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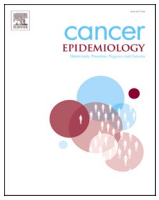

Healthy lifestyle and the risk of endometrial cancer

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ABSTRACT

Background: The incidence and mortality rate of endometrial cancer (EC) is increasing worldwide. Modifiable lifestyle factors associated with an increased or decreased risk of cancer typically cluster. Therefore, this study aimed to investigate the association between a healthy lifestyle, measured with a Healthy Lifestyle Index (HLI), based on diet, smoking, alcohol consumption, physical activity and Body Mass Index (BMI), and the risk of EC.
Methods: A case-cohort analysis was conducted using data from the prospective Netherlands Cohort Study on Diet and Cancer (n = 62,573). At baseline in 1986, participants (aged 55–69) completed a questionnaire on potential cancer determinants. Data on aforementioned risk factors were used to calculate an HLI-score, ranging 0–20, with higher scores reflecting a healthier lifestyle. Cox regression analyses were used to estimate hazard ratios (HR's) and 95 % confidence intervals (CI's) for the association between HLI-score and EC risk in 414 cases and 1593 subcohort women, after 20.3 years of follow-up. After stratification by smoking status, Cox regression was applied using an HLI-score without smoking.
Results: The HR for the total HLI score was 0.86 (95 %CI 0.78–0.94) per 1 standard deviation (SD) increment. The HR for the HLI score without smoking component was 0.75 (95 %CI 0.67–0.83) for non-smokers (never smoked or former smoker >10 years ago) and 0.85 (95 %CI 0.70–1.02) for recent smokers (current or former smoker <10 years ago), all per 1 SD increment. Sensitivity analyses excluding each HLI component show that BMI and physical activity are the main drivers of the inverse association between HLI-score and EC.
Conclusion: A healthier lifestyle, measured with an HLI based on diet, alcohol consumption, physical activity, BMI and smoking is associated with a reduced EC risk. The association is stronger for non-smokers.

1. Introduction

Endometrial cancer (EC) is the seventh most common cancer in women worldwide [1]. The highest incidence rates are observed in Northern America, Northern and Western Europe, resulting in approximately 661,021 new cases and 348,189 deaths worldwide in 2022 [1]. The incidence and mortality rate and consequently the burden of EC is increasing worldwide (2018 incidence rate: 382,069 and mortality rate 89,929) [2].

Age and a family history of EC are established non-modifiable risk factors for EC [3,4]. Exposures associated with increased oestrogen exposure, such as high body mass index (BMI), use of oestrogen hormone therapy, early age at menarche and late age at menopause are associated with an increased risk of EC. Factors associated with a greater progestogen exposure such as the use of oral contraceptives, parity and having an older age at last childbirth are well-known protective factors for EC [3,5–8]. These associations can be explained by the unopposed oestrogen hypothesis. This theory states that the development of EC is associated with exposure to endogenous or exogenous oestrogen unopposed simultaneously by a progestogen [7,9].

Literature suggests that a diet with a high glycaemic load is a probable risk factor for EC, while physical activity of all types is probably a lifestyle-related factor associated with a reduced risk of developing EC [3,4,10,11]. Cigarette smoking is associated with a reduced risk of developing EC, in contrast to the increased risk for other cancers. Previous research attributed this to smokers having less body fat and lower levels of endogenous oestrogen [3,4,12,13]. The effect of alcohol consumption on EC is still inconclusive [4].

Most previous research has focused on understanding the etiology of EC by examining individual risk factors. However, lifestyle factors

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typically cluster and these clusters may be associated with increased or decreased risk of chronic disease. This combined association of lifestyle risk factors can be assessed using a Healthy Lifestyle Index (HLI) [14]. The selected components are modifiable risk factors that are associated with the risk of cancer and other lifestyle-related chronic diseases (i.e. diabetes mellitus, hypertension and coronary heart diseases) [15,16].

