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# Lifestyle changes and postmenopausal breast cancer risk in women from the European Prospective Investigation into Cancer and Nutrition

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## Abstract

**Background** The risk of breast cancer has been associated with various lifestyle factors, yet the evidence regarding how lifestyle modifications affect this risk remains limited. This study examines the relationship between changes in the Healthy Lifestyle Index (HLI) and postmenopausal breast cancer risk in women participating in the European Prospective Investigation into Cancer (EPIC).

**Methods** HLI scores (ranging from 0 to 16) were computed based on smoking habits, alcohol consumption, body mass index (BMI), and physical activity levels, using data from baseline and follow-up questionnaires, which were separated by a median interval of 10 (IQR: 5.2–12.0) years. Among the 125,746 women included in the analyses, 2,175 developed breast cancer over a median follow-up period of nearly 4 (IQR: 2.9–8.4) years starting from the date of the second lifestyle questionnaire. Cox proportional hazards models were employed to estimate hazard ratios (HRs) and confidence intervals (CIs) for the relationship between changes in HLI and postmenopausal breast cancer risk, analysed both overall and by estrogen receptor (ER) status. Individual components of the HLI were also analysed, with sensitivity analyses addressing potential reverse causation by delaying the start of follow-up by 1 to 3 years.

**Results** Each unit increase in the HLI—reflecting a healthier lifestyle—was not associated with the overall risk of postmenopausal breast cancer. Among individual components, only a one-unit increase in the BMI score, corresponding to a shift towards a healthier BMI, was inversely associated with overall (HR = 0.936; 95% CI 0.880–0.996) and ER-positive (HR = 0.930; 95% CI 0.865–1.000) postmenopausal breast cancer risks.

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**Conclusions** Lifestyle changes, as measured by the HLI, during mid-adulthood were not significantly associated with the risk of postmenopausal breast cancer. More specifically, the results of this study suggested that a shift towards a healthier BMI may contribute to breast cancer prevention. Further research involving diverse and larger study populations and lifestyle assessments at earlier life stages could provide deeper insights.

**Keywords** Healthy lifestyle index, Lifestyle changes, Risk, Breast cancer, Longitudinal, Prospective cohort

## Background

The breast represents the most common site of cancer among women worldwide, accounting for over 2.3 million newly diagnosed cases and approximately 670,000 fatalities in 2022 [1]. Recent evidence from 38 European countries estimates that around 45% of female breast cancer cases could be avoided by reducing exposure to modifiable risk factors, which include lifestyle [2]. Studies further underscore that a healthy lifestyle, which includes avoiding smoking, limiting alcohol intake, sustaining a healthy weight, engaging in regular physical activity, and adhering to a varied and balanced diet, is linked to a reduced risk of developing breast cancer [3, 4]. Given that these behavioural risk factors are frequently correlated and may synergistically influence the risk of breast cancer [5], recent investigations have adopted a more holistic approach. Within the framework of the European Prospective Investigation into Cancer (EPIC) study, these five lifestyle factors were integrated into a single composite score known as the Healthy Lifestyle Index (HLI) to evaluate adherence to a healthy lifestyle. In postmenopausal women, higher HLI scores, indicating healthier overall lifestyle behaviours, were associated with a lower risk of breast cancer, with a 3% decrease in risk per one-point difference in the score [6]. A recent systematic review and a meta-analysis of observational studies reported a 20% reduction in breast cancer risk when comparing the highest to the lowest HLI category [5].

Most epidemiological studies concerning healthy lifestyles and breast cancer risk have predominantly relied on single-time-point measurements, typically conducted at the time of study recruitment. This approach implicitly assumes the stability of lifestyle behaviours throughout adulthood and presumes that cross-sectional comparisons between groups with different lifestyle profiles can provide insight into the effects of potential lifestyle modifications on breast cancer risk. While this pragmatic approach may facilitate analysis, it overlooks a critical dimension: the impact of actual lifestyle changes over time [7], particularly for postmenopausal women who have undergone a transitional period characterised by profound physiological changes and lifestyle adaptations [8–10]. As prevention strategies seek to promote healthier behaviours across the life course, risk estimates that incorporate longitudinal lifestyle changes remain a largely underexplored area. Most prior prospective cohorts investigating lifestyle changes in relation to breast cancer

risk have concentrated on individual components such as weight change [11], fluctuations in physical activity levels [12], or alcohol consumption [13]. A limited number of prospective studies have examined the impact of lifestyle changes across multiple behavioural factors. The Swedish Women's Lifestyle and Health Cohort Study (SWLH) analysed such changes using a lifestyle score based on multiple behaviours (smoking status, alcohol consumption, body mass index (BMI), and physical activity) and found that women who improved their lifestyle exhibited a lower risk of lifestyle-related cancers overall, as well as a reduced risk of breast cancer specifically, when compared to those with consistently poor lifestyle habits [14]. However, this study did not employ a standardised measure such as the HLI. More recently, the Norwegian Women and Cancer Study (NOWAC) utilised the HLI (consisting of smoking behaviour, alcohol consumption, BMI, physical activity level, and a dietary score) to evaluate changes in lifestyle and their association with cancer incidence [15]. While positive lifestyle changes were inversely associated with the incidence of several lifestyle-related cancers, no significant association was observed for breast cancer specifically. To date, no study on the scale of Europe has explicitly evaluated the association between changes in a standardised lifestyle score, such as the HLI, and breast cancer risk.

To examine the impact of implementing lifestyle changes during adulthood on postmenopausal breast cancer risk, this study evaluated the relationship between variations in the HLI, as well as its individual components, and the incidence of postmenopausal invasive breast cancer among women from the EPIC cohort.

