Index. BMI was calculated using self-reported height and body weight at time of survey, and categorized according to WHO ranges [19]. When examining the relationship between BMI and HRQoL, responders were dichotomized into normal weight (BMI <25 kg/m^2) and overweight (BMI ≥25 kg/m^2). As most women with endometrial carcinoma are overweight, additional analyses were performed with BMI ≥30 kg/m^2 (Supplementary Table 2).

2.1.1.3. Smoking. Smoking was assessed with the question "Do you smoke?". Responses were dichotomized into current smokers (smoking daily or smoking now and then) and non-smokers (smoked previously or never smoked).

2.1.2. HRQoL measurements

EORTC QLQ-C30 [20] was used to asses HRQoL, containing 30 items covering global health status, five functional subscales (physical-, role-, cognitive-, emotional-, and social functioning), and nine symptom subscales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scores are transformed into a 0–100 scale; on the functional scales, high scores represent better functioning, on the symptom scales high scores represent higher symptom burden. We used thresholds for clinical importance established by the EORTC QoL Group [9], to interpret and compare scores between groups. Confidence intervals (CI) were used to compare mean values between groups for global health status as threshold values are not established for this item.

2.2. Statistical analysis

Continuous variables were normally distributed and therefore described with mean and standard deviation (SD), categorical data were presented as counts and percentages. Crude comparisons between responders and non-responders were performed using cross

tabulations and chi-square tests. Possible association between HRQoL subscales and selected lifestyle factors, demographic and disease related variables were modeled using univariate and multivariate linear regression. As the selected possible predictive factors were measured on different scales, the results are expressed as effect sizes (standardized B) to allow comparisons of regression coefficients, e.g. to allow for direct comparisons of the strength of association between given variables and the outcome. The effect size (ES) was calculated as Cohen's *d* and is interpreted as small (0.2–0.49), medium (0.5–0.8), and large (>0.8) effect. Cohen's *d* describes the mean difference to variability and ranges from −1 (the largest negative effect) to 0 (no effect) to 1 (the largest positive effect) [21]. Scoring manuals for EORTC QLQ-C30 were used [22]. All tests were two-sided and *p*-values <0.05 were considered statistically significant. All analyses were considered exploratory so no correction for multiple testing was done. Data were analyzed using the Statistical Package for the Social Sciences version 28 [23].

3. Results

In total, 1226 women responded to the questionnaire, yielding a response rate of 61%. Twenty-six women were not evaluable by EORTC QLQ-C30, leaving 1200 evaluable survivors (Fig. 1). Patient characteristics are presented in Table 1. Mean age at survey was 70.5 years (SD 9.2), mean BMI was 28 kg/m^2 (SD 5.6). Of note, 46% had received primary treatment >5 years ago, 88% of women had stage I/II disease, and 69% had undergone minimal invasive surgery. With regards to WHO recommendations; 532/1200 (46%) met physical activity recommendations, 368/1200 (32%) had BMI <25 kg/m^2 and 1067/1200 (92%) did not smoke (Table 2). Compared to non-responders, responders were significantly younger, had fewer comorbidities, were more likely to have received adjuvant chemotherapy and to have undergone minimally invasive surgery (Supplementary Table 1). Time since treatment was not statistically significantly associated with any of the explored variables.