Only three previous studies have investigated the joint effects of determinants on the development of EC, by assessing the combined association between lifestyle-related risk factors with an HLI and the risk of EC. They concluded that an overall healthy lifestyle reduces the risk of EC [14,17,18]. By examining the relationship between HLI and endometrial cancer risk in another population as in the previous studies, this study adds additional evidence. The population in this cohort used less hormonal replacement therapy and oral contraceptives than in the earlier studies.

In this study we investigated the association between a healthy lifestyle, operationalised by an HLI consisting of diet, smoking, alcohol consumption, physical activity and BMI and the risk of EC. This study was conducted within the framework of the Netherlands Cohort Study on Diet and Cancer (NLCS), a large prospective cohort study with a large number of cases, a long follow-up and detailed information regarding relevant confounders.

In addition, because of the inverse association between smoking and EC observed in the literature, a sensitivity analysis was performed by recalculating the HLI without smoking and repeating the analyses. Finally, other risk factors identified in the literature such as the use of oral contraceptives, parity and hormone replacement therapy were explored to identify modification or distortion in the effect of a healthy lifestyle measured with an HLI and the risk of EC.

2. Materials and method

2.1. Cohort

The NLCS is a prospective cohort study initiated in September 1986 to investigate the association between diet and cancer. The cohort consists of 120 852 subjects aged 55–69 years from the general population, sampled from 204 municipal population registries. Inclusion was based on the return of the baseline self-administered questionnaire on potential determinants of cancer. Of the subjects, 51.8 % were women (n = 62,573).

For efficiency of data entry and vital status follow-up, a case-cohort approach was used by selecting a random subcohort of 2 589 women immediately after baseline of the NLCS in 1986 to estimate the person-time-at-risk for the entire cohort. Follow-up of cancer incidence in the entire cohort was performed by record linkage with the Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank (PALGA). For follow-up of migration status and vital status, subcohort members were followed up by mail every two years until the year 2000, and thereafter by record linkage with the automated municipal population registries. Details of the study have been described elsewhere [19]. After excluding women with cancer at baseline, data were available for analysis on 579 cases of EC (ICD-10-CM code C54 - malignant neoplasm of corpus uteri) occurring during 20.3 years of follow-up and 2 432 subcohort members.

2.2. Questionnaire

At baseline, subjects completed a 150-item semi-quantitative food frequency questionnaire (SFFQ) about their dietary habits over the past year, supplemented with questions about potential risk factors for cancer. Height (centimetres) and weight at baseline (kilograms) were requested to calculate participants BMI (kg/m^2). Information on smoking habits and alcohol consumption was collected. To obtain information on non-occupational physical activity (minutes/day), the number of minutes spent walking or cycling to work was added to the number of minutes spent shopping, walking the dog, gardening, odd jobs, recreational walking or cycling and other sports [20,21].

Information was collected on whether a participant had children, the number of children and the age at first childbirth, and on the history of cancer and type of cancer in parents and siblings. Hormonal determinants were obtained by asking questions about age at menarche/menopause, oral contraceptives (use, age when started, years of use) and hormone replacement therapy (use, years of use) [19]. The validity and reliability of the SFFQ have been assessed and found to be adequate [22,23].

In the NLCS, participants with incomplete and inconsistent dietary information were excluded from the analyses (7 %). The exclusion criteria used were based on the number of questions or blocks with blank items and the number of items that were eaten once a month [23].

