Lifestyle changes in middle age and risk of cancer: evidence from the European Prospective Investigation into Cancer and Nutrition

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Abstract

In this study, we aimed to provide novel evidence of the impact of changing lifestyle habits on cancer risk. In the EPIC cohort, 295,865 middle-aged participants returned a lifestyle questionnaire at baseline and during follow-up. At both timepoints, we calculated a healthy lifestyle index (HLI) score based on cigarette smoking, alcohol consumption, body mass index and physical activity. HLI ranged from 0 (most unfavourable) to 16 (most favourable). We estimated the association between HLI change and risk of lifestyle-related cancers - including cancer of the breast, lung, colorectum, stomach, liver, cervix, oesophagus, bladder, and others - using Cox regression models. We reported hazard ratios (HR) with 95% confidence intervals (CI). Median time between the two questionnaires was 5.7 years, median age at follow-up questionnaire was 59 years. After the follow-up questionnaire, we observed 14,933 lifestyle-related cancers over a median follow-up of 7.8 years. Each unit increase in the HLI score was associated with 4% lower risk of lifestyle-related cancers (HR 0.96; 95%CI 0.95-0.97). Among participants in the top HLI third at baseline (HLI>11), those in the bottom third at follow-up (HLI≤9) had 21% higher risk of lifestyle-related cancers (HR 1.21; 95%CI 1.07-1.37) than those remaining in the top third. Among participants in the bottom HLI third at baseline, those in the top third at follow-up had 25% lower risk of lifestyle-related cancers (HR 0.75; 95%CI 0.65-0.86) than those remaining in the bottom third. These results indicate that lifestyle changes in middle age can have a significant impact on cancer risk.

Keywords: lifestyle changes; healthy lifestyle index; cancer risk; cohort study.

Introduction

Cancer is a leading global cause of death. Estimates from the Global Cancer Observatory (GLOBOCAN) indicate that in 2020 there were approximately 19.3 million new cases of cancer and 10 million cancer deaths [1]. A large proportion of cancer cases could potentially be prevented by following public health recommendations on lifestyle habits. It has been estimated that cigarette smoking, alcohol consumption, high body mass index (BMI), low physical activity levels, and poor diet, account together for 22 to 40% of the total cancer burden [2-9]. Several large cohort studies have shown a joint effect of those five risk factors in increasing the incidence of cancer in different organs, such as colorectum [10-15], breast [12, 16, 17], pancreas [18, 19] and liver [14, 20] as well as all cancers combined [12, 17, 21].

The evidence on the association between lifestyle and risk of certain cancers is strong, but data on how lifestyle changes affect risk of cancer are scarce [22]. Apart from smoking cessation and smoking reduction, which have long been shown to reduce the risk of lung cancer, [23, 24] lifestyle changes and their impact on the risk of cancer have been investigated only recently and in a limited number of studies. Improving adherence to healthy lifestyle behaviours has been reported to reduce the risk of lifestyle-related cancers, particularly breast cancer and colorectal cancer [25-27]; becoming more physically active has been suggested to lower overall cancer mortality [28, 29]; while gaining weight [30] and increasing alcohol consumption [31] have been suggested to increase the risk of breast cancer in postmenopausal women.

With the aim of contributing to this limited knowledge, we examined the role of changing smoking habits, BMI, physical activity levels, alcohol consumption, and a lifestyle index which combines those four factors, on the subsequent risk of all cancers and lifestyle-related cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The analyses were carried out in the overall study population, as well as in subgroups defined by population characteristics, such as sex, age, level of education, and country of

residence. In addition, we estimated the proportion of cancers observed in EPIC potentially attributable to unhealthy lifestyle changes.

Methods

The rationale, study design, and methods of EPIC have been described in detail elsewhere [32]. Briefly, from 1992 to 2000, 521,323 participants, mainly aged from 35 to 70 years, were recruited from the general population across 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. All participants completed a lifestyle questionnaire at baseline.

We excluded 28,561 participants from Greece due to lack of available data, 24,550 with a history of cancer at baseline, 9,064 with extreme energy intakes (i.e., below the 1st and above the 99th percentiles of the energy intake over energy requirement ratio distribution) and 3,137 without follow-up (Supplementary Figure 1). After a median of 5.7 years (interquartile range 5.0-9.9) from recruitment, a second lifestyle questionnaire was administered. Since the exposure of interest was lifestyle changes, we additionally excluded 100,828 participants with no follow-up lifestyle assessment in the centralized EPIC data in October 2020, and 16,816 participants diagnosed with an incident cancer between the two questionnaires. We then excluded 3,426 participants with no follow-up time after the follow-up questionnaire, and 5,900 and 11,419 participants for whom information about all four lifestyle factors of interest - smoking status, alcohol consumption, BMI, and physical activity - was missing in the baseline and follow-up questionnaires, respectively. We finally excluded 21,757 participants for whom information of at least one of the four factors of interest was missing both at baseline and follow-up. Thus, the final analysis included 295,865 participants.

All participants provided informed consent to participate in the study. Ethical approval was obtained from the participating centres and the International Agency for Research on Cancer (IARC) ethics committee (reference number 20-02).

Exposure assessment

We focused on four lifestyle factors: cigarette smoking, alcohol consumption, BMI and physical activity. For each factor, scores that ranged from 0 to 4 were assigned to increasingly healthy behavioural categories. The "healthiest" behaviours were never smoking (never smoked=4 points, smoke cessation>10 years=3, smoke cessation≤10 years=2, current smoking≤15 cigarettes/day=1, current smoking>15 cigarettes/day=0), low consumption of alcohol (<6.0 g/day=4 points, 6.0–11.9=3, 12.0–23.9=2, 24.0–59.9=1, ≥60=0), top fifth of physical activity based on recreational and household metabolic equivalent of task units (METs) (5th fifth=4 points, 4th fifth=3, 3rd fifth=2, 2nd fifth=1, 1st fifth=0) and low BMI (<22 kg/m^2=4 points, 22-23.9=3, 24–25.9=2, 26–29.9=1, ≥30=0). A healthy lifestyle index (HLI) was obtained by summing the scores of the four lifestyle factors, thus ranging from 0 to 16 [21, 27]. Changes in the HLI score from the baseline questionnaire to the follow-up questionnaire was our main exposure of interest.