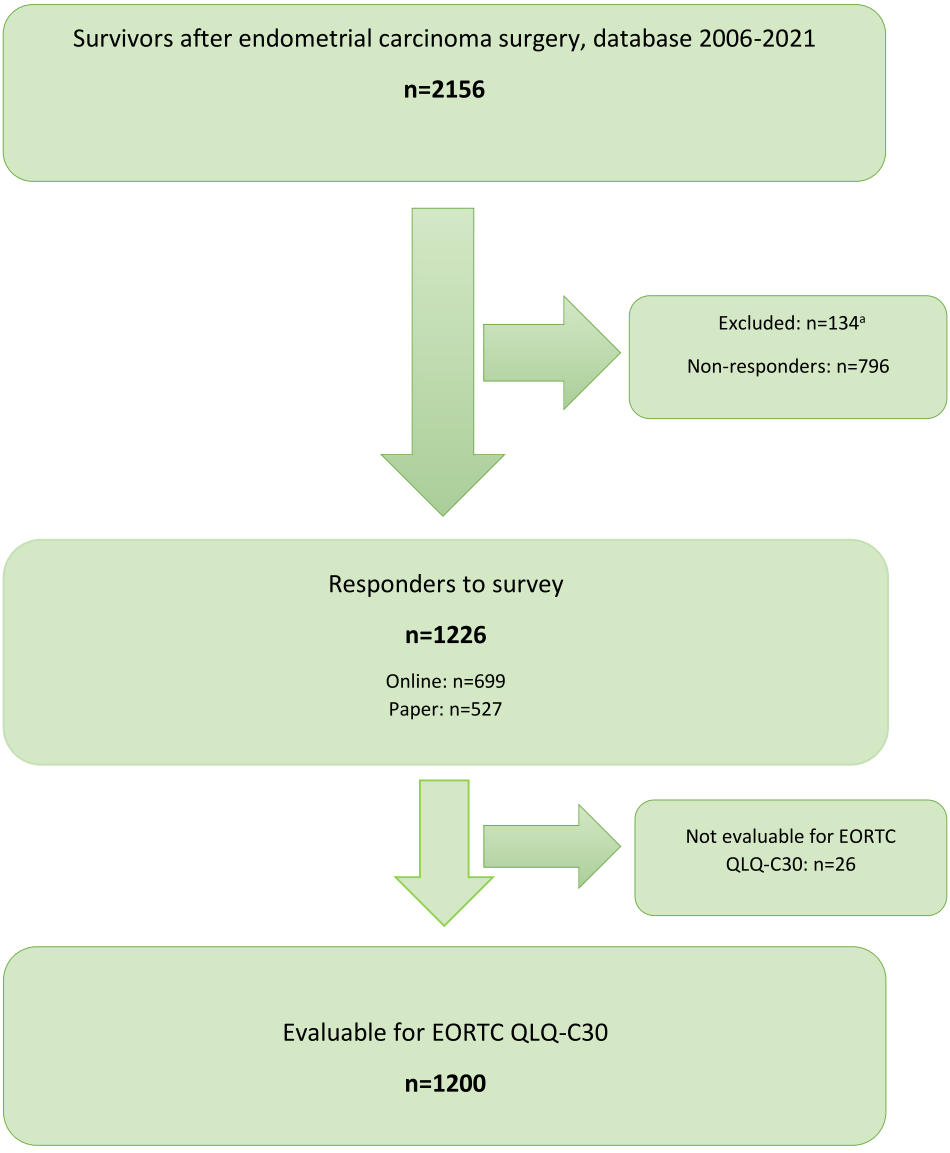

Fig. 1. Flow chart showing participation recruitment.
[a] Withdrawal of consent: n = 91.
Unknown postal address: n = 20.
Deceased during study period: n = 23.
Response rate = 61%.
Evaluable for EORTC QLQ-C30 = 59%.

Table 1
Clinicopathological characteristics of responders.

Age at survey Mean (SD) 71 (9)	n	%	Self-reported comorbidities	n	%
18–49	25	2	None	78	7
50–59	130	11	Low morbidity (<2)	120	10
60–69	376	31	High morbidity (≥2)	401	33
70–79	499	42	Missing	601	50
80+	170	14	Time since treatment		
Race			0–1 years	218	18
Caucasian	1184	99	1–3 years	240	20
Non-Caucasian	16	1	3–5 years	196	16
Marital status	1197		5+ years	546	46
Married/living with partner	744	62	FIGO stage		
Separated/divorced	105	9	I and II	1060	88
Single	138	12	III and IV	140	12
Widowed	210	18	Surgical modality		
Education level			Minimal invasive surgery	828	69
High school graduate or less	610	51	Laparotomy	372	31
Some college/college graduate	264	22	Chemotherapy		
Some graduate school or graduate degree	301	25	Yes	418	35
Missing	25	2	No	773	64
Employment status			Missing	9	1
Employed/homemaker	103	9	Radiation		
Retired	457	38	Yes	8	1
Unemployed/on disability/other	107	9	No	1183	99
Missing	533	44	Missing	9	1
BMI self-reported Mean (SD) 28 (6)			Recurrence		
0–18.4	15	1.3	Yes	66	6
18.5–24.9	351	29	No	1125	94
25–29.9	431	36	Missing	9	1
30–34.9	248	21			
35–39.9	74	6			
40+	38	3			
Missing	43	4			

SD = Standard deviation.

Table 2
Quality of Life measured by EORTC QLQ-C30 reported as the number and % of women being over thresholds for clinical importance determined by the EORTC QoL group, stratified by meeting or not meeting WHO lifestyle recommendations for physical activity, BMI, and smoking.

Lifestyle factors	Physical activity			BMI at survey			Smoking		
	≥2.5 points	<2.5 points		<25	≥25		No	Yes	
n (%)	532 (46)	622 (54)		368 (32)	791 (68)		1067 (92)	92 (8)	
EORTC QLQ-C30 Global health status[a] Mean (95% CI)	76.3 (74.6–78.0)	67.5 (65.8–69.2)		76.9 (74.9–79.1)	68.9 (67.5–70.4)		71.8 (70.5–73.1)	67.2 (62.3–72.0)	
Functional scales (Threshold value)	n (%)	n (%)	p-value	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Physical functioning (83)	327 (65)	206 (35)	<0.001	218 (63)	325 (43)	<0.001	498 (49)	42 (49)	0.9
Role functioning (58)	460 (90)	474 (80)	<0.001	307 (87)	629 (83)	0.1	866 (85)	69 (79)	0.2
Cognitive functioning (75)	392 (78)	461 (77)	0.8	283 (81)	571 (75)	<0.05	792 (77)	60 (71)	0.2
Emotional functioning (71)	408 (81)	461 (78)	0.2	286 (82)	581 (77)	0.1	804 (79)	62 (73)	0.2
Social functioning (58)	453 (89)	481 (80)	<0.001	314 (89)	622 (82)	<0.05	869 (85)	67 (79)	0.2
Symptom scales (Threshold value)	n (%)	n (%)	p-value	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Fatigue (39)	118 (23)	220 (37)	<0.001	82 (24)	264 (35)	<0.001	314 (31)	36 (41)	<0.05
Pain (25)	188 (37)	298 (51)	<0.001	119 (34)	370 (49)	<0.001	442 (43)	43 (51)	0.2
Nausea and vomiting (8)	81 (16)	96 (16)	0.9	56 (16)	129 (17)	0.8	166 (16)	16 (19)	0.5
Dyspnea (17)	178 (35)	286 (47)	<0.001	100 (28)	367 (48)	<0.001	419 (41)	45 (52)	<0.05
Insomnia (50)	119 (23)	161 (27)	0.2	92 (26)	192 (25)	0.7	250 (24)	30 (35)	<0.05
Appetite loss (50)	9 (2)	37 (6)	<0.001	18 (5)	29 (4)	0.3	36 (4)	8 (9)	<0.05
Constipation (50)	39 (12)	40 (12)	0.8	31 (15)	47 (11)	0.1	72 (12)	4 (9)	0.5
Diarrhea (17)	169 (33)	202 (34)	0.8	88 (25)	290 (38)	<0.001	337 (33)	40 (47)	<0.05
Financial difficulties (17)	59 (12)	71 (12)	0.9	25 (7)	105 (14)	<0.05	112 (11)	18 (21)	<0.05