2.3. Healthy lifestyle index

The HLI used in this analysis to examine the different determinants of interest and their joint effects is based on the HLI developed by McKenzie et al. Like this original HLI, our HLI consists of five lifestyle-related determinants, including diet, smoking, alcohol consumption, non-occupational physical activity and BMI [24]. These determinants were collected at baseline in the NLCS using the self-administered questionnaire. Each component is scored on a scale of 0–4, with cut-off values for BMI and smoking identical to those used by McKenzie et al. [24]. For alcohol consumption and physical activity, the commonly used cut-off values from the NLCS were chosen because of the small number of participants with a high alcohol consumption in the NLCS and the otherwise skewed distribution, and the fact that the NLCS only asked about- non-occupational physical activity [25]. Occupational and household physical activity were not taken into account. To assess participant's dietary habits, a dietary score was obtained based on the energy-adjusted intake of fibre, red/processed meat, the ratio of poly-unsaturated to saturated fat, trans-fats, glycaemic load, and vegetables and fruit. Each component was divided into sex-specific deciles in the subcohort (0: unhealthiest behaviour; 9: healthiest behaviour). The sum score of these dietary components was divided into sex-specific quintiles (0−4). This score was summed up with the BMI score (0 = > 30 kg/m^2, 1 = 26–29.9 kg/m^2, 2 = 24–25.9 kg/m^2, 3 = 22–23.9 kg/m^2, 4 = < 22 kg/m^2), the alcohol score (0 = > 30 g/day, 1 = 15–29.9 g/day, 2 = 5–14.9 g/day, 3 = 0–4.9 g/day, 4 = 0 g/day), the smoking score (4 = never smoked, 3 = quit smoking > 10 years ago, 2 = quit smoking ≤ 10 years ago, 1 = current smoker ≤ 15 cigarettes/day, 0 = current smoker ≥ 15 cigarettes/day), and the non-occupational physical activity score (0 = 0–27 min/day, 1 = 27–44 min/day, 2 = 44–66 min/day, 3 = 66–93 min/day, 4 = > 93 min/day) (see Appendix A, Figure A.1.).

The total HLI score ranges from zero to 20, with a higher score indicating a healthier lifestyle. The HLI has been divided into four categories. The cut-off values were chosen, based on data from the subcohort (including males), with the intention of creating a balanced number of individuals in each category (category 1: 0–7, category 2: 8–10, category 3: 11–13, category 4: 14–20) [25].

2.4. Data analysis

First, descriptive statistics of baseline exposure variables were calculated for cases and subcohort women using frequency and percentage analysis or median and interquartile range, when the assumption of a normal distribution was violated. Cox Proportional Hazard Regression models were used to estimate age-adjusted and multivariable-adjusted hazard ratios (HR) and their 95 % confidence intervals (95 % CI's) to assess the association between the HLI category (1−4) and the development of EC (yes/no). Women in the subcohort contributed to the person-time-at-risk as long as they were at risk of developing EC, thus until EC-diagnosis, death, migration, loss to follow-up or the end of the study. For statistical reasons, cases that were not in

the subcohort and therefore did not contribute to the person-time-at-risk, were given a minimum follow-up period.

To account for the additional variance in the analysis, due to the case-cohort design of the NLCS and the resulting sampling of the subcohort, the robust Huber-White sandwich estimator was used to calculate standard errors. This correction is similar to Barlow's variance-covariance estimator [26]. There was no evidence of violation of the proportional hazards assumption when examining the Schoenfeld residuals and the log-log transformations of the survival curves.

The HLI component smoking has been associated with a reduced risk of EC in the literature. Previous research suggests that the degree of protection depends on the time since women quit smoking, with an Italian study finding a significantly lower risk of EC in women who quit smoking less than 10 years ago [3,4,12,13,27]. We therefore created strata of non-smokers (including former smokers who quit ten years before baseline) and smokers (including the current and recent former smokers).

Age (years; continuous), oral contraceptive use (never/ever; categorical, number of years; continuous) and parity (number of children given birth to; continuous) were predefined confounders based on the literature. Parity (yes/no; categorical), use of hormone replacement therapy (never/ever; categorical, number of years; continuous), age at menarche (years; continuous), age at menopause (years; continuous) and family history of EC (yes/no; categorical) were tested as confounders. No determinant changed the HR with more than 10 %, so no additional confounders were added to the multivariable analysis. Only the predefined confounders of age, oral contraceptive use and the number of children given birth to, were included in the multivariable analyses. In the stratified analysis by smoking status, the duration of cessation in former smokers, was included as a predefined confounder. To investigate potential effect modification between the HLI and the covariates, interaction terms were computed, entered into the regression model and tested with the Wald test (with $p < 0.05$ indicating effect modification).

To investigate the contribution of individual components of the HLI to the association between HLI and EC risk, additional analyses were performed by removing each component of the HLI individually and recalculating the HLI and the association with the EC risk. HR's for the total HLI score and the sensitivity analyses were calculated per 1 unit SD increase (SD range: 2.52–3.04).