Information on diet was available only at baseline and was therefore not included in the HLI for the current analysis. Intakes of six dietary factors – namely cereal fiber, red and processed meat, the ratio of polyunsaturated to saturated fat, margarine (as a marker for industrially produced trans-fats), glycemic load, and fruits and vegetables - were combined in a diet score [16], which was used as an adjustment variable in all analyses.

Outcome assessment

First primary cancer cases were identified through population cancer registries in Denmark, Italy (except Naples), the Netherlands, Norway, Spain, Sweden, and the United Kingdom. A combination of methods was used, including health insurance records, contacts with cancer and pathology registries, and active follow-up of EPIC participants and their next of kin in Naples, France and Germany. Based on indications from the International Agency for Research on Cancer [33, 34], we divided the cancer cases into five lifestyle-related cancer subgroups, defined using the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD10):

1. Smoking-related cancers: cancers of the upper aero-digestive tract (including cancer of the mouth [C01–C10 without C08 = salivary gland], larynx [C32], pharynx [C11–C14], oesophagus [C15]), stomach [C16], colorectum [C18–C20], liver (hepatocellular carcinoma) [C22], pancreas [C25], trachea [C33], lung [C34], cervix uteri [C53], ovary [C56], kidney [C64], renal pelvis and ureter [C65, C66], bladder [C67], and acute myeloid leukaemia [C92.0];

2. Alcohol-related cancers: upper aero-digestive tract (including cancer of the mouth [C01–C10 without C08 = salivary gland], larynx [C32], pharynx [C11–C14], oesophagus [C15]), cancers of the colorectum [C18–C20], liver (hepatocellular carcinoma) [C22], and female breast [C50];

3. BMI-related cancers: cancers of the oesophagus (adenocarcinoma) [C15], cardia [C16.0], colorectum [C18-C20], liver (hepatocellular carcinoma) [C22], gallbladder [C23], pancreas [C25], female breast (after menopause) [C50], corpus uteri [C54], ovary [C56], kidney [C64], brain meningioma [C70.0], thyroid [C73], and multiple myeloma [C90.0];

4. Physical activity-related cancers: cancers of the colorectum [C18–C20] and female breast [C50];

5. Lifestyle-related cancers: combination of all cancers listed above.

Statistical methods

We described categorical variables using frequencies and percentages, and continuous variables using means and standard deviations (SD), or medians and the 25^{th} and 75^{th} percentiles. Many participants had incomplete lifestyle data (Supplementary Figure 1), therefore we imputed missing data by running a multivariate normal missing imputation (MI) model on the analytic dataset of 295,865 participants. In the imputation model we included the baseline and follow-up scores for smoking status, alcohol consumption, BMI, and physical activity. We additionally included EPIC centre, sex, educational level, age at follow-up questionnaire, log-time between questionnaires, diet score at baseline, cancer status, and the log-time to end of follow-up. For the ordinal variables, we followed the projected distance rounding method, based on indicators [35]. We generated 15 imputed datasets, analysed each dataset individually, and then combined the estimates and the associated standard errors using the Rubin's rules [36].

Study participants were followed-up from the date of follow-up questionnaire administration until the date of cancer diagnosis (including any first cancer except non-melanoma skin cancer), death, emigration, or administrative censoring, whichever came first. We used multivariable Cox regression models to estimate the association between lifestyle changes and the risk of any cancer and lifestyle-related cancers, and we reported hazard ratios (HR) with the corresponding 95% confidence intervals (CI). We considered participants' age as the underlying time scale. We stratified the models by study centre, age at recruitment in 1-year categories, and sex, and we adjusted for the highest education level achieved (none or primary; technical, professional or secondary; university or higher; missing), diet score at baseline, calendar date of follow-up questionnaire, and HLI score at baseline as a continuous variable. To define lifestyle changes we used the difference between the HLI score at follow-

up and the HLI score at baseline as a continuous variable (Model 1) and as a categorical variable (seven categories: ≤-3, -2, -1, 0, 1, 2, and ≥3; Model 2). In two additional models, we estimated the association between changes in the four individual components (mutually adjusted) and the risk of any cancer and lifestyle-related cancers. To test for possible synergistic associations of lifestyle changes on the risk of lifestyle-related cancers, pairwise interaction terms (e.g., changes in smoking score * changes in BMI score) were, in turn, included in the Cox model. We finally built four additional models using four different outcomes: smoking-related, alcohol-related, BMI-related, and physical activity-related cancers. We used two decimals for the CIs, but we reported three decimals in some cases to show full statistical significance.

We computed estimates of Model 1 separately by sex, age at recruitment (≤55 or >55 years), education, country of residence, and time between questionnaires (≤ or > median value). We investigated heterogeneity of the estimates between the specified subgroups using the Cochran's Q test. We repeated Model 1 after removing one lifestyle component at a time from the HLI and adjusting the model for that component. To assess reverse causality, we fitted models with follow-up time starting one, two, three, four, and five years after the follow-up questionnaire. We also presented Kaplan-Meier curves for lifestyle-related cancer free survival stratified by thirds of HLI at follow-up. To visualize how lifestyle evolved over time in the study population, we presented Sankey flow diagrams for the individual lifestyle component scores, as well as for the total HLI score in thirds, and we reported mean HLI changes by country in a forest plot.