## Methods

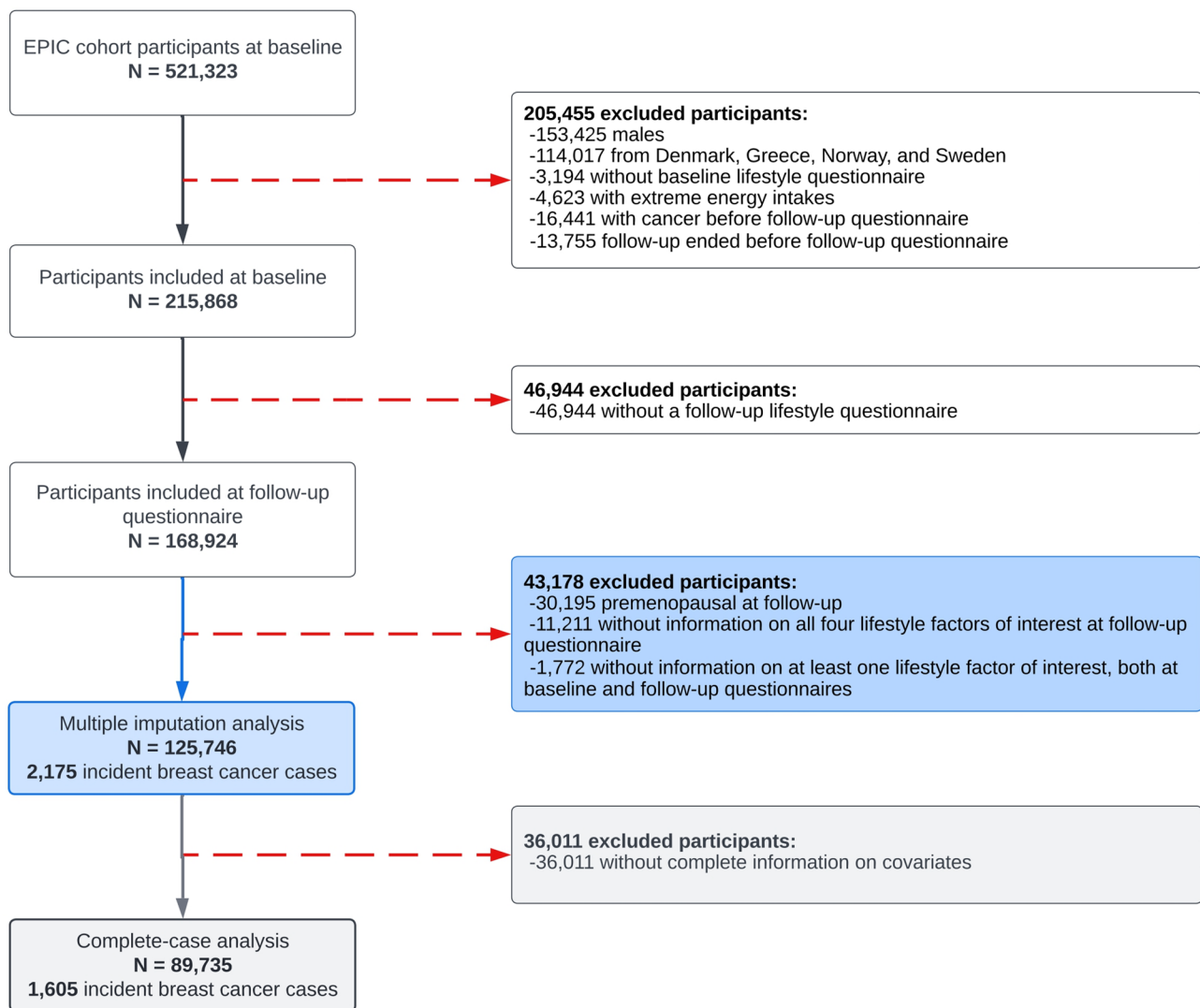
### Study population

EPIC is a large prospective multicentre study involving 521,323 healthy adults from the general population, aged 35–70 years, who were recruited between 1992 and 2000 across 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. This cohort was primarily designed to investigate the relationship between diet and lifestyle factors and cancer risk, as well as other chronic diseases across a diverse European population. A detailed description of EPIC's rationale, study design, data collection, and methodology has been provided elsewhere [16, 17].

At the time of recruitment, participants completed validated self-administered, country or study-centre-specific dietary and lifestyle questionnaires to obtain information about their diet and lifestyle prior to the inclusion. Informed consent was obtained from them as well during questionnaire completion. For the current study, participants also filled out a follow-up lifestyle questionnaire with completion dates ranging from 1996 to 2013. The International Agency for Research on Cancer (IARC) Ethics Committee and all participating centres granted ethical approval.

The study population underwent exclusions based on specific criteria, as illustrated in Fig. 1. Firstly, male participants were excluded as this study focuses exclusively on female breast cancer. Greek, Norwegian, and Swedish participants were also excluded due to administrative restrictions regarding data usage. Denmark was further

excluded due to the complete absence of information concerning alcohol consumption from the follow-up assessment. Female participants who did not complete a baseline questionnaire were excluded, as well as those whose energy intake was below the 1st percentile and above the 99th percentile of the energy intake to energy requirement ratio distribution, to reduce the influence of potential misreporting or outliers in dietary data. Additional exclusions were applied to participants who had a cancer diagnosis prior to completing the follow-up questionnaire, if their follow-up period ended before they could complete the questionnaire, or if they failed to complete it. Participants who remained premenopausal at follow-up were excluded as menopausal status constitutes a significant effect modifier in the association between BMI and breast cancer risk [3, 18]. Furthermore, given that the primary exposure of interest was lifestyle



**Fig. 1** Selection of the study population in EPIC. Note: there were no participants without information on all four lifestyle factors of interest at baseline questionnaire

changes, women who had missing information about all four lifestyle factors at follow-up or lacked information on at least one lifestyle factor at both baseline and follow-up were also excluded from the analysis. Following these initial exclusions, the dataset included 125,746 women, among whom 2,175 cases of incident invasive postmenopausal breast cancer were identified after the follow-up questionnaire. The main analysis was performed on this dataset after applying multivariate imputation by chained equations (MICE) to handle missing data in HLI component scores at baseline and follow-up, from which HLI changes were subsequently derived, along with other covariates. As part of the sensitivity analyses, we subsequently conducted a complete-case analysis, excluding approximately 29% of participants due to missing data on HLI change and covariates. This resulted in a sample of 89,735 women with 1,605 cases of incident invasive postmenopausal breast cancer.

#### Assessment of HLI changes

This study examined four lifestyle factors: smoking habits, alcohol consumption, BMI, and physical activity levels. Although diet is usually part of commonly studied lifestyle patterns, it was not included in the construction of the HLI in this analysis, since detailed dietary information in EPIC was available solely at baseline. However, a diet score at baseline was calculated and used as an adjustment variable (further details provided in the statistical analysis section).