P-values for trend were obtained by fitting the HLI as a continuous variable. All statistical analyses were performed in STATA (version 16) and all tests were two-tailed. An alpha of 0.05 was used as the cut-off for statistical significance.

3. Results

For this case-cohort analysis, cases with a non-epithelial tumour (n = 23), cohort members who reported a probable hysterectomy at baseline (n = 365), with missing data for one or more HLI components (n = 573), and with missing data for any of the confounders (n = 43) were excluded, resulting in 414 EC cases and 1 593 subcohort members available for analysis (see Appendix A, Figure A.2.).

Cases had, on average, used fewer oral contraceptives, were less likely to have given birth, were more likely to have used hormone replacement therapy and were more likely to report a family history of EC than subcohort members. With regard to the HLI, cases were, on average, less likely to be in the healthiest category of the HLI, ate less vegetables and more fruit, had a higher glycaemic load, had fewer years of smoking if classified as ever smoker/current smoker, consumed less alcohol if classified as alcohol drinker, were less active and had a higher BMI than women in the subcohort (see Table 1).

Table 2 shows the baseline distribution of the potential determinants for all members of the subcohort in relation to HLI category, where women in HLI category 1 (unhealthiest) had an older age at menarche, used less oral contraceptives, were more parous, used less hormone replacement therapy, and had less chance of having a family history of EC (1st degree), than women in HLI category 4.

Results of the multivariable analyses between HLI category and EC, adjusted for age (years), oral contraceptive use (never/ever) and parity (number of children), showed that women in HLI categories 2, 3, and 4 had a HR of 1.25 (95 % CI: 0.85–1.85), 0.89 (95 % CI: 0.61–1.31) and 0.78 (95 % CI: 0.52–1.15), respectively, compared with women in HLI category 1. The p for trend was 0.001. The HR per SD increment for the

Table 1
Distribution of baseline descriptives among subcohort members and endometrial cancer cases (median, Inter Quartile Range or proportion) in the Netherlands Cohort Study, 1986-2006.

Baseline characteristics	Female subcohort (n = 1 593)	EC cases (n = 414)
Age (median, IQR)	61 (58;65)	61 (58;65)
Age at menarche (median, IQR)	13 (12;15)	13 (12;14)
Use of oral contraceptives		
Never (%, n)	74.9 (1 193)	86.2 (357)
Ever (%, n)	25.1 (400)	13.8 (57)
Number of years[a] (median, IQR)	7.0 (2.8;12.0)	3.0 (1.0;8.0)
Parity		
Yes (%, n)	81.3 (1 295)	73.7 (305)
No (%, n)	18.7 (298)	26.3 (109)
When parous – number of children given birth to (median, IQR)	3.0 (2.0;4.0)	3.0(2.0;4.0)
Age at menopause (median, IQR)	50 (47;52)	50 (48;53)
Hormone replacement therapy		
Yes (%, n)	11.4 (180)	15.6 (64)
No (%, n)	85.5 (1 352)	82.5 (339)
Don't know (%, n)	3.1 (49)	1.9 (8)
Number of years[a] (median, IQR)	2.0 (1.0;4.0)	2.0 (1.0;7.0)
Family history of EC (1th degree)		
Yes (%, n)	2.9 (46)	4.6 (19)
No (%, n)	97.1 (1 547)	95.4 (395)
HLI		
Total score (median, IQR)	12.0 (10.0;14.0)	12.0 (9.0;14.0)
Category 1 - Unhealthiest (%, n)	7.4 (118)	7.5 (31)
Category 2 (%, n)	22.0 (350)	29.7 (123)
Category 3 (%, n)	38.8 (618)	36.5 (151)
Category 4 - Healthiest (%, n)	31.8 (507)	26.3 (109)
Diet[b]		
Fibres in grams (median, IQR)	25.0 (21.7;29.2)	25.5 (22.3;28.7)
Meat in grams (median, IQR)	86.7 (62.4;111.8)	86.2 (65.3;117.4)
Saturated fat in grams (median, IQR)	15.7 (13.7;18.2)	15.5 (13.5;18.0)
Unsaturated fat in grams (median, IQR)	7.4 (5.3;10.2)	7.4 (5.3;10.4)
Trans-fats in grams (median, IQR)	2.3 (1.6;3.0)	2.1 (1.4;2.8)
Vegetables in grams (median, IQR)	185.7 (150.4;234.5)	177.2 (130.1;234.4)
Fruit in grams (median, IQR)	177.6 (112.6;273.2)	207.1 (133.2;259.4)
Glycemic load in grams (median, IQR)	97.2 (90.7;109.9)	102.3 (94.3;110.0)
Smoking		
Never (%, n)	58.2 (927)	66.7 (276)
Ever (%, n)	20.8 (332)	18.4 (76)
Current (%, n)	21.0 (334)	15.0 (62)
Number of cigarettes/day when ever smoked (median, IQR)	10 (20;5)	10 (15;5)
Number of smoking years when ever smoked (median, IQR)	30.0 (18.0;39.0)	28.0 (20.0;38.0)
Alcohol		
No alcohol drinker (%, n)	513 (32.2)	130 (31.4)
Alcohol drinker (%, n)	1080 (67.8)	284 (68.6)
Alcohol intake in grams (median, IQR)	2.4 (0;10.3)	1.1 (0;7.1)
Alcohol intake when alcohol drinker in grams (median, IQR)	4.2 (1.6;12.1)	3.3 (1.0;10.7)
Non-occupational physical activity (%, n)		
Very little active	25.4 (404)	31.2 (129)
Moderate active	35.5 (566)	35.0 (145)
Active	27.8 (442)	23.4 (97)
Very active	11.4 (181)	10.4 (43)
BMI (median, IQR)	24.5 (22.6;26.9)	25.8 (23.7;28.6)