To quantify the proportion of lifestyle-related cancer cases attributable to a decrease in the HLI score, we estimated population-attributable fractions (PAF), using the method described by Spiegelman et al.[37] PAF models were adjusted for the same variables used in the main analysis. HLI score changes were categorized as increase (reference category; HLI

changes>0), no change (HLI changes=0) or decrease (HLI changes<0). The decrease category was further categorized as 1 point decrease, 2 points decrease and >2 points decrease.

As a sensitivity analysis, we repeated Model 1 and Model 2 limiting the analysis to only participants with non-missing data for all four HLI components in both questionnaires (complete case analysis, Supplementary Figure 1).

Results with p-value <0.05 were considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The median time from the baseline to the follow-up questionnaire was 5.7 years (mean 7.0 years, interquartile range 5.0-9.9). Participants' characteristics at the time of the follow-up questionnaire are reported in Table 1. In women, the median age was 58.6 years, the median BMI 24.5 kg/m2, median physical activity 76.0 METs and median alcohol consumption was 4.1 grams/day (g/d). Corresponding figures in men were 59.2 years, 26.4 kg/m^2, 60.0 METs, and 13.5 g/d. The proportion of current smokers was 15.1% in women and 21.0% in men.

Mean HLI score was 10.04 units (SD 2.8) at baseline and 9.95 (SD 2.7) at follow-up (mean change -0.09 units [SD 2.1]; Supplementary Figure 2). The largest positive HLI change was observed in Denmark, while the largest negative HLI change occurred in Norway. Participants' age at baseline tended to be higher in countries with positive HLI changes than in countries with negative HLI changes. Men made healthier changes than women, in total and in each country. Participants' characteristics at follow-up by HLI score changes are reported in Supplementary Table 1. Increases in the HLI score were larger in men with higher education (mean HLI change=0.20) than men with lower education (0.11); decreases in HLI score were

smaller in women with higher education (-0.18) than women with lower education (-0.29). Smoking was the HLI component that varied the less between the two questionnaires, while physical activity varied the most (Figure 1).

Among 295 865 participants, we observed 24 245 cancers, of which 14 933 were lifestyle-related. The median follow-up time after administration of the follow-up questionnaire was 7.8 years. The association between lifestyle changes and the risk of lifestyle-related cancer is shown in Table 2. A one-unit increase in HLI score from baseline to follow-up was associated with a 4% lower risk of lifestyle-related cancer (HR=0.96; 95% CI 0.95-0.97). The association was stronger in men (HR 0.94; 95% CI 0.93-0.96) than women (HR 0.97; 95% CI 0.96-0.98; p-value for heterogeneity 0.007; Figure 2). In women, we evaluated the association in different subgroups defined by menopausal status at follow-up and by changes in menopausal status from baseline to follow-up, and results were similar (data not shown). Age, education, country, and time between questionnaires did not significantly influence the association. Compared to no change in HLI score, decrements of ≥3 units were associated with a 16% higher risk of lifestyle-related cancer (HR 1.16; 95% CI 1.09-1.25), while increments of ≥3 units were associated with a 13% lower risk of lifestyle-related cancer (HR 0.87; 95% CI 0.81-0.94).

When analysing the single components of the HLI, we observed that increases in the smoking score, obtained for example by quitting smoking, were associated with a reduced risk of smoking-related cancers, increases in the BMI score (i.e., decreases in BMI) were associated with a reduced risk of BMI-related cancers, and increases in the physical activity score (i.e., increases in physical activity level) were associated with a reduced risk of physical activity-related cancers (Table 3). Increases in the alcohol score showed a trend towards a risk reduction of alcohol-related cancers. We evaluated the interactions between changes in one factor and changes in another factor and their association with the risk of lifestyle-related cancer, and we did not find any significant result (data not shown). When we removed one component at a time

from the HLI, we found that removal of smoking had the largest impact on the association between changes in HLI score and the risk of lifestyle-related cancers (Figure 2).

Changes in HLI score according to HLI thirds are represented in Supplementary Figure 3. Among participants in the top HLI third at baseline (HLI>11), those in the bottom third at follow-up (HLI≤9) had a 21% higher risk of lifestyle-related cancers (HR 1.21; 95%CI 1.07-1.37) than those remaining in the top third (Figure 3). The crude incidence rates of lifestyle-related cancers in the two groups were 6.0 and 4.9 per 100,000 person-years, respectively. Among participants in the bottom HLI third at baseline, those in the top third at follow-up had a 25% lower risk of lifestyle-related cancers (HR 0.75; 95%CI 0.65 to 0.86) than those remaining in the bottom third. The crude incidence rates of lifestyle-related cancers in the two groups were 6.8 and 8.0 per 100,000 person-years, respectively.

We estimated that, regardless of the baseline HLI score, 5.6% (95%CI 3.8-7.5) of the observed lifestyle-related cancers were attributable to negative HLI score changes (i.e., HLI changes <0; 4.7%, 95%CI 2.2-7.2 in females and 7.1%, 95%CI 3.8-10.3 in males; supplementary Table 2): 1.6% (95%CI 0.7-2.9) attributable to HLI decreases of 1 point, 1.6% (95%CI 0.9-2.3) to decreases of 2 points and 2.4% (95%CI 1.7-2.9) to decreases of 3 points or more. We estimated that, if all EPIC participants had increased their HLI score by at least one point (i.e., HLI changes >0), we would have observed 7.4% (95%CI 4.6-10.2) fewer lifestyle-related cancers (6.7%, 95%CI 3.1-10.3 in females and 8.5%, 95%CI 3.8-13.3 in males).

We also found associations between lifestyle changes and overall cancer risk, with a similar pattern but weaker associations than for lifestyle-related cancer (Supplementary Tables 3 and 4). Notably, we did not find an association between HLI score changes and those cancer types that were not included in the lifestyle-related cancers (n=9 312; HR 1.00; 95% CI 0.99-1.01 for each unit HLI increase). Compared to participants in the main analysis, participants in the complete-case analysis were younger (mean age 55.3 vs. 58.3 years) and included a larger

proportion of men (34.7% vs 28.1%) at the follow-up questionnaire. In the complete-case analysis the associations were similar to those observed in the main analysis (Supplementary Table 5). The results did not change when the first year, two years, three years, four years, and five years of follow-up were excluded from the analysis (Figure 2).