CI = Confidence interval.
p-values describe the statistical differences between women who met and did not meet WHO lifestyle recommendations for physical activity, BMI and smoking statistically significant *p*-values in bold.
[a] Mean score with 95% Confidence interval (no threshold for clinical importance).

(a)

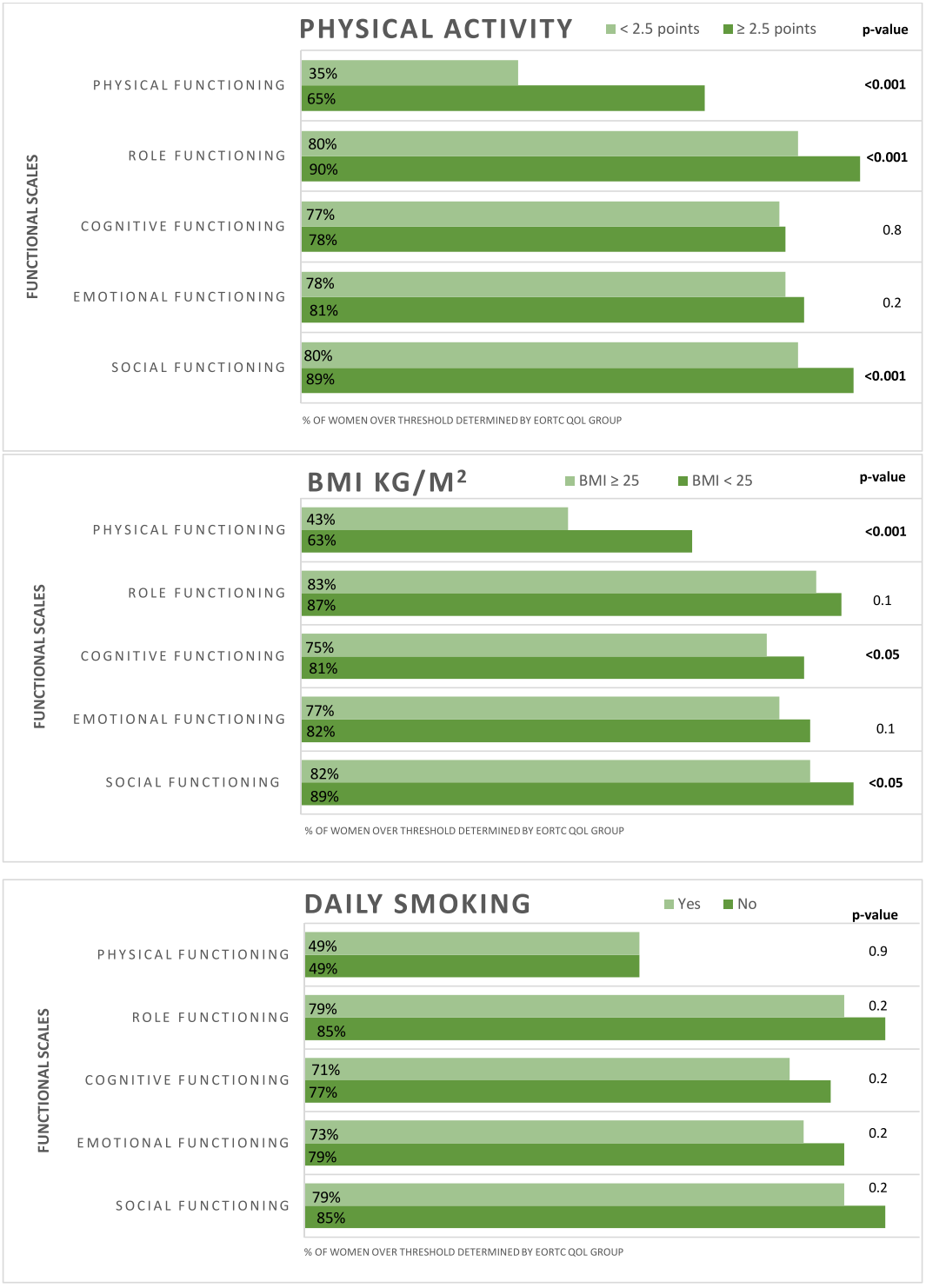

Fig. 2. a and b: EORTC QLQ-C30 functional- and symptom scales. Proportions of women who are over thresholds for clinical importance, stratified by if they met WHO recommendations or not. Bars in light green and dark red represent women not meeting WHO recommendations regarding physical activity, BMI and smoking.