Table 2
Distribution of determinants in subcohort in relation to primary exposure in the Netherlands Cohort Study, 1986-2006.

Baseline Characteristics	Female Subcohort (N = 1 593)				p-value
	HLI category 1	HLI category 2	HLI category 3	HLI category 4	
Age (median, IQR)	61 (58;65)	62 (58;65)	61 (58;65)	61 (58;65)	*0.91*
Age at menarche (median, IQR)	14 (12;15)	13 (12;14)	13 (12;15)	13 (12;15)	*0.22*
Use of oral contraceptives					
Never (%, n)	78.8 (93)	74.0 (259)	76.5 (473)	72.6 (368)	*0.23*
Ever (%, n)	21.2 (25)	26.0 (91)	23.5 (145)	27.4 (139)	
Number of years[a] (median, IQR)	6.0 (1.0;14.0)	8.0 (3.0;11.0)	7.0 (2.0;12.0)	7.0 (3.0;11.0)	*0.94*
Parity					
Yes (%, n)	83.1 (98)	80.9 (283)	83.3 (515)	78.7 (399)	*0.27*
No (%, n)	17.0 (20)	19.1 (67)	16.7 (103)	21.3 (108)	
When parous – number of children given birth to (median, IQR)	3 (2;4)	3 (2;4)	3 (2;4)	3 (2;4)	*0.31*
Age at menopause (median, IQR)	50 (46;52)	50 (46;52)	50 (47;52)	50 (48;52)	*0.10*
Hormone replacement therapy					
Yes (%, n)	11.1 (13)	10.4 (36)	11.9 (73)	11.5 (58)	*0.55*
No (%, n)	83.8 (98)	85.5 (295)	85.4 (525)	86.1 (434)	
Don't know (%, n)	5.1 (6)	4.1 (14)	2.8 (17)	2.4 (12)	
Number of years[a] (median, IQR)	2.0 (1.0;10.0)	2.0 (1.0;5.0)	2.0 (1.0;5.0)	1.0 (0.5;4.0)	*0.55*
Family history of EC (1th degree)					
Yes (%, n)	0.9 (1)	2.9 (10)	3.6 (22)	2.6 (13)	*0.58*
No (%, n)	99.2 (117)	97.1 (340)	96.4 (596)	97.4 (494)	

n, number of persons; HLI, Healthy Lifestyle Index; SD, standard deviation;
[b] Chi² or Oneway ANOVA
[a] in ever users only

Table 3
Hazard Ratios and 95 % confidence intervals between the Healthy Lifestyle Index, based on diet, alcohol consumption, physical activity, Body Mass Index and smoking and endometrial cancer among women in the Netherlands Cohort Study, 1986-2006.