Each factor was assigned a score ranging from 0 to 4 according to progressively healthier categories of behaviour (Supplementary Fig. 1). “Favourable” behaviours were defined as follows: never smoking (never smoked = 4; smoking cessation > 10 years = 3; smoking cessation ≤ 10 years = 2; current smoking ≤ 15 cigarettes/day = 1; current smoking > 15 cigarettes/day = 0), low alcohol consumption (< 0.1 (g/day) = 4; 0.1–4.9 (g/day) = 3; 5.0–9.9 (g/day) = 2; 10.0–19.9 (g/day) = 1; ≥ 20 (g/day) = 0), low BMI (< 22 = 4; 22–23.9 = 3; 24–25.9 = 2; 26–29.9 = 1; ≥ 30 = 0), and the top quintile of physical activity, measured using weekly recreational and household metabolic equivalent of task units (in MET-hours/week with baseline (B) and follow-up (F) respectively: B: ≥ 136; F: ≥ 126 = 4; B: 96–135.9; F: 90–125.9 = 3; B: 68–95.9; F: 63–89.9 = 2; B: 44–67.9; F: 39–62.9 = 1; B: < 44; F: < 39 = 0). HLI scores were computed by aggregating the scores of all four factors at both baseline and follow-up, resulting in a total score ranging from 0 to 16, consistent with the methodology employed in a prior EPIC study on HLI changes and colorectal cancer risk [19]. The primary exposure of interest was the change in HLI score between baseline and follow-up, calculated by subtracting the baseline score from the follow-up score. This yielded a

possible range from –16 (maximum worsening) to +16 (maximum improvement).

#### Ascertainment of postmenopausal invasive breast cancer cases

Breast cancer cases within the EPIC cohort were identified through national cancer registries in Italy, the Netherlands, Spain, and the United Kingdom, in conjunction with health insurance records, cancer and pathology registries, as well as through active follow-up conducted in France and Germany [17]. Invasive breast cancer cases were defined as the first primary invasive breast tumours (categories under the codes C50.0–C50.9, using the 10th revision of the International Classification of Diseases, ICD-10). Estrogen receptor (ER) status has been documented in pathology reports subsequent to 1997 [6]. Consequently, cases were classified as ER-positive (ER+), ER-negative (ER–), or unknown.

#### Menopausal status definition

Menopausal status at baseline and follow-up was determined from questionnaire data collected at these two relevant time points. Participants were classified into three categories: premenopausal, perimenopausal, and postmenopausal. As previously mentioned, premenopausal women at follow-up were excluded.

Premenopausal women were characterised as those who experienced regular menstrual cycles within the last 12 months. Perimenopausal women were categorised as those who experienced irregular menstrual cycles in the past 12 months or had menstrual periods in the previous year but were no longer menstruating. Postmenopausal women were identified as those who had no menstrual periods in the past 12 months or had undergone a bilateral ovariectomy, resulting in a surgically induced menopause.

In cases where women had missing or incomplete questionnaire data, reported a previous hysterectomy, or indicated the use of exogenous hormones (oral contraceptives (OC) or menopausal hormone treatment (MHT)), their menopausal status was determined based on age cut-off points. Women younger than 46 years at recruitment were considered premenopausal, those between 46 and 55 years old were categorised as perimenopausal, and women aged 55 or older were classified as postmenopausal.

For analytical purposes, women who were classified as perimenopausal, postmenopausal, or surgically postmenopausal at baseline were grouped into a single “postmenopausal” category. Indeed, according to the updated Stages of Reproductive Aging Workshop criteria, published 10 years later (STRAW + 10), perimenopause includes both the menopausal transition and the first 12 months after the final menstrual period (early

postmenopause), reflecting a physiological continuum rather than distinct phases [10]. Grouping these stages allows for consistent categorisation and improves the robustness of subgroup analyses. The detailed distribution of menopausal status transitions from baseline to follow-up, without merging these subgroups, is presented in descriptive analyses.

### Statistical analysis

Descriptive analyses across the categories of HLI changes (where  $< -1$  = “worsen”;  $[-1;1]$  = “stable”;  $> 1$  = “improve”; and “missing HLI change”) were conducted using cross-tabulations that included frequencies and percentages for categorical variables, as well as medians and the 25th–75th percentiles for continuous variables.

In order to address missing data on HLI changes ( $n=22,937$ ) and covariates, MICE was applied, under the assumption that missingness occurs at random [20, 21]. The model incorporated all four HLI components at baseline and follow-up (i.e., smoking, alcohol, BMI, and physical activity), including covariates identified as potential confounders. A total of 15 imputed datasets were generated, each consisting of 20 iterations, which was deemed sufficient to ensure convergence of the imputation models given the sample size and number of variables.

The validity of the imputed data was assessed by comparing variable distributions between the complete and imputed datasets for categorical variables, along with employing density plots for continuous variables. The convergence of the algorithm was evaluated through visual inspection of trace plots corresponding to each imputed variable. The imputed datasets were used in the primary analyses, with estimates pooled in accordance with Rubin’s rules [21].

In faceted dot plots, the mean changes in individual components are summarised both overall and by HLI change categories, using imputed data.

Participants were followed from the lifestyle questionnaire completed at the follow-up assessment until the first occurrence of cancer (excluding non-melanoma skin cancers), death, emigration, loss to follow-up or the end of the follow-up period, whichever came first. The end of follow-up dates varied by country, with maximum dates ranging from 2008 to 2012. Multivariable Cox proportional hazards regression models, using participants’ age as the underlying time scale, were used to estimate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the association between changes in HLI and the risk of postmenopausal breast cancer. Changes in HLI were initially examined as a continuous variable and subsequently as a categorical variable, as previously described. Associations between continuous changes in the four individual HLI components and

postmenopausal breast cancer risk were assessed in a single, mutually adjusted, model. To evaluate whether specific lifestyle components disproportionately influenced the association, the relationship between continuous HLI change and postmenopausal breast cancer risk was also modelled using HLI scores recalculated with one component excluded at a time (e.g. smoking, alcohol, BMI, physical activity). The corresponding baseline HLI score, excluding the same component, was included in each model as an adjustment variable. HRs were estimated overall and stratified by breast cancer subtype, based on the ER status (“ER- +”, “ER-”, or “Unknown”), with all categories included in the analyses. To account for competing risks, the Lunn & McNeil approach was applied [22]. This methodology involves data augmentation, where each subject is assigned a separate observation for each ER status, followed by stratification by event type in the Cox model. Additionally, associations between categorical HLI levels at follow-up ( $[0-8]$ ;  $[8-11]$ ;  $\geq 11$ ) with breast cancer risk, were also assessed within each baseline HLI category ( $[0-8]$ ;  $[8-11]$ ;  $\geq 11$ ). For each stratum, HRs were estimated by follow-up HLI level, using women who remained in the same category over time as the reference group.