3.1. Global health status

Women who met WHO recommendations for physical activity and those who reported BMI <25 kg/m^2 had significantly higher mean global health status scores compared to those who did not meet these two criteria: 76.3 points, (95% CI [74.6–78.0]) vs. 67.5 points (95% CI [65.8–69.2]) and 76.9 points (95% CI [74.9–79.1]) vs. 68.9 points (95% CI [67.5–70.4]), respectively. There was no statistically significant difference in global health status scores between smokers and non-smokers (Table 2).

3.2. Functional- and symptom scales

Results are reported in Table 2 and Fig. 2a and 2b.

(b)

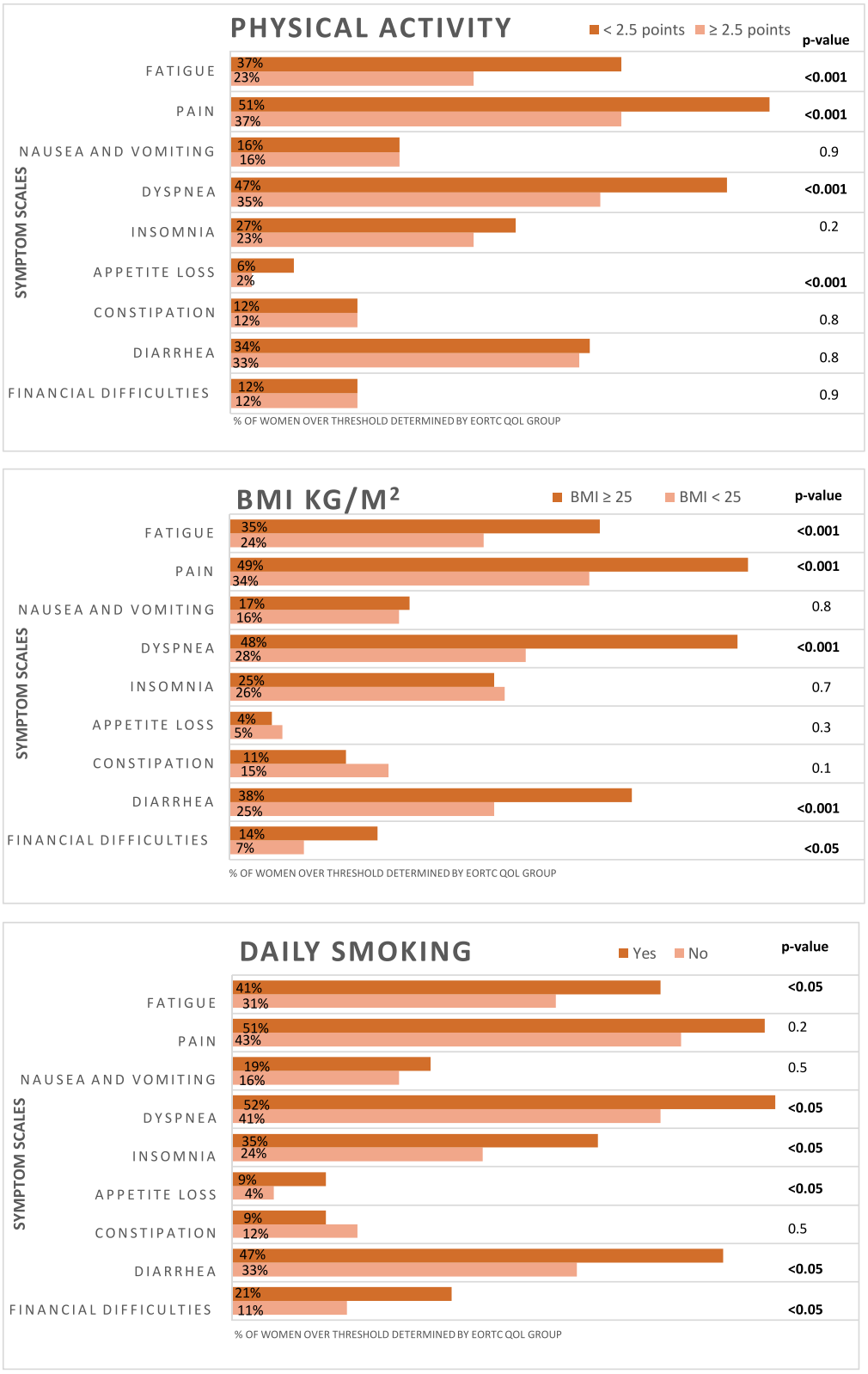

Fig. 2 (*continued*).