		Age Adjusted Analyses		Multivariable Adjusted Analyses: All[b]	
	N cases / person years subcohort	HR	95 % CI	HR	95 % CI
HLI					
Category 1 (HLI score 0–7)	31/1 937	1	*Reference*	1	*Reference*
Category 2 (HLI score 8–10)	123/6 034	1.23	0.83–1.82	1.25	0.85–1.85
Category 3 (HLI score 11–13)	151/11 042	0.88	0.60–1.29	0.89	0.61–1.31
Category 4 (HLI score 14–20)	109/9186	0.76	0.51–1.13	0.78	0.52–1.15
P for trend		*0.001*		*0.001*	
HLI[a]	414/28 199	0.86	0.78–0.94	0.86	0.78–0.94
HLI without diet[a]		0.85	0.78–0.93	0.85	0.78–0.93
HLI without smoking[a]		0.78	0.71–0.86	0.78	0.71–0.85
HLI without alcohol[a]		0.84	0.77–0.92	0.85	0.77–0.93
HLI without physical activity[a]		0.91	0.83–1.00	0.91	0.83–0.99
HLI without BMI[a]		0.98	0.89–1.08	0.98	0.89–1.08
HLI					
Non-smokers[a,c,e]	324/20 319			0.75	0.67–0.83
Recent smokers[a,d,e]	90/7 880			0.85	0.70–1.02

HR, Hazard ratio; CI, confidence interval; HLI, Healthy Lifestyle Index; BMI, Body Mass Index
[a] : Hazards ratios per standard deviation increment (SD range 2.52–3.04)
[b] : adjusted for age (years), use of oral contraceptives (never/ever) and parity (number of children)
[c] : when never smoked or being a former smoker > 10 years ago
[d] : when current smoker or former smoker < 10 years ago
[e] : HLI without smoking

total HLI score was 0.86 (95 % CI: 0.78–0.94; 1 SD represents ~3 points of the HLI score).

Because of the inversed association between smoking and the risk on EC, multivariable analyses were conducted stratified on smoking status, with a total HLI score excluding the smoking component. An HR of 0.75 for non-smokers (95 % CI 0.67–0.83) and 0.85 for recent-smokers (95 % CI 0.70–1.02), all adjusted for age (years), oral contraceptive use (never/ever) and parity (number of children) and per SD increment (SD range: 2.52–3.04) (see Table 3).

The interaction of possible determinants (age, age at menarche, oral contraceptive use, years of oral contraceptive use, number of children, age at menopause, hormone replacement therapy use, number of years of use of hormone replacement therapy and family history of EC), on the association between the HLI and the development of EC were investigated. No significant interactions were found (range p-value, 0.25–0.98; see Appendix A, Table A.3.).

Sensitivity analyses with a recalculated HLI after excluding each individual component of the HLI showed HR's per SD increment (SD range 2.55–2.86) of 0.85 (95 % CI: 0.78–0.93) when using an HLI without diet, 0.78 (95 % CI: 0.71–0.85) without smoking, 0.85 (95 % CI: 0.77–0.93) without alcohol consumption, 0.91 (95 % CI: 0.83–0.99) without physical activity and 0.98 (95 % CI: 0.89–1.08) without BMI (see Fig. 1).

3.1. Discussion

This prospective analysis using data from the NLCS investigated the association between a healthy lifestyle, measured by an HLI based on diet, smoking, alcohol consumption, physical activity and BMI and EC risk. The multivariable results show that a healthier lifestyle is associated with a reduced risk of EC. This association is stronger in non-smokers than in recent-smokers.