Discussion

In this cohort including almost 300 000 longitudinally followed European adult men and women, we observed important changes in cancer risk associated with changes in lifestyle behaviours. Specifically, healthy changes equivalent to one point increase in the HLI score were followed by a 4% reduced risk of lifestyle-related cancers and a 2% reduced risk of all cancers. Compared to remaining in the same third, improvements from the lowest third of the HLI score (0-9 points) to the highest (12-16 points) were associated with a 25% risk reduction of lifestyle-related cancers, while declines from the highest to the lowest third were associated with a 21% risk increase of lifestyle-related cancers. We estimated that 5.6% of the observed lifestyle-related cancers were attributable to unhealthy lifestyle changes (i.e., HLI score changes <0).

Only a small number of studies have investigated the association between changes in multiple lifestyle behaviours and risk of cancer. A Norwegian randomized intervention trial showed that men at high risk of coronary heart disease who made healthy improvements in their smoking habits and diet when aged in their 40s had a lower subsequent risk of lifestyle-related cancers, compared to men who did not [26]. A Swedish cohort study among middle-aged women showed that improvements in a combination of lifestyle behaviours, namely smoking habits, BMI, physical activity level and alcohol consumption, were associated with a reduced risk of lifestyle-related cancers, and in particular breast cancer [25]. A recent analysis within the EPIC cohort found that healthy lifestyle changes in the same four lifestyle behaviours were associated with a decreased colorectal cancer risk, while unhealthy changes were associated

with an increased colorectal cancer risk [27]. Finally, a recent cohort study with long-term follow-up conducted in the US showed that participants who maintained a healthy lifestyle through their mid-life and late life had a higher probability to reach 85 years of age without major chronic diseases, including cancer, compared to individuals who did not [38]. All this evidence is in line with our results, which showed a clear association between lifestyle changes and risk of lifestyle-related cancer. It is important to emphasise that the association between lifestyle changes and risk of lifestyle-related cancer was bidirectional, meaning that changing from an unfavourable to a favourable lifestyle was associated with a reduced risk of lifestyle-related cancer, while changing from a favourable to an unfavourable lifestyle was associated with increased risk of lifestyle-related cancer. In addition, our results showed that the maintenance of a healthy lifestyle was associated with the lowest risk of lifestyle-related cancers.

The association between lifestyle changes and risk of lifestyle-related cancer was stronger in men than in women: healthy changes equivalent to one point increase in the HLI score were followed by a 6% (95% CI 4%-7%) reduced risk of lifestyle-related cancers in men, and 3% (95% CI 2%-4%) in women. This could be due to the fact that, within the same lifestyle change patterns, men experienced larger and possibly more impactful changes than women. For example, among participants who smoked at baseline but not at follow-up, men smoked 15 cigarettes/day on average at baseline, while women smoked 11 cigarettes/day; among participants who consumed alcohol at baseline but not at follow-up, men consumed 9 grams/day of alcohol on average at baseline, while women consumed 3 grams/day.

When evaluating changes in the single lifestyle behaviours, smoking was the most stable over time. Changes in smoking were mainly determined by smoking reduction and cessation among initial smokers, and sustained smoking abstinence in initial ex-smokers. We found that increases in the smoking score were associated with a decreased risk of smoking-related

cancers. This is in line with the existing literature showing that smoking cessation, reduction and sustained abstinence after quitting decrease the risk of cancer in the lung [23, 24], upper aerodigestive tract [39, 40], and colorectum [41]. We also observed that removal of smoking from the HLI score weakened the association between HLI changes and cancer risk more than the removal of alcohol consumption, BMI or physical activity. This observation can potentially be explained by the fact that the impact of smoking on the risk of common lifestyle-related cancers, such as lung cancer and cancer of the upper aero-digestive tract, is larger than the impact of the other three factors on any lifestyle-related cancer type. Therefore, changes in smoking might be more important than changes in the other three factors. We found that increases in the BMI score were associated with a decreased risk of BMI-related cancers. In accordance with these findings, previous studies suggested that weight gain increased the risk of colorectal cancer, endometrial cancer, and breast cancer in postmenopausal women, while weight loss decreased the risk of endometrial cancer [30, 42, 43]. In earlier studies, cessation of alcohol consumption in adult age has been found to reduce the risk of several alcohol-related cancers [44-46], whereas increases in alcohol consumption have been suggested to increase the risk of breast cancer [31]. In our study, we found only weak evidence suggesting an association between changes in alcohol consumption and alcohol-related cancers. A possible explanation is that the alcohol score was inadequate to study the association of interest, as it did not incorporate information on alcohol consumption before the baseline questionnaire. We observed a large variability in physical activity changes, and we found an association between changes in physical activity levels and physical activity-related cancers, namely breast and colorectal cancer. Previous observational studies suggested that increases in physical activity level and fitness were associated with lower cancer risk and mortality [28, 29].

Despite the substantial literature on the PAF of cancer incidence related to lifestyle factors [2-9], there are, to our knowledge, no prior studies estimating PAF of cancer incidence

related to changes in lifestyle factors. The present analysis found that preventing unhealthy lifestyle changes (i.e., HLI changes < 0) could have reduced the burden of the lifestyle-related cancers in EPIC by 5.6%, regardless of baseline lifestyle. Moreover, we estimated that if all participants had improved their lifestyle by any extent (i.e., HLI changes > 0), we would have observed 7.4% fewer lifestyle-related cancers. These results highlight the vast potential for reducing cancer morbidity through the implementation of lifestyle preventive measures. Future research should investigate which measures can result in beneficial and impactful lifestyle changes at population level.