3.2.1. Functional scales

3.2.1.1. Physical activity. Among women who met WHO recommendations for physical activity, 65% were over thresholds for clinical importance for physical functioning, compared to 35% of women who did not meet recommendations, respectively ($p < 0.001$). The proportions were as follows for the two remaining significant associations for the functional scales; role- (90% vs. 80%, $p < 0.001$) and social functioning (89% vs. 80%, $p < 0.001$).

3.2.1.2. Body Mass Index. Regarding BMI; 63% of women with BMI <25 kg/m^2 were over thresholds for clinical importance for physical

functioning compared to 43% of women with BMI ≥25 kg/m^2, respectively ($p < 0.001$). The proportions being as follows for the remaining two significant associations for functional scales: cognitive- (81% vs. 75%, $p < 0.05$) and social functioning (89% vs. 82%, $p < 0.05$). When exploring for BMI >30 kg/m^2, cognitive functioning was no longer significant.

3.2.1.3. Smoking. No statistically significant differences were detected between smokers and non-smokers for any investigated domains.

3.2.2. Symptom scales

3.2.2.1. Physical activity. Among women who met WHO recommendations for physical activity, 23% were over thresholds for clinical importance for fatigue compared to 37% among women who did not meet recommendations for physical activity, respectively ($p < 0.001$). The proportions were as follows for the remaining significant associations for symptom scales; pain (37% vs. 51%, $p < 0.001$), dyspnea (35% vs. 47%, $p < 0.001$) and appetite loss (2% vs. 6%, $p < 0.001$) for women who met or did not meet WHO recommendations, respectively.

3.2.2.2. Body Mass Index. Among women with BMI <25 kg/m^2, 24% were over thresholds for clinical importance for fatigue compared to 35% among women with BMI ≥25 kg/m^2, respectively ($p < 0.001$). The proportions were as follows for the remaining significant associations for symptom scales; pain (34% vs. 49%, $p < 0.001$), dyspnea (28% vs. 48%, $p < 0.001$), diarrhea (25% vs. 38%, $p < 0.001$), and financial difficulties (7% vs. 14%, $p = 0.001$) for women with BMI <25 kg/m^2 compared to ≥25 kg/m^2, respectively.

3.2.2.3. Smoking. Among non-smokers, 31% were over thresholds for clinical importance for fatigue compared to 41% among smokers, respectively ($p < 0.05$). The proportions were as follows for the remaining significant associations for symptom scales; dyspnea (41% vs. 52%, $p < 0.05$), insomnia (24% vs. 35%, $p < 0.05$), appetite loss (4% vs. 9%, $p < 0.05$), diarrhea (33% vs. 47%, $p < 0.05$), and financial difficulties (11% vs. 21%, $p < 0.05$) for non-smokers compared to smokers, respectively.

3.2.3. Adjustment for demographics and disease related factors

After adjusting for demographics and disease related factors (age, marital status, education, comorbidity, FIGO stage, surgical modality, adjuvant chemotherapy, and recurrence) (Table 3); physical activity and BMI remained significantly associated with global health status, ES = 0.18 and ES = −0.11, respectively.

After adjustment, physical- (ES = 0.31), role- (ES = 0.15), and social functioning (ES = 0.15) remained significantly associated with meeting WHO recommendations for physical activity. BMI remained significantly associated with social functioning (ES = −0.10). Smoking became significantly associated with emotional functioning (ES = −0.09), even though there was no difference between smokers and non-smokers when comparing shares over threshold for clinical importance. Of the independent variables used in multivariate analysis, physical activity demonstrated the strongest association with physical- (ES = 0.31), role- (ES = 0.15), and social functioning (ES = 0.15). Age demonstrated the strongest association with cognitive- and emotional functioning (ES = 0.17 and 0.18) respectively.

After adjustment, fatigue (ES = −0.16), pain (ES = −0.10), and appetite loss (ES = −0.15) remained significantly associated with meeting WHO recommendations for physical activity. BMI was significantly associated with pain (ES = 0.13) and dyspnea (ES = 0.12). Smoking was significantly associated with diarrhea (ES = 0.10). Among all independent variables used in the multivariate analysis the following factors were the strongest predictive factors: physical activity for fatigue (ES = −0.16) and appetite loss (ES = −0.15), BMI for pain (ES = 0.13) and dyspnea (ES = 0.12), smoking for diarrhea (ES = 0.10), recurrence for nausea and vomiting (ES = 0.13) and constipation (ES = 0.17), and age for financial difficulties (ES = −0.37). None of the variables tested were significant predictive factors for insomnia.

When exploring the effect of BMI as <25, 25–29.9 and ≥30 kg/m^2 on the QoL domains, BMI is only statistically significant for BMI ≥30 kg/m^2 and associated with the domains of physical functioning, fatigue, appetite loss and diarrhea (Supplementary Table 2).

4. Discussion

This large population-based study aimed to investigate the strengths of associations between modifiable lifestyle factors and HRQoL among endometrial carcinoma survivors. Overall, our findings demonstrate that self-reported adherence to WHO recommendations for physical activity levels and having a BMI <25 kg/m^2 are associated with better global health status, better functioning, and lower symptom burden. Abstaining from smoking was not associated with global health status but with better function status and lowered symptom burdens. Overall, the effect sizes for lifestyle factors and other relevant clinical variables were small. This is in line with previously reported data both for endometrial carcinoma survivors and survivors of other cancers such as breast, colorectal and prostate [24,25].