Our study is consistent with the few cohort studies that have examined the association between an index based on the same lifestyle components (diet, smoking, alcohol consumption, physical activity and BMI) and the risk of EC. In the Women's Health Initiative (WHI) study, an HR of 0.94 was found for each unit increase in total HLI score ($p < 0.05$, n = 80, 123). A non-linear relationship was found between the HLI categories (total HLI score of 11–12; 13; 14–15; ≥16) and the risk of EC with HR's of 0.70, 0.79, 0.65 and 0.61 respectively, compared to women with a total HLI score ≤ 10 [14]. In the French E3N Cohort study (n = 64,732), an HR of 0.45 was found for EC when comparing women with the highest and lowest adherence to health recommendations ($p < 0.05$) [28]. The Canadian Study of Diet, Lifestyle and Health (n = 2 519), found a 47 % risk reduction for EC when comparing women in the lowest category of the HLI with those in the highest category (95 % CI: 0.33–0.86) [17]. A recent prospective Norwegian study, found an HR of 0.93 (95 % CI: 0.91–0.95) per 1-point increase in HLI score

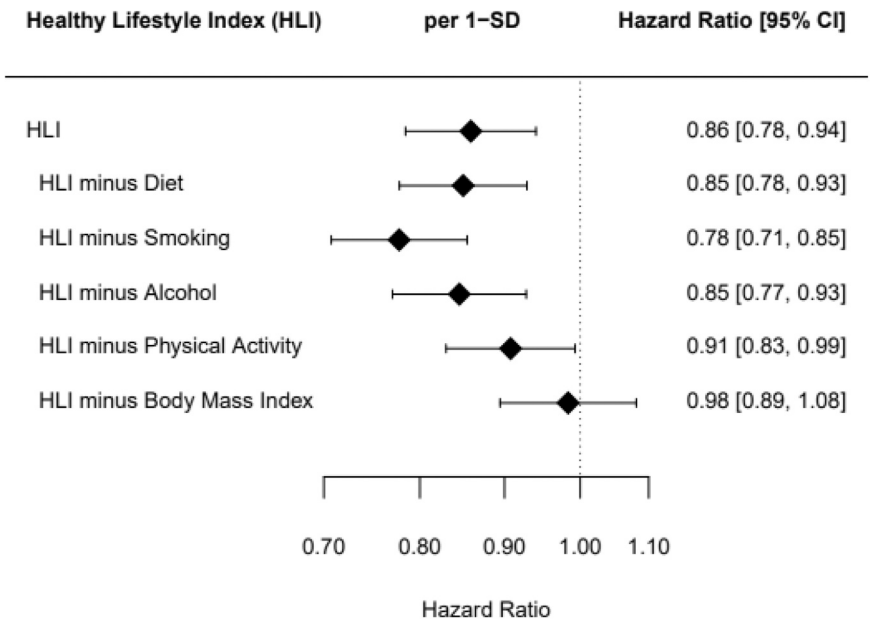

Fig. 1. Association between the Healthy Lifestyle Index score and the risk of Endometrial Cancer in the Netherlands Cohort Study (1986–2006). Hazard Ratios were calculated per 1-SD increment. The standard deviation was calculated for every HLI score type. One standard deviation corresponded to 2.55–2.86 units of HLI score, depending on the HLI score type. HLI=Healthy Lifestyle Index, C.I.=confidence interval.

(n = 96,869) [18].

All studies included postmenopausal women, had the same HLI components, and gave the highest HLI score to women with the healthiest behaviour. There were differences in the reference category, in the measurement of the HLI components, in the cut-off values of the index and of the different HLI components, in the included population, and in the exclusion criteria. The follow-up period in the studies ranged from 11 years to 17.9 years [14,17,18,28].