To our knowledge, this is the largest study to assess the relationship between multifactorial lifestyle changes and the risk of cancer. The major strengths of the analysis include the large sample size, the prospective multicentre design and multifactorial lifestyle assessment. We used a scoring system that was successfully applied previously in EPIC publications [21, 27] to ensure consistency and comparability across analyses and studies. Furthermore, we compared two consecutive lifestyle assessments to estimate lifestyle changes and, in doing so, we limited the risk of recall bias, which conversely can affect those studies that retrospectively calculate past exposure trajectories to define lifestyle changes. Finally, the fact that we did not find any association between HLI changes and the risk of those cancer types that are thought to be unrelated to lifestyle indicates that residual confounding causing spurious associations is unlikely.

This study has several limitations. The lack of data on dietary changes between baseline and follow-up may have led to inadequately adjusted risk estimates and residual confounding. Improvements in diet might be positively associated with improvements in the HLI score and inversely associated with the risk of cancer. If this is the case, the observed associations between the HLI score and cancer risk were possibly overestimated. In addition, the lack of diet in the lifestyle score might hamper the comparison between our study and previous studies that

included diet in their lifestyle scores. Dietary data at follow-up are currently being harmonized in EPIC. Moreover, educational level was used as a proxy for socioeconomic status. The lack of other important socioeconomic variables, such as ethnicity or income, may have introduced residual confounding. Also, the HLI score assumed equal strengths of associations between each lifestyle component and cancer risk and may inadequately capture the complex relationship between lifestyle habits and risk of cancer. The main aim of the present study was, however, to investigate the association between the changes over time in a pre-defined version of the HLI and the risk of cancer. Another limitation is that changes between two timepoints can only roughly represent real lifestyle changes, and this might have led to non-differential misclassification bias and underestimation of the associations of interest. The relatively short follow-up time after the assessment of lifestyle changes is a further limitation, as the effect of lifestyle changes on certain cancer types might emerge after a longer time. A longer follow-up might have led to stronger association estimates.

In conclusion, this analysis of a large European cohort indicates that lifestyle changes during adulthood can have a significant impact on cancer risk in both men and women, but even more so in men. We showed that favourable lifestyle changes are associated with reduced cancer risk, and that unfavourable changes are associated with increased cancer risk. The reduction of cancer risk derived from even small lifestyle improvements and from avoidance of unhealthy lifestyle changes, even in adults or elderly people, should be emphasized by policy makers when planning health measures, and by clinicians and general practitioners when giving advice to their patients.

Figure 1. Sankey diagrams for the healthy lifestyle index individual component scores at baseline and at follow-up

BMI: body mass index.

Figure 2. Association between one unit increase in the healthy lifestyle index score from baseline to follow-up and risk of lifestyle-related cancers

HR: hazard ratio. CI: confidence interval. The overall model was stratified by study centre, age and sex, and adjusted for education, diet score at baseline, continuous healthy lifestyle index score at baseline, and calendar year of follow-up questionnaire. When the model was stratified by a variable, that variable was removed from the model. We reported Cochran's Q test p-values for heterogeneity between the strata. We repeated the overall model after removing from the HLI one lifestyle component at a time, and adjusting the model for that component. We repeated the overall model after excluding the first year, two years, three years, four years, and five years of follow-up.

Figure 3. Survival analysis by thirds of the healthy lifestyle index score at follow up in: A) participants in the bottom third at baseline (healthy lifestyle index from 0 to 9); B) participants in the middle third at baseline (healthy lifestyle index of 10 and 11); C) participants in the top third at baseline (healthy lifestyle index from 12 to 16).

LRC: lifestyle-related cancer. HLI: healthy lifestyle index. PY: person-years. HR: hazard ratio. CI: confidence interval.

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IARC disclaimer

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Data availability

Access to the EPIC data is governed by the EPIC access policy, as detailed in https://epic.iarc.fr/docs/EPIC-Europe_AccessPolicy_01Feb2023.pdf. Please contact the corresponding author, Dr Pietro Ferrari, for more information.

Competing interests

The authors have no relevant interests to disclose.

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Table 1. Characteristics of the cohort at administration of the follow-up questionnaire

	Total	Females	Males
No. of participants	295 865	212 719	83 146
BMI (kg/m^2)	25.1 (22.7-28)	24.5 (22.2-27.6)	26.4 (24.4-28.7)
METS recreational and household activity	70 (42-107.5)	76.0 (46.4-115.3)	60.0 (35.5-92.0)
Alcohol (g/d)	5.9 (0.9-15.7)	4.1 (0.6-11.8)	13.5 (4.3-28.7)
Smoking status			
Never	138 653 (49.9)	110 648 (56.1)	28 005 (34.7)
Former	92 509 (33.3)	56 793 (28.8)	35 716 (44.3)
Current	46 750 (16.8)	29 765 (15.1)	16 985 (21.0)
Age (years)	58.7 (52.4-64.8)	58.6 (52.1-64.7)	59.2 (53.3-65.1)
Highest school level			
None or primary	85 568 (30.0)	58 515 (28.6)	27 053 (33.4)
Secondary	125 443 (43.9)	95 922 (46.9)	29 521 (36.4)
University or higher	74 419 (26.1)	49 934 (24.4)	24 485 (30.2)
Country			
France	48 209 (16.3)	48 209 (22.7)	0 (0.0)
United Kingdom	45 937 (15.5)	33 126 (15.6)	12 811 (15.4)
Germany	41 973 (14.2)	24 235 (11.4)	17 738 (21.3)
Denmark	40 151 (13.6)	21 997 (10.3)	18 154 (21.8)
Spain	37 895 (12.8)	24 287 (11.4)	13 608 (16.4)
Italy	29 036 (9.8)	20 571 (9.7)	8465 (10.2)
Norway	23 332 (7.9)	23 332 (11.0)	0 (0.0)
Sweden	18 484 (6.3)	10 931 (5.1)	7553 (9.1)
The Netherlands	10 848 (3.7)	6031 (2.8)	4817 (5.8)
Diet score at baseline	28 (23-32)	28 (23-32)	27 (23-32)
HLI score at baseline	10 (8-12)	11 (9-12)	9 (7-11)
HLI score at follow-up	10 (8-12)	11 (9-12)	9 (7-11)

BMI: body mass index. METs: metabolic equivalent of task. HLI: healthy lifestyle index. Continuous variables are summarized as median and interquartile range, categorical variables as frequency and column percentage.