Given that endometrial carcinoma survivors represent an older, overweight/obese population with a substantial period of survivorship after initial treatment, adherence to a number of lifestyle recommendations is beneficial [8]. Previous studies investigating lifestyle factors and their relation to HRQoL have used different ways of classifying lifestyle behaviors, as well as a variety of different measurement tools for capturing HRQoL. Although the EORTC QLQ-C30 is most used [26–29], there is no general consensus or gold standard for HRQoL questionnaires, making direct comparisons between studies challenging. Our study is, to the best of our knowledge, the first to use EORTC QoL working group thresholds for clinical importance to compare HRQoL between groups. We believe this is a clinically meaningful tool and hope to see it utilized in future publications and studies from other groups.

4.1. Meeting WHO lifestyle recommendations

The WHO 2020 guidelines [17] on physical activity and sedentary behavior, recommend average weekly volumes of aerobic and muscle-strengthening activities of 150–300 min of moderate intensity or 75–150 min of vigorous intensity, or an equivalent combination. In our study, almost half of the study cohort was sufficiently physically active. This is in contrast to a previous cross-sectional study published 15 years ago, reporting 34% of endometrial carcinoma survivors being sufficiently physically active [27]. There is evidence that elderly women today have better physical functioning, compared to a decade ago, which may explain the noted difference [30]. Nearly 70% of women in our study were overweight or obese, with a BMI ≥25 kg/m^2. This is in line with findings from previous studies [26–28] and is expected in a population of endometrial carcinoma survivors as obesity or overweight is one of the main risk factors for this disease [1]. The cut-off of BMI ≥30 kg/m^2 may be more relevant for endometrial carcinoma survivors than BMI ≥25 kg/m^2. We therefore further explored the associations between BMI categorized as BMI <25-, 25–29.9- and ≥30 kg/m2 and EORTC QLQ-C30 subscales. The associations became stronger with the addition of statistical significance for more subscales and the associations were no longer statistically significant for women with BMI <30 kg/m2. The new effect sizes remained small, with small changes when compared with the analysis where BMI was dichotomized. The proportion of women with BMI ≥25 kg/m^2 in our study is much higher than in the general Norwegian population; 52% for women 65–74 years and 47% for women ≥75+ years [31]. The high proportion

Table 3
Multivariate linear regression with lifestyle factors, demographics and disease related factors as independent variables, and EORTC QLQ-C30 subscales as dependent variables. Displayed numbers are effect sizes (standardized B).

	Global Health Status	Functional scales					Symptom scales								
		Physical functioning	Role functioning	Cognitive functioning	Emotional functioning	Social functioning	Fatigue	Pain	Nausea and vomiting	Dyspnea	Insomnia	Appetite loss	Constipation	Diarrhea	Financial difficulties
Lifestyle															
Physical activity[a]	**0.18****	**0.31****	**0.15***	−0.03	0.03	**0.15***	**−0.16****	−0.10*	−0.08	−0.05	0.02	**−0.15***	−0.09	0.02	−0.03
BMI[b]	−0.11*	−0.08	−0.03	−0.05	0.01	−0.10*	0.08	**0.13***	−0.01	**0.12***	0.02	−0.09	−0.08	0.07	0.02
Smoking[b]	−0.02	−0.01	−0.01	−0.08	−0.09*	0.00	0.01	0.01	−0.02	0.01	0.02	0.03	0.00	**0.10***	0.07
Demographics															
Age[c]	0.04	−0.17**	−0.01	**0.17****	**0.18****	0.12*	−0.03	−0.04	−0.09*	0.03	−0.07	−0.03	0.01	−0.03	**−0.37****
Marital status[d]	−0.02	−0.04	−0.02	−0.05	0.03	−0.01	0.02	−0.01	−0.08	0.07	−0.06	0.00	−0.14*	0.00	0.07
Education[e]	0.10*	0.06	0.09*	0.04	0.07	0.03	0.00	−0.11*	−0.03	−0.06	−0.04	−0.07	−0.06	−0.10*	−0.10*
Comorbidity[f]	−0.05	−0.01	−0.01	−0.04	−0.06	−0.01	0.04	0.02	0.11*	−0.03	0.02	0.04	−0.02	0.01	0.02
Disease related															
FIGO stage[g]	0.06	0.01	0.04	−0.00	−0.05	−0.02	−0.03	0.03	−0.03	−0.02	**−0.07**	−0.06	0.00	−0.03	0.01
Surgical Modality[h]	0.01	0.06	0.02	−0.01	−0.04	0.03	0.03	−0.01	−0.02	0.03	0.01	0.02	0.01	−0.04	−0.03
Adjuvant chemotherapy[i]	−0.08	−0.06	−0.04	−0.07	0.05	−0.07	0.04	0.01	−0.03	−0.00	0.04	0.03	0.02	−0.02	−0.03
Recurrence[i]	−0.09*	−0.08	−0.14*	−0.09*	−0.10*	−0.12*	0.11*	0.08	**0.13***	0.01	0.04	0.15**	**0.17***	0.09	0.12*