All models were stratified by study centre and age at recruitment rounded to the nearest year, and adjusted for confounders selected a priori in accordance with the literature [6] for the relative inequality index (a regression-based measure of socioeconomic status ranging from 0 to 1, with higher values indicating lower socioeconomic status [23]), height (cm), prior use of OCs up to recruitment (“yes”; “no”), prior use of MHT up to recruitment (“premenopausal”; “yes”; “no”), age at menarche ( $< 12$  years;  $12-14$  years;  $> 14$  years), age at first full-term pregnancy (“nulliparous”;  $< 21$  years;  $21-30$  years;  $> 30$  years), number of full-term pregnancies (“nulliparous”; 1 FTP; 2 FTPs;  $\geq 3$  FTPs, with FTP standing for full-term pregnancy), HLI score at baseline (ranging from 0 to 16), diet score at baseline (based on the combination of seven dietary factors at baseline including cereal fibre; folate; polyunsaturated to saturated fat ratio; fatty fish, as a marker for omega-3 fatty acids; margarine, as a marker for industrially produced trans-fats; glycaemic load; vegetable; and fruits, [24]), and the time interval between baseline and follow-up questionnaires. These adjustment variables were obtained from lifestyle questionnaires and food frequency questionnaires (FFQs) administered at baseline.

As sensitivity analyses, the observation period was initiated one to three years after the follow-up questionnaire to account for potential reverse causation stemming from lifestyle changes induced by early symptoms of undiagnosed breast cancer. A complete-case analysis was also conducted after excluding participants with incomplete

data on HLI change and covariates. Finally, the main analysis was also repeated in non-MHT users.

Statistical significance was defined as results with a p-value below 0.05. All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) via the RStudio® interface.

## Results

Table 1 summarises the characteristics of the 125,746 women included in the study, both overall and by categories of HLI change. Women whose HLI deteriorated had a higher median HLI score at baseline (median: 11.0, IQR: 9.0–12.0, with IQR standing for interquartile range) in comparison to those who improved their HLI (median: 8.0, IQR: 6.0–10.0). Nonetheless, the HLI score at follow-up was higher in the “Improve” group (median: 11.0, IQR: 9.0–13.0) than in the “Worsen” group (median: 8.0, IQR: 7.0–10.0). The “Worsen” group exhibited the shortest time interval between questionnaires (median: 6.2, IQR: 5.0–11.4 years), whereas the “Improve” group displayed the longest (median: 11.1, IQR: 6.0–12.0 years). Additionally, the duration of follow-up was shortest in the “Improve” group, with a median of 2.9 years compared to 6.0 years for the “Worsen” group.

Overall, the median age at recruitment was 52.1 years and 61.1 years at the follow-up questionnaire, with minimal socioeconomic disparities across categories of HLI change (median relative inequality index overall: 0.6, IQR: 0.2–0.7). The median age at menarche was 13 years, while the median age at first full-term pregnancy was 24 years. The majority of women had two children (42%), while 12% were nulliparous. A total of 70% reported having ever breastfed their children. Prior uses of MHT and OC were reported by 28% and 58% of participants, respectively. Regarding the menopausal status transition from baseline to follow-up, most women remained postmenopausal at follow-up (around 43 to 47% across categories), while others transitioned from pre to postmenopause (around 18 to 22% across categories), or from peri to postmenopause (around 15 to 22% across categories). Other socio-demographic and reproductive characteristics, as well as the diet score at baseline, remained consistent across the categories of HLI change.

Smoking rates and BMI at baseline were relatively comparable across the various categories of HLI change, 13% of the overall study population identified as current smokers and median BMI was 24 kg/m<sup>2</sup>. Alcohol consumption at baseline was lowest in the “Worsen” group (median: 3.0, IQR: 0.5–8.2 g/day) and highest in the “Improve” group (median: 6.8, IQR: 1.0–16.3 g/day). Conversely, baseline physical activity levels exhibited an inverse pattern, being the highest in the “Worsen” group (median: 108.7, IQR: 76.0–147.1 MET-hours/week) and the lowest in the “Improve” group (median: 61.1, IQR:

40.1–91.7 MET-hours/week). At follow-up: women who improved their HLI demonstrated lower rates of smoking and alcohol consumption, lower BMI, and higher levels of physical activity compared to those whose HLI worsened.

In Fig. 2, participants whose HLI worsened demonstrated mean decreases in the physical activity (mean: –1.46), alcohol (mean: –0.71) and BMI (mean: –0.52) components, while there was a negligible alteration in the smoking component (mean: –0.02). Individuals maintaining a stable HLI presented minor fluctuations across all components. In contrast, those with an improved HLI exhibited mean increases in the physical activity (mean: 1.16), smoking (mean: 1.21), alcohol (mean: 0.60) and BMI (mean: 0.10) components. Overall, mean changes across the entire sample were modest, with the largest observed in the smoking component (mean: 0.48).

Mean changes in HLI and its components across EPIC countries are presented in Supplementary Fig. 2. The most prominent improvement and worsening of the HLI were observed in France (mean: 1.02) and Germany (mean: –0.54), respectively. For individual lifestyle components, Italy (mean: 0.35), Germany (mean: 0.25) and Spain (mean: 0.25) exhibited the largest increases in the alcohol component, and France (mean: 0.93) and Italy (mean: 0.71) for the smoking component. France (mean: –0.27) and the Netherlands (mean: –0.31) showed the largest decreases in the BMI component. Finally, the physical activity component increased the most in France (mean: 0.52) and Italy (mean: 0.71) but decreased considerably in Germany (mean: –0.81).

The associations between lifestyle changes from baseline to follow-up and the risk of postmenopausal breast cancer, overall and by ER status, are shown in Table 2. For continuous HLI change, associations did not reach statistical significance, but the effect differed significantly by ER status: HR=0.979 (95% CI 0.953–1.006) for the ER-positive breast cancer and HR=1.062 (95% CI 0.998–1.130) for the ER-negative breast cancer (P for heterogeneity=0.018). No significant associations were observed for categorical HLI changes and breast, either overall or by subtype.

Excluding individual components from the HLI calculation had minimal impact on the association between HLI change and breast cancer risk. However, the removal of the alcohol component slightly strengthened the inverse association with overall (HR: 0.974, 95% CI 0.948–1.002) and ER-positive breast cancer risks (HR: 0.965, 95% CI 0.934–0.997). In contrast, the exclusion of the BMI component yielded a modest positive association with ER-negative breast cancer risk (HR: 1.071; 95% CI 1.002–1.146). The p-values for the interaction term between ER-positive and ER-negative breast cancer were less than 0.05 in models excluding the smoking, alcohol or BMI component individually, but not when excluding