Table 2. Association between lifestyle changes from baseline to follow-up and risk of lifestyle-related cancers

		Total (n=295 865)	Females (n=212 719)	Males (n=83 146)
	No. cases (rate*1000 PY)	14 933 (6.5)	10 634 (6.7)	4299 (5.9)
		HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Model 1: changes in HLI score in continuous	One unit increase	0.96 (0.95-0.97)	0.97 (0.96-0.98)	0.94 (0.93-0.96)
Model 2: changes in HLI score in categories	≤ -3 vs 0 units	1.16 (1.09-1.25)	1.09 (1.01-1.18)	1.38 (1.20-1.60)
	-2 vs 0 units	1.07 (1.00-1.15)	1.03 (0.95-1.12)	1.17 (1.01-1.36)
	-1 vs 0 units	1.02 (0.95-1.08)	0.98 (0.91-1.05)	1.12 (1.00-1.27)
	1 vs 0 units	0.94 (0.88-0.999)	0.94 (0.87-1.01)	0.95 (0.85-1.07)
	2 vs 0 units	0.89 (0.83-0.97)	0.88 (0.80-0.98)	0.93 (0.82-1.05)
	≥ 3 vs 0 units	0.87 (0.81-0.94)	0.88 (0.80-0.97)	0.85 (0.76-0.96)

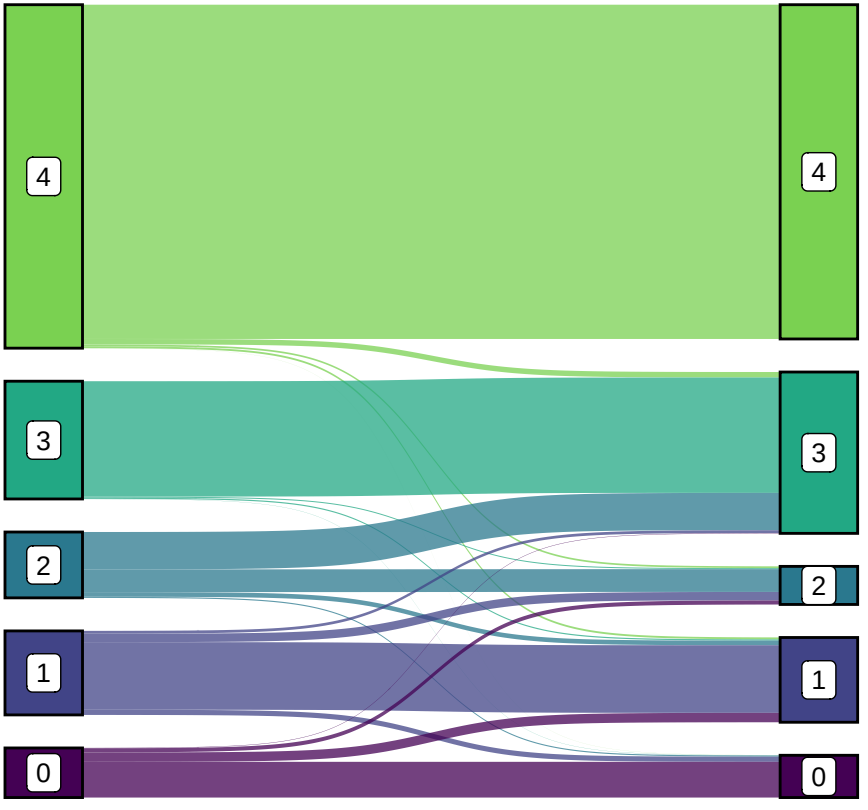
HLI: healthy lifestyle index. PY: person-years. HR: hazard ratio. CI: confidence interval. Models were stratified by study centre, age and sex, and adjusted for education, diet score at baseline, continuous healthy lifestyle index score at baseline, and calendar year of follow-up questionnaire.

Table 3. Association between changes in each individual lifestyle factor from baseline to follow-up and risk of lifestyle-related cancers