A sensitivity analysis was performed with an HLI without each HLI component. Compared with the five-component HLI, the HR attenuates when BMI or physical activity is excluded, is stronger when smoking is excluded and remains relatively constant when diet and alcohol are excluded, suggesting that BMI and physical activity are the HLI components that explain most of the association between the HLI and the development of EC. The HR of an HLI without BMI or physical activity is closer to 1 than an HLI score without alcohol consumption or diet. This is consistent with the literature where a high BMI and low level of physical activity are strong risk factors for the development of EC [3,4]. When smoking was removed as a component of the HLI the association between HLI and EC risk became stronger. These results are consistent with those of the prospective Norwegian study, where the exclusion of smoking status from the HLI resulted in a decrease in HR from 0.93 (95 % CI: 0.91–0.95) to 0.89 (95 % CI: 0.87–0.91) [18]. When the analyses were stratified by smoking status, the association between HLI score and the risk of EC was the weakest in smokers. This may be explained by the observations that smoking is associated with a lower risk of EC, probably due to the lower body fat and lower oestrogen levels of smokers [3,4,12,13]. This may create a ceiling effect, limiting the potential of other risk factors (i.e., BMI) that lower oestrogen levels to further reduce the EC risk. This sensitivity analysis confirms the findings in the literature.

In this case-cohort analysis, no statistically significant interactions were found between the hormonal and reproductive determinants, HLI and the development of EC. Despite our findings, there was some evidence in the WHI study that the association between the HLI and the development of EC might be modified by the use of HRT with a HR of 0.92 per unit increase in HLI score for women who had never used HRT (95 % CI 0.89–0.93) compared with to an HR of 0.98 per unit increase in HLI score for current HRT users (95 % CI 0.96–1.01) [14]. A possible explanation could be the small number of women who used HRT in the NLCS, resulting in low power.

By using an HLI in which each factor has the same weight in the overall HLI score, we create an expectation that each lifestyle factor has the same effect on EC. When investigating the effect of an HLI on a disease, another approach may be to adjust the different components of the HLI score for the specific disease under investigation. Although the HLI score would then be more specific to EC, it will result in separate HLI scores for each specific disease being studied.

This study has several notable strengths, including its prospective design, which reduces the chance of selection and information bias, the large cohort, the information on many confounders, the almost complete follow-up of the study population through linkage to cancer registries and the long follow-up. Limitations of this study include the single measurement with the questionnaire at baseline, the self-reported questionnaire, and the small number of women in HLI category 1.

The first limitation and potential source of bias stems from the fact that exposure data were collected only at baseline. No information was available on changes in exposure during follow-up. A study within the NLCS examining the reliability of the SFFQ showed that subjects' food habits remained fairly stable over the five years after baseline [22]. No studies were done regarding changes in smoking habits, physical activity or BMI. Measurement error may still have attenuated associations.

The second limitation was that the questionnaire was self-reported, which may have led to a difference between reported and true exposure, and thus possible attenuation of associations. There was no possibility to validate the self-reported data by physical measurements because of the nationwide design of the study and limited resources.

The third limitation was the relatively small reference category (HLI category 1). The HLI score was developed as much as possible based on the recommendations of previous studies to facilitate comparison [17,24]. The same score was applied in a previous publication regarding kidney cancer [25]. The publication of Meer et al. includes both males and females, with the cut-offs chosen based on the distribution in both sexes. Alternatives were considered, but the decision was made to use the same cut-offs and reference category as in the previous publication [25]. The small reference category has resulted in wider confidence intervals.

4. Conclusion

In conclusion, this study highlights the importance of the combined effect of modifiable risk factors in reducing the risk of developing EC. Further studies are needed to confirm our findings and to investigate possible effect modification. When more consistent results are available in the literature, adjusted prevention strategies and risk reduction interventions focused on improving physical activity, and diet quality and reducing obesity, and alcohol consumption can be established to reduce the burden of EC.

Ethics

Participants consented to be included in the cohort and follow-up by returning their completed questionnaires. The institutional review boards of the Netherlands Organization for Applied Scientific Research TNO (Zeist) and Maastricht University (Maastricht) approved the execution of the NLCS and the informed consent procedure (MEC 85–012.1). The study complies with the medical ethical standards of the Declaration of Helsinki.

CRediT authorship contribution statement

Schouten Leo: Writing – review & editing, Visualization, Supervision, Methodology, Data curation, Conceptualization. **Coemans Eveline:** Writing – original draft, Formal analysis. **van den Brandt Piet:** Writing – review & editing, Methodology, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2025.102798.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available because the informed consent does not allow for that.

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