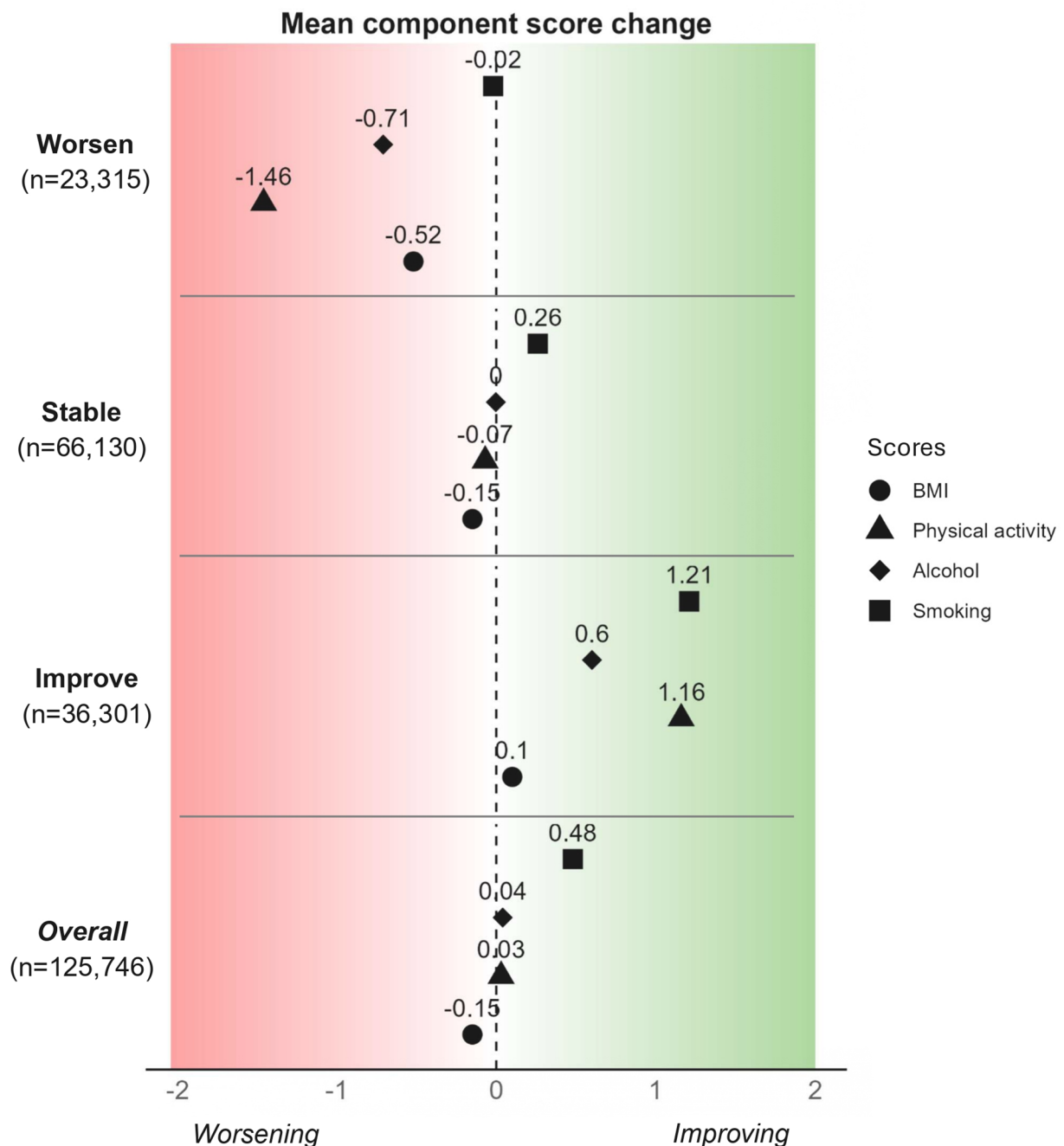
**Table 1** Characteristics of included EPIC women according to categorised healthy lifestyle index change

Characteristics	Worsen (< -1)	Stable (-1 to 1)	Improve (> 1)	Missing HLI change	Total
<b>Number of participants</b>	19,251	55,362	28,196	22,937	125,746
<b>Number of BC cases</b>	394	1,053	465	263	2,175
<b>Healthy Lifestyle Index for both questionnaires</b>					
HLI at baseline, median (IQR)	11.0 (9.0–12.0)	10.0 (8.0–12.0)	8.0 (6.0–10.0)	9.0 (7.0–11.0)	10.0 (8.0–11.0)
HLI at follow-up, median (IQR)	8.0 (7.0–10.0)	10.0 (8.0–12.0)	11.0 (9.0–13.0)	9.0 (7.0–11.0)	10.0 (8.0–12.0)
Time in between questionnaires (y), median (IQR)	6.2 (5.0–11.4)	7.0 (4.9–11.9)	11.1 (6.0–12.0)	11.9 (10.0–12.6)	10.0 (5.2–12.0)
Time until censoring (y), median (IQR)	6.0 (2.9–9.3)	5.9 (2.9–10.6)	2.9 (2.8–7.0)	2.9 (2.5–4.0)	3.7 (2.9–8.4)
<b>Covariates at baseline</b>					
Age at recruitment (y), median (IQR)	52.0 (46.5–58.8)	52.3 (47.2–58.2)	52.2 (47.4–57.5)	51.4 (46.4–57.5)	52.1 (47.0–58.0)
Age at follow-up (y), median (IQR)	59.9 (54.8–66.2)	60.4 (55.6–66.1)	61.9 (57.4–67.1)	62.4 (57.7–68.4)	61.1 (56.4–66.8)
Relative inequality index, median (IQR)	0.6 (0.2–0.7)	0.6 (0.2–0.7)	0.6 (0.2–0.7)	0.6 (0.2–0.7)	0.6 (0.2–0.7)
Height (cm), median (IQR)	161.2 (157.1–165.5)	160.6 (156.3–165.0)	160.7 (156.9–165.0)	160.0 (156.0–165.0)	160.7 (156.5–165.0)
Age at menarche (y), median (IQR)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)
Age at 1st FTP (y), median (IQR)	24.0 (21.0–27.0)	24.0 (21.0–27.0)	24.0 (21.0–27.0)	24.0 (21.0–27.0)	24.0 (21.0–27.0)
<i>Number of FTP, n (%)</i>					
Nulliparous	2,115 (12)	6,785 (13)	3,371 (12)	2,374 (12)	14,645 (12)
1 FTP	3,301 (18)	8,848 (17)	4,813 (18)	3,172 (16)	20,134 (17)
2 FTP	7,926 (44)	21,792 (41)	11,438 (42)	8,661 (43)	49,817 (42)
Over 3 FTP	4,875 (27)	15,380 (29)	7,481 (28)	5,884 (29)	33,620 (28)
Breastfeeding, n ever (%)	12,871 (72)	36,852 (71)	18,113 (68)	67,836 (71)	81,449 (70)
HRT use, n ever (%)	5,536 (29)	15,473 (28)	8,321 (30)	5,421 (24)	34,751 (28)
OC use, n ever (%)	11,954 (62)	31,846 (58)	15,971 (57)	12,475 (56)	72,246 (58)
<i>Menopausal status transition from B to F*, n (%)</i>					
Pre to perimenopausal	2,575 (14)	6,121 (11)	1,806 (7)	1,815 (8)	12,317 (10)
Pre to surgically postmenopausal	189 (1)	612 (1)	336 (1)	197 (1)	1,334 (1)
Remained perimenopausal	470 (3)	1,130 (2)	306 (1)	154 (1)	2,060 (2)
Peri to surgically postmenopausal	151 (1)	484 (1)	324 (1)	263 (1)	1,222 (1)
Peri to postmenopausal	2,866 (15)	9,355 (17)	5,780 (21)	4,991 (23)	22,992 (19)
Pre to postmenopausal	3,083 (17)	8,789 (16)	5,427 (20)	4,869 (22)	22,168 (18)
Remained postmenopausal	8,755 (47)	25,381 (47)	12,646 (46)	9,489 (43)	56,271 (46)
Remained surgically postmenopausal	480 (3)	1,803 (3)	809 (3)	356 (2)	3,448 (3)
Diet score at baseline, median (IQR)	27.0 (23.0–32.0)	28.0 (23.0–32.0)	28.0 (24.0–33.0)	28.0 (24.0–33.0)	28.0 (23.0–32.0)
<b>Index components at baseline</b>					
Smokers, n current (%)	2,311 (12)	6,664 (12)	3,461 (12)	3,509 (15)	15,945 (13)
Alcohol (g/day), median (IQR)	3.0 (0.5–8.2)	3.3 (0.4–11.2)	6.8 (1.0–16.3)	4.2 (0.5–12.7)	4.0 (0.5–12.0)
BMI (kg/m <sup>2</sup> ), median (IQR)	23.8 (21.8–26.9)	24.3 (21.8–27.6)	23.9 (21.5–26.8)	23.9 (21.7–26.9)	24.0 (21.7–27.2)
Physical activity (METS/week), median (IQR)	108.7 (76.0–147.1)	88.6 (55.0–131.1)	61.1 (40.1–91.7)	71.0 (41.0–113.6)	81.5 (49.5–124.6)
<b>Index components at follow-up</b>					
Smokers, n current (%)	2,607 (14)	5,332 (10)	1,828 (6)	1,165 (5)	10,932 (9)
Alcohol (g/day), median (IQR)	8.0 (1.4–17.5)	3.6 (0.0–12.3)	3.3 (0.0–9.6)	6.4 (1.1–16.8)	4.3 (0.3–13.2)
BMI (kg/m <sup>2</sup> ), median (IQR)	25.3 (22.9–28.1)	24.8 (22.2–28.0)	23.7 (21.5–26.6)	24.5 (22.1–27.7)	24.6 (22.1–27.7)
Physical activity (METS/week), median (IQR)	50.5 (30.6–78.0)	78.8 (47.1–118.3)	96.0 (64.5–132.8)	67.5 (40.0–103.2)	76.0 (45.0–114.7)