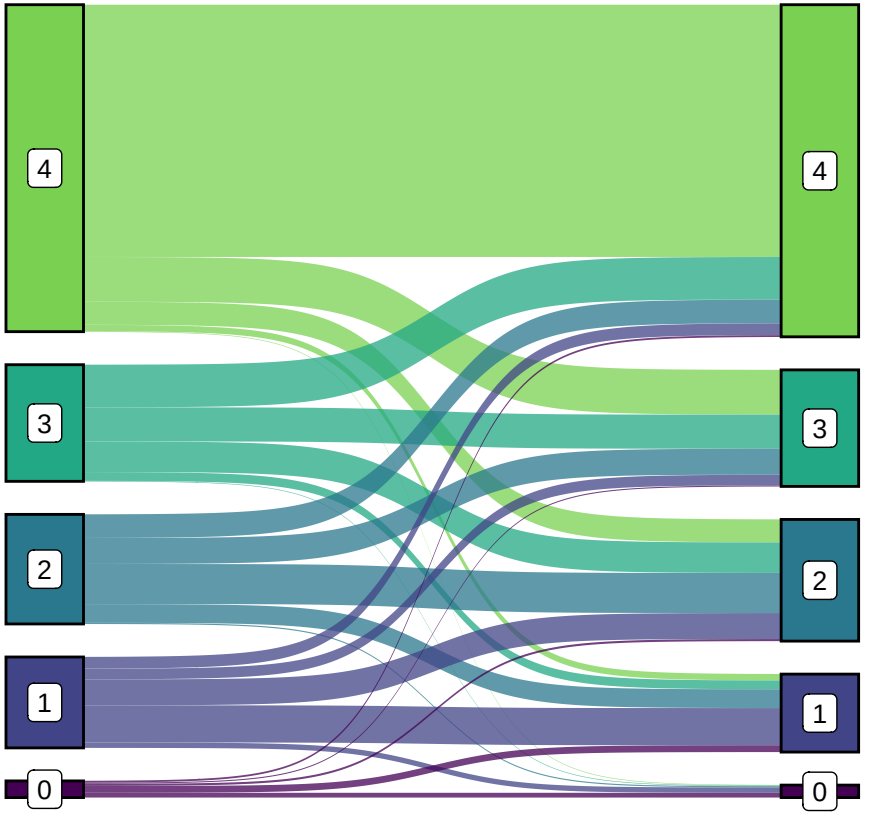
		Total (n=295 865)		Females (n=212 719)		Males (n=83 146)	
		No. cases (rate*1000 PY)	**HR (95% CI)**	**No. cases (rate*1000 PY)**	**HR (95% CI)**	**No. cases (rate*1000 PY)**	**HR (95% CI)**
One unit increase in smoking score	**Lifestyle-related cancers**	14 933 (6.5)	0.97 (0.94-1.01)	10 634 (6.7)	0.98 (0.93-1.03)	4299 (5.9)	0.94 (0.88-0.996)
	Smoking-related cancers	8513 (3.7)	0.94 (0.90-0.99)	4389 (2.8)	0.94 (0.87-1.02)	4124 (5.7)	0.94 (0.88-0.997)
One unit increase in alcohol score	**Lifestyle-related cancers**	14 933 (6.5)	1.00 (0.98-1.02)	10 634 (6.7)	1.00 (0.97-1.03)	4299 (5.9)	1.00 (0.97-1.04)
	Alcohol-related cancers	8578 (3.7)	0.98 (0.96-1.01)	6738 (4.3)	0.99 (0.96-1.03)	1840 (2.5)	0.97 (0.91-1.02)
One unit increase in BMI score	**Lifestyle-related cancers**	14 933 (6.5)	0.98 (0.95-1.00)	10 634 (6.7)	0.98 (0.95-1.00)	4299 (5.9)	0.99 (0.94-1.05)
	BMI-related cancers	8893 (3.9)	0.94 (0.91-0.98)	6638 (4.2)	0.95 (0.92-0.99)	2255 (3.1)	0.92 (0.85-0.99)
One unit increase in physical activity score	**Lifestyle-related cancers**	14 933 (6.5)	0.97 (0.96-0.99)	10 634 (6.7)	0.97 (0.96-0.99)	4299 (5.9)	0.97 (0.95-0.995)
	Physical activity-related cancers	7753 (3.4)	0.97 (0.95-0.99)	6455 (4.1)	0.97 (0.95-0.998)	1298 (1.8)	0.96 (0.91-1.01)

BMI: body mass index. PY: person-years. HR: hazard ratio. CI: confidence interval. The five models for lifestyle-related, smoking-related, alcohol-related, BMI-related and physical activity-related cancers were stratified by study centre, age and sex, and adjusted for education, diet score at baseline, continuous index components scores at baseline, and date of follow-up questionnaire. All models also included changes in the four individual lifestyle factors simultaneously.