Bold = highest effect size.
[a] Sorted ascending from insufficient physically active to sufficiently physically active.
[b] Sorted ascending from BMI <25 to BMI ≥25 and smoking no to yes.
[c] Numeric.
[d] Sorted ascending as follows: Married/living with partner ➔ separated/divorced ➔ single ➔ widowed.
[e] Sorted ascending as follows: high school graduate or less ➔ some college/college degree ➔ some graduate school/graduate school.
[f] Sorted ascending as follows: none ➔ low ➔ high.
[g] Sorted ascending as follows: Stage I/II ➔ III/IV.
[h] Sorted ascending as follows: minimal invasive ➔ laparotomy.
[i] Sorted ascending from no to yes.
* $p < 0.05$.
** $p < 0.001$.

of obese survivors, renders BMI a modifiable factor with room for clinical improvement. The low percentage of smokers in our study is comparable to the general population in Norway [32], and to that previously reported by Beesley et al. [27] and Grimmett et al. [33] The small percentage of daily smokers can lead to lack of statistical power and may have impacted our results.

4.2. Global health status

Our study showed a positive association between being sufficiently physically active and/or having a BMI <25 kg/m^2, and better global health status. Similar associations have previously been demonstrated for colorectal cancer survivors [25,33]. The study by Schleisinger and collegues [25], investigated several lifestyle factors and found the strongest association between BMI and global health status. Zainordin and colleagues, could however not demonstrate this association in a recent study among breast and gynecological cancer survivors [26]. This study assessed intensity of physical activity and sitting time by the international physical activity questionnaire (IPAQ). Respondents were younger (mean age 52 years) with shorter time since surgery, and only 12 of 95 responders were endometrial carcinoma survivors. These differences may explain the contrasting findings. In line with previous studies [27,33], smoking was not associated with global health status in our study.

4.3. Functional scales

Our study found that physical-, role-, emotional-, and social functioning were the functional domains where meeting WHO recommendations for one or more lifestyle factors was favorable. Physical functioning was significantly better among those meeting recommendations for physical activity, and a substantial higher proportion of women meeting recommendations for physical activity were over thresholds for clinical importance for physical functioning. Robertson and colleagues [29] recently published findings that increasing levels of physical activity led to improvements in both physical health and overall health in endometrial carcinoma survivors, further supporting our findings.

BMI and smoking did not have a significant effect on physical function after adjusting for demographics and disease related factors. However, when comparing the proportion of women over thresholds for clinical importance for physical functioning between women who met WHO recommendations for BMI and those who did not, there was a significantly higher percentage of women with BMI <25 kg/m^2 who were over thresholds for physical functioning. This finding suggests that among women with BMI <25 kg/m^2, other factors may affect their physical functioning. This is supported by a recent systematic review where sufficient levels of physical activity were found to be more beneficial for reducing obesity-related diseases than focusing on reducing obesity itself. This review found that the risk of obesity-related diseases is more likely caused by insufficient physically activity among obese than the effect of obesity Itself [34].

Role functioning was significantly better among those meeting recommendations for physical activity, and a larger portion of women who were sufficiently physically active were over thresholds for clinical importance than those who were insufficiently active. The domain for role functioning contains questions regarding if responders are limited in their work, daily activities, or hobbies. Some women with lower scores for role functioning may have been limited in these areas due to not being able to be sufficiently physically active. Previous studies have not found this association between physical activity and role functioning in colorectal, breast or gynecologic cancer survivors [26,33].

Emotional functioning was significantly reduced for smokers. We did however not detect a significant difference between non-smokers and smokers when exploring proportions over thresholds for clinical importance for emotional functioning, although it still had a small predictive effect. Our findings are in contrast to studies among colorectal cancer survivors exploring the association between smoking and HRQoL measured by EORTC QLQ-C30 [25,33], as well as studies exploring this association measured by other HRQoL measurement tools among gynecological cancer survivors [27,35]. Despite a statistically significant difference detected in our study, the effect size is small and may not be clinically significant. This is reflected in our finding of no difference in proportions over and under thresholds for clinical importance and highlights the importance of reliable tools for measuring clinically meaningful differences in HRQoL.

In our study, social functioning was significantly better by being sufficiently physically active and having a BMI <25 kg/m^2. Zainordin and colleagues [26] did not find the same association between physical activity and social functioning in a recent study. In fact, in their study, participants with increased sitting time (hours per day sitting or lying down excluding time spent sleeping) had higher social functioning than those who were sufficiently physically active. The authors hypothesize that although the underlying endometrial carcinoma and its related therapy can lead to social isolation, the support of close friends and family could have led to better social functioning. Interestingly, the EORTC thresholds for clinical importance used in our study, are based on patient reported limitations of daily living, perceived need for help or care, and disease- or treatment-related worries by the patient *or family/partner* [9]. These thresholds therefore account for both the patient and caregiver perspectives, as may be reflected in our findings.

Social functioning was the only functioning domain where BMI was a predictive factor. High BMI (≥25 kg/m^2) was negatively correlated with social functioning. People who are obese are reported to have an increased fear of social rejection compared to those with a normal BMI [36]. This may have contributed to our findings. Our results are in contrast to those for colorectal cancer survivors [25,33] and to the cross-sectional study by Beesley et al. from 2008 [27] where no such association was found for endometrial carcinoma survivors. As expected, there are more women with obesity in our study population than in studies for colorectal cancer survivors, which may have influenced the differing findings.