\*B to F, baseline to follow-up

Percentages are rounded to the nearest whole number, and medians (IQR) are rounded to one decimal place.

Note: the “Missing HLI change” group includes participants with known questionnaire dates but missing data for at least one of the four individual HLI components at baseline or follow-up, precluding computation of HLI change.



**Fig. 2** Mean changes of individual component scores by categories of HLI change. Negative mean values indicate a deterioration in the corresponding component score (e.g., increased alcohol consumption, higher BMI, or more smoking, and reduced physical activity), whereas positive mean values indicate an improvement

the physical activity component, indicating potential heterogeneity by tumour subtype.

In a single model including changes in all individual HLI components, a one-unit increase in the BMI score was inversely associated with overall breast cancer risk (HR: 0.936, 95% CI 0.880–0.996), with similar trends observed for the ER-positive (HR: 0.930, 95% CI

0.865–1.000) and unknown ER status subgroups (HR: 0.914, 95% CI 0.792–1.055), but not ER-negative cases (HR: 1.022, 95% CI 0.860–1.215). No significant associations were observed for changes in smoking, alcohol, or physical activity scores across breast cancer subtypes.

No statistically significant association was observed between categorised HLI scores at follow-up and

**Table 2** Association between lifestyle changes from baseline to follow-up and postmenopausal breast cancer risk (n = 125,746 women)

Outcome		Overall	ER+	ER-	Unknown ER status	Phet ER+ vs. ER-
<b>Breast cancer events, n</b>		<b>2,175</b>	<b>1,511</b>	<b>268</b>	<b>396</b>	
Difference in continuous HLI score	1-unit increase*	0.992 (0.969–1.016)	0.979 (0.953–1.006)	1.062 (0.998–1.130)	0.998 (0.948–1.051)	<b>P=0.018</b>
Difference in categorical HLI score	Worsen vs Stable	1.071 (0.956–1.201)	1.081 (0.942–1.240)	1.035 (0.737–1.454)	1.061 (0.821–1.372)	P=0.818
	Improve vs Stable	1.014 (0.907–1.132)	0.978 (0.858–1.115)	1.219 (0.905–1.641)	1.023 (0.786–1.331)	P=0.179
	Improve vs Worsen	0.946 (0.822–1.089)	0.905 (0.766–1.069)	1.178 (0.802–1.728)	0.964 (0.705–1.318)	P=0.213
Difference in continuous HLI score, without smoking	1-unit increase*	0.987 (0.963–1.012)	0.975 (0.947–1.004)	1.052 (0.984–1.126)	0.991 (0.938–1.047)	<b>P=0.039</b>
Difference in continuous HLI score, without alcohol	1-unit increase*	0.974 (0.948–1.002)	<b>0.965 (0.935–0.997)</b>	1.048 (0.976–1.127)	0.961 (0.904–1.023)	<b>P=0.037</b>
Difference in continuous HLI score, without BMI	1-unit increase*	1.003 (0.978–1.029)	0.990 (0.961–1.020)	<b>1.071 (1.002–1.146)</b>	1.013 (0.958–1.072)	<b>P=0.030</b>
Difference in continuous HLI score, without physical activity	1-unit increase*	1.006 (0.975–1.037)	0.987 (0.952–1.023)	1.078 (0.992–1.171)	1.034 (0.963–1.110)	P=0.053
Difference in continuous smoking score	1-unit increase*	1.016 (0.952–1.086)	1.017 (0.941–1.099)	1.132 (0.966–1.326)	1.054 (0.888–1.252)	P=0.203
Difference in continuous alcohol score	1-unit increase*	1.039 (0.995–1.086)	1.016 (0.965–1.071)	1.096 (0.973–1.234)	1.094 (0.994–1.205)	P=0.251
Difference in continuous BMI score	1-unit increase*	<b>0.936 (0.880–0.996)</b>	0.930 (0.865–1.000)	1.022 (0.860–1.215)	0.914 (0.792–1.055)	P=0.319
Difference in continuous in physical activity score	1-unit increase*	0.980 (0.945–1.018)	0.973 (0.932–1.016)	1.045 (0.953–1.147)	0.964 (0.893–1.041)	P=0.156