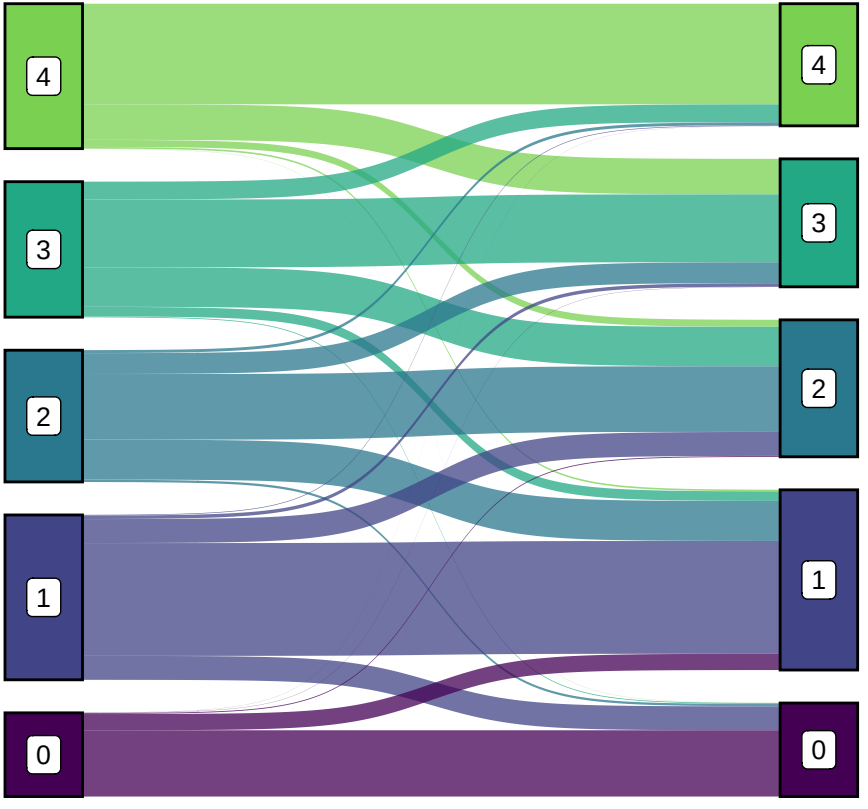
Smoking score



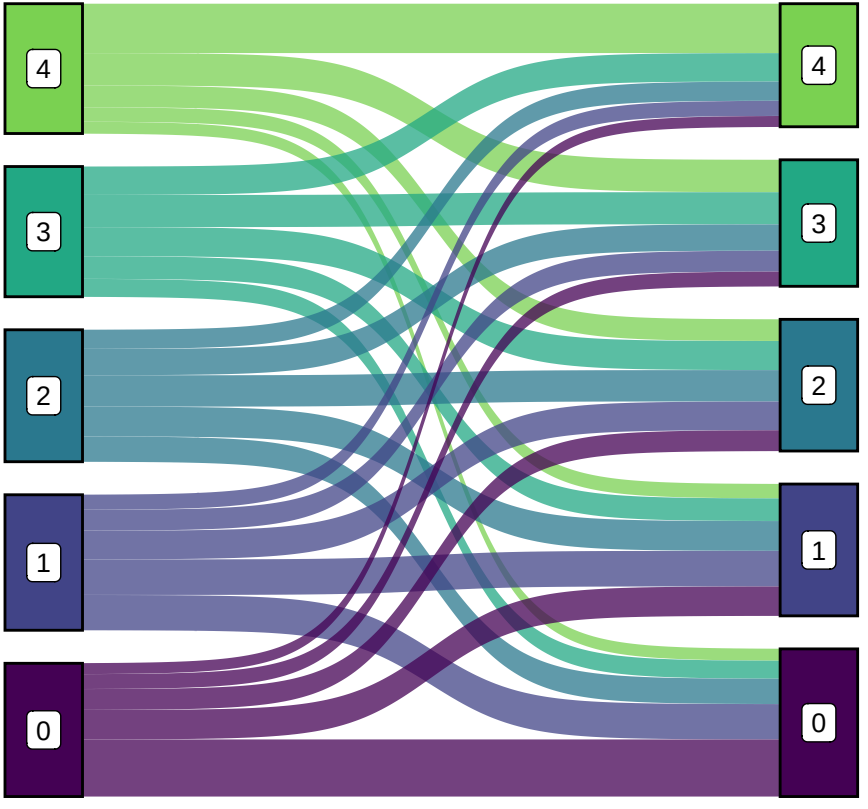
Alcohol score

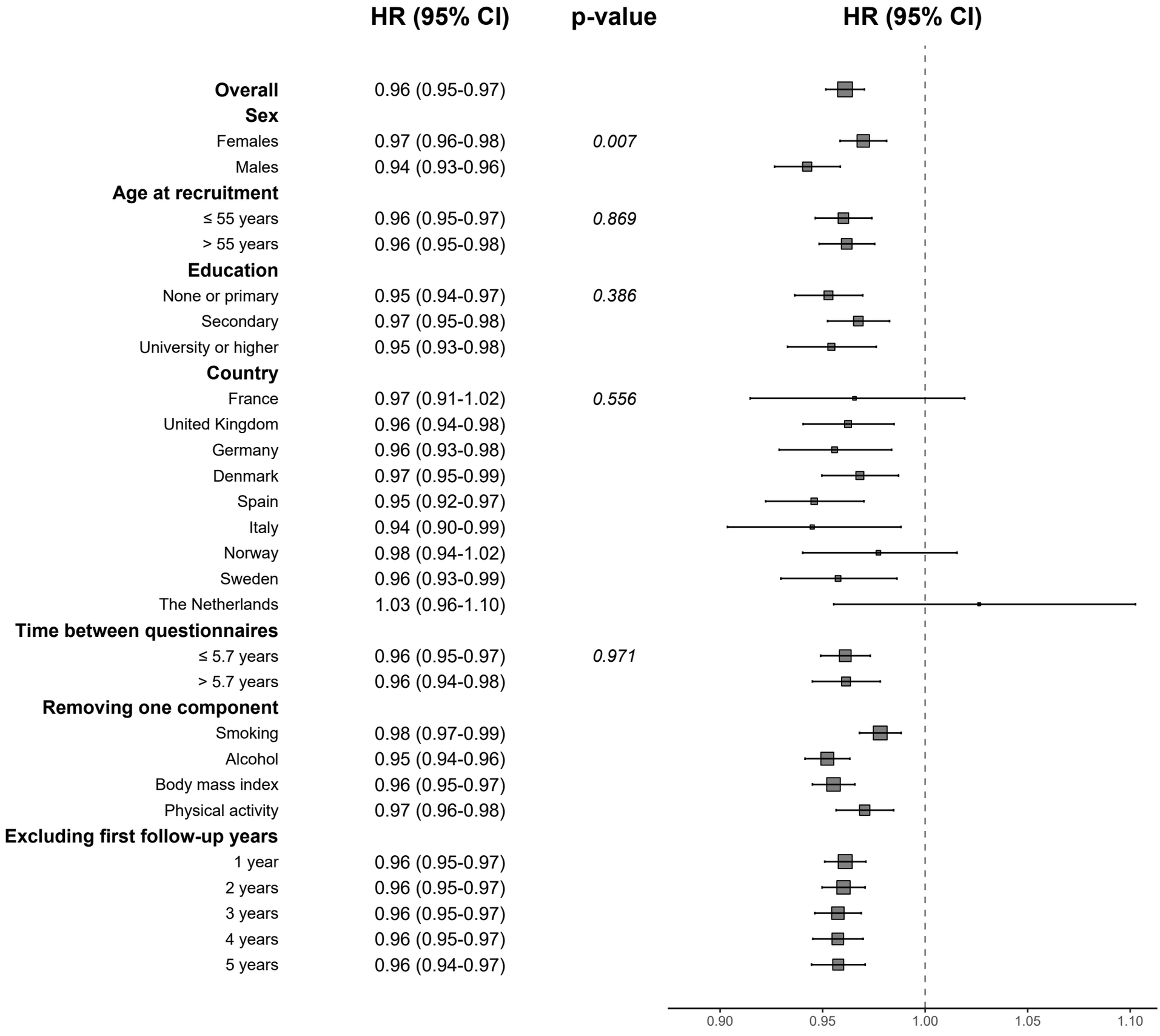