None of the lifestyle factors were significant predictive factors for cognitive functioning. Also, when comparing women who met and did not meet the WHO recommendations for lifestyle factors there were no significant differences between the groups for this domain. In contrast, Grimmett et al. [33] found that being overweight resulted in better cognitive functioning. In their study, about 50% of responders were overweight, compared to 68% in our study. Also, our study only included women, whereas reports on colorectal cancer survivors include both genders, which could influence results.

The proportions of women over thresholds for clinical importance were high for all functional scale domains for all lifestyle factors in our study. Age was the strongest predictive factor for cognitive functioning, suggesting that overall, endometrial carcinoma survivors have good cognitive functioning.

4.4. Symptom scales

Our study revealed that meeting WHO recommendations for one or more lifestyle factors was positively associated with fatigue, pain, dyspnea, appetite loss and diarrhea. Previous studies have presented conflicting findings regarding the association between physical activity and fatigue [26,33]. Fatigue is a commonly noted sequelae after cancer therapy. Increased levels of fatigue may lead to lower levels of physical activity [37]. However, once physically active, this may reverse the treatment-related fatigue. Our findings would support this hypothesis.

In line with our findings, increased levels of physical activity have previously been associated with decreased levels of pain [29]. Grimmett

and colleagues found that obesity was associated with less pain in colorectal cancer survivors [33]. The cross-sectional design of our study does not allow us to draw firm conclusions, however obesity in general is linked to joint pain [38], and our findings could partly by explained this. By the same token, our finding of an association between obesity (BMI ≥25 kg/m^2) and higher symptom burden for dyspnea is in line with the literature for colorectal cancer survivors [33] and the population at large [39].

Our study revealed an association between being sufficiently physically active and decreased symptom burden for appetite loss. We also found a higher symptom burden of diarrhea in smokers. This is in contrast to previously published results from studies in colorectal cancer survivors [25,33] and gynecologic cancer survivors [27,35]. This discrepancy could be due to the small number of smokers in our study-population.

Previous studies have reported associations between BMI and nausea [33] and between physical activity and constipation [26]. In our study, lifestyle factors did not influence nausea and vomiting or constipation. In our study-population, recurrence was the strongest predictive factor for these symptoms, which could be explained by potentially receiving tumor-directed therapy. We could *not* find an association between lifestyle factors and insomnia or financial difficulties. Our finding regarding financial difficulties is in line with previous studies. However, previous studies have reported that sufficient physical activity in cancer survivors is associated with decreased symptom burden for insomnia [26,33].

4.5. Strengths and limitations

Our study confirms findings previously reported in smaller studies. It adds knowledge about modifiable lifestyle factors and their associations with HRQoL, assessed by the novel EORTC thresholds of clinical importance. As our study is based on responses from an unselected population in a public health care system, with small differences between responders and non-responders, we believe our findings are generalizable to endometrial carcinoma survivors in countries with similar demographics.

Limitations to our study include the retrospective design with its inherent biases. Our results suggest that identifying and motivating women who are not sufficiently physically active, or who have a BMI ≥25 kg/m^2 could benefit their HRQoL and well-being. In this cross-sectional study design, causality can not be inferred. It is also possible that detected difference can be explained by other underlying variables which were not assessed in our study. Some of which may be biological, non-modifiable factors. Additionally, self-reported data on HRQoL, weight, height, smoking, and physical activity level can be biased, as behaviors thought to be favorable such as physical activity are often over-reported and behaviors and traits thought to be negative such as smoking and high BMI are frequently under-reported [40]. Finally, we have not reported alcohol consumption, another modifiable behavior which could influence HRQoL.

5. Conclusions

In conclusion, modifiable lifestyle factors can impact HRQoL in endometrial carcinoma survivors. Women after initial therapy for endometrial carcinoma should be informed that being physically active and maintaining a normal BMI may ensure better global health status, better functioning, and lower symptom burdens. There is currently paucity of high-quality evidence to determine the effect of lifestyle interventions on quality of life and survival in endometrial carcinoma survivors. This should be the focus of future studies.

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Author contribution section

Linn Ø. Opheim: Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, final approval. **Ida Engeskaug:** Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, final approval. **Pernille K. Bjerre Trent:** Conceptualization, Investigation, Formal analysis, Writing - review & editing, final approval. **Lene Thorsen:** Conceptualization, Writing – review & editing, final approval. **Anne Cathrine Staff:** Conceptualization, Writing – review & editing, final approval. **Nina Jebens Nordskar:** Conceptualization, Writing - review & editing, final approval. **Inger Utne:** Conceptualization, Data curation, Writing – review & editing, final approval. **Milada Hagen:** Conceptualization, Data curation, Formal analysis, Writing – review & editing, final approval. **Ane Gerda Z. Eriksson:** Conceptualization, Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, final approval.

Consent statement

Written informed consent was obtained from study participants for publication of this study. A copy of the written consent is available for review by the Editors-in-Chief of this journal on request.

Declaration of Competing Interest

Ane Gerda Z. Eriksson reports receiving speakers' fees from Intuitive surgical and GSK.

Other authors report no conflict of interest.

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