\*1-unit increase, one-unit increase towards a healthier lifestyle. Bold font indicates statistical significance (P < 0.05). All models are stratified by age at recruitment – rounded to one year—and study centre, and adjusted for height, relative inequality index, oral contraceptive intake, menopausal hormone therapy intake, age at first menses, age at first full-term pregnancy, number of full-term pregnancies, HLI score at baseline, diet score at baseline, and the time in between baseline and follow-up questionnaires (log-transformed). Differences in individual HLI components were estimated simultaneously in a single model, with mutual adjustment for the other components

**Table 3** Association between categorised follow-up HLI score by categories of baseline HLI (n = 125,746 women)

Categorical HLI score at baseline	n (breast cancer events)	Categorical HLI score at follow-up		
		"0–8"	"8–11"	"11 +"
"0–8"	30,082 (479)	ref	0.851 (0.697–1.038)	0.848 (0.496–1.450)
"8–11"	67,259 (1,205)	1.050 (0.881–1.249)	ref	1.043 (0.897–1.213)
"11 +"	28,405 (491)	1.574 (0.759–3.266)	1.070 (0.880–1.302)	ref

All models are stratified by age at recruitment—rounded to one year—and study centre, and adjusted for height, relative inequality index, oral contraceptive intake, menopausal hormone therapy intake, age at first menses, age at first full-term pregnancy, number of full-term pregnancies, HLI score at baseline, diet score at baseline, and the time in between baseline and follow-up questionnaires (log-transformed).

postmenopausal breast cancer risk, stratified by baseline HLI tertiles (Table 3). Although some HRs suggested possible trends—such as an increased risk among women who decreased from the highest baseline HLI tertile (11+) to the lowest (0–8)—these estimates were imprecise and not statistically significant.

In the complete-case analysis (Supplementary Tables 1 and 2), the associations mainly persisted, with a notably stronger inverse association observed for each one-unit increase in BMI score and the risk of ER-positive breast cancer (HR: 0.895, 95% CI 0.822–0.975).

The results remained largely unchanged when the first, second, and third years of follow-up were omitted from the analyses (Supplementary Tables 3 and 4).

Results in non-MHT users at baseline (Supplementary Table 5) were generally consistent with the main analysis, except that the association with change in continuous BMI score lost statistical significance overall. Meanwhile, the association between change in continuous HLI score and risk of ER-negative breast cancer became significant

and remained robust when excluding each of its components in turn.

## Discussion

In a large prospective cohort of European women, we investigated changes in lifestyle habits over a median duration of 10 years and subsequent risk of postmenopausal breast cancer. Overall, we did not observe significant associations between HLI change and risk of postmenopausal breast cancer, although some associations seemed to differ by ER status. Among the individual lifestyle components, a one-unit improvement in the BMI score was associated with a 6.4% reduction in postmenopausal breast cancer risk.

The lack of any significant association between variations in HLI and the risk of postmenopausal breast cancer is consistent with findings from the NOWAC Study, which similarly reported no significant association between overall lifestyle changes, assessed using a five-component HLI (including the four-component HLI used in the present study plus a diet component) and breast cancer incidence [15]. However, other prospective studies have yielded contrasting results. A Swedish cohort study involving women aged 30 to 50 identified that improvements in a lifestyle score, which incorporated smoking and drinking habits, BMI, and physical activity, were linked to a reduced risk of lifestyle-related cancers, including breast cancer. The authors also reported a similar inverse association for breast cancer specifically ( $n = 685$  cases) [14]. The stronger associations reported in this prior Swedish study may reflect a combination of a younger participant profile at recruitment and an earlier age at behavioural change. Lifestyle modifications were assessed at a median age of around 52 years, with a substantial proportion of premenopausal women at follow-up, a group for whom certain lifestyle modifications may exert a different impact on risk trajectories.

When exploring the individual components of the HLI change, a one-unit increase in the BMI score (reflecting a shift towards a healthier BMI category) was significantly associated with a reduction in the risk of postmenopausal breast cancer of approximately 6.4%. Although there is evidence that weight gain since early adulthood, as well as in later life, increases the risk of postmenopausal breast cancer, data on weight loss or weight stabilisation in late adulthood remains limited [11, 25]. One recent study from the Pooling Project of Prospective Studies of Diet and Cancer is in agreement with our findings [26]. In this study conducted on 10 cohorts from the United States, Australia and Asia (the final analytic cohort included 180,885 women, among whom 6,930 breast cancer cases were identified), sustained weight loss, measured at two consecutive intervals with a median length of 5.2 and 4.6 years, in women aged 50 years and older, was

associated with a significantly lower risk of postmenopausal breast cancer compared with women with stable weight. The risk reduction was dose-dependent and observed exclusively among women who were not using postmenopausal hormones at the start of breast cancer follow-up, with HRs decreasing from 0.82 for a 2–4.5 kg weight loss (95% CI 0.70–0.96) to 0.68 for a loss of 9 kg or more (95% CI 0.50–0.93). In contrast, our study assessed lifestyle, including BMI, changes at a single interval and classified non-MHT users at baseline rather than at follow-up, which may limit comparability. Nonetheless, the analysis restricted to baseline non-MHT users showed similar trends to the main results, although the association with BMI change lost statistical significance overall.

Importantly, we did not observe an association between changes in the smoking score, the physical activity score or the alcohol score and breast cancer risk.

While a large-scale meta-analysis has established a modest but consistent dose–response relationship between active smoking and increased breast cancer risk [27], the potential risk reduction following smoking cessation remains unclear. Some studies suggest that quitting smoking does not significantly lower breast cancer risk compared to never smoking [28]. Moreover, no consistent reduction in risk has been observed with increasing time since cessation, smoking intensity, or duration [29], suggesting that the adverse effects of smoking on breast tissue may persist long after quitting.

Our results on physical activity were similar to those reported in the NOWAC study, which included premenopausal women at follow-up [15]. Consistent findings were also observed in the E3N cohort, the French component of EPIC, where repeated assessments of recreational physical activity showed that engaging in at least 12 MET-hours/week of recent activity (within the 4 previous years) was associated with a 10% lower risk of postmenopausal invasive breast cancer compared to less active women (HR = 0.90; 95% CI 0.82–0.99) [30]. These benefits were evident even with modest or less recent activity levels, and were independent of BMI, weight change, or ER/PR subtype.

Regarding alcohol, two previous cohort studies also did not observe any significant association between reduction in alcohol consumption and breast cancer risk. One Danish study observed non-significant trends towards an *increased* risk of postmenopausal breast cancer with decreasing alcohol consumption [13], a pattern that mirrors the direction of associations found in the current study. In contrast, the NOWAC study found that a one-unit improvement in the alcohol score was associated with a borderline statistically significant decrease in risk of postmenopausal breast cancer [15]. In our study, we observed a weak, non-significant trend suggesting higher risk with increasing alcohol scores (i.e., reduced intake).

We observed some differential associations based on ER status. Although confidence intervals largely overlapped with 1, point estimates suggested a decreased risk of ER-positive breast cancer and a potential increase in ER-negative breast cancer risk with HLI improvement. However, the number of ER-negative cases was relatively low ( $n=268$ ), limiting statistical power and increasing the likelihood of chance findings. Leave-one-out analyses also showed component-specific variations by ER status, particularly for alcohol and BMI, suggesting distinct contributions of these lifestyle factors by ER status. Among individual components, the inverse association observed for BMI was also seen for ER-positive breast cancer cases, consistent with prior evidence linking higher BMI with increased ER-positive breast cancer risk for postmenopausal women, as adipose tissue becomes the main source of circulating estrogens after menopause [31]. By contrast, findings remain more uncertain for the ER-negative subtype [32]. The literature on changes in overall lifestyle indices, such as the HLI, in relation to breast cancer risk by ER status remains very limited. Most existing studies have focused on individual lifestyle factors—such as body weight or BMI [33], or alcohol consumption [34]—rather than composite lifestyle scores.

This study's main strengths lie in its large sample size and prospective design across multiple countries and centres within the EPIC cohort. Additionally, our findings were robust across various analytical strategies, including multiple imputation and complete case analysis to address data missingness, and sensitivity analyses to account for potential reverse causality.

This study also has several limitations, the main one being the relatively short follow-up period for identifying incident breast cancer cases (a median of 3.7 years), which may have been too short to capture the full impact of lifestyle modifications on cancer development. For comparison, the Swedish Women's Lifestyle and Health Cohort Study had a longer median follow-up period of approximately 9.5 years after the second lifestyle assessment, while NOWAC had a median follow-up time of 14.2 years, potentially allowing a greater window to observe risk modifications. Moreover, variations across countries in follow-up duration, time intervals between questionnaires, and patterns of HLI change (results not shown) complicate the interpretation of how recent lifestyle modifications influence postmenopausal breast cancer risk. These differences may obscure clear associations, making it difficult to distinguish the effects of recent versus earlier exposures and possibly explaining the lack of strong, significant findings. Additionally, it remains uncertain whether the observed changes are sustained or substantial enough to affect risk. Another potential limitation is the fact that the HLI assigned equal weight to each component, despite evidence that

some, like smoking, may have a lesser influence on breast cancer risk than others, such as BMI. This might have attenuated the associations observed [35]. In addition, due to ongoing harmonisation of dietary data at follow-up in EPIC, no dietary component could be included in the HLI, despite its potential relevance to breast cancer risk [6]. Besides, although physical activity questionnaires differed between baseline and follow-up in some EPIC centres (e.g., household activities were only captured at follow-up in France, while Naples joined EPIC at a later stage), a standardised recoding protocol was implemented to harmonise non-dietary variables across centres and time points [17]. Thus, while some measurement error cannot be excluded, the observed changes in activity are likely to reflect true behavioural shifts rather than questionnaire artefacts. Lastly, we cannot exclude the possibility of exposure misclassification, as lifestyle data reflect the participants' habits at the time of follow-up assessment and may not represent long-term behaviours.

## Conclusions

In conclusion, this analysis of a large European cohort indicates that modest lifestyle modifications during midlife were not strongly associated with a reduction in risk of postmenopausal breast cancer. However, favourable BMI changes were associated with a decreased risk of postmenopausal breast cancer. This risk reduction, which arises from minor improvements in BMI during late adulthood—even during the menopausal transition, a period typically marked by weight gain—highlights the potential benefits of supporting healthy weight management in middle-aged women.

## Abbreviations

BMI	Body mass index
CI	Confidence interval
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
FFQ	Food frequency questionnaire
FTP	Full-term pregnancy
HLI	Healthy lifestyle index
HR	Hazard ratio
IARC	International Agency for Research on Cancer
MHT	Menopausal hormone treatment
MET	Metabolic equivalent of task
MICE	Multivariate imputation by chained equations
NOWAC	Norwegian Women and Cancer Study
OC	Oral contraceptive
SWLH	Swedish Women's Lifestyle and Health Cohort Study

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13058-025-02148-w>.

Supplementary Material 1

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#### IARC disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer /World Health Organisation.

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The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the WHO, its representatives, or the countries they represent.

#### Authors' information

The work reported in this paper was performed during Agnès Fournier's term as a Visiting Scientist at the International Agency for Research on Cancer. It was also performed during Bertrand Hemon's tenure as Senior Research Assistant in Data Management/Analysis, prior to his retirement from the International Agency for Research on Cancer.

#### Author contributions

FV, KM, LD, PF: conceptualisation of the study, primary data analyses, and drafting of the manuscript; CB: data provision, data management, preparation of documentation, assistance with programming; KM: close guidance throughout the analysis process and input in the interpretation of results; LD and PF: supervision of the study, conceptual input, and critical revision of the manuscript; EB: contribution to data analysis and manuscript drafting; CSA, AF, CM, CC, CLC, RTF, MBS, SS, SP, RT, FR, GM, AEH, EMM, AA, MG, SMCY, MJS, AL, STT, IGJ, MJG: provision of original data for the study, interpretation of results, manuscript reviewing and editing.

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#### Data availability

Access to EPIC data is regulated by the EPIC data access policy, as described in: [epic-europe-accesspolicy-01feb2023.pdf] (<https://epic.iarc.fr/docs/epic-europe-accesspolicy-01feb2023.pdf>). For further information, please contact the corresponding author, Dr Laure Dossus.

#### Declarations

##### Ethics approval and consent to participate

All study participants provided written informed consent in compliance with applicable ethical standards. Ethical approval was granted by all participating centres and the International Agency for Research on Cancer (IARC) Ethics Committee (reference number 25–21). The conduct of the EPIC cohort complied with the ethical principles for research involving human participants, as outlined in the Declaration of Helsinki.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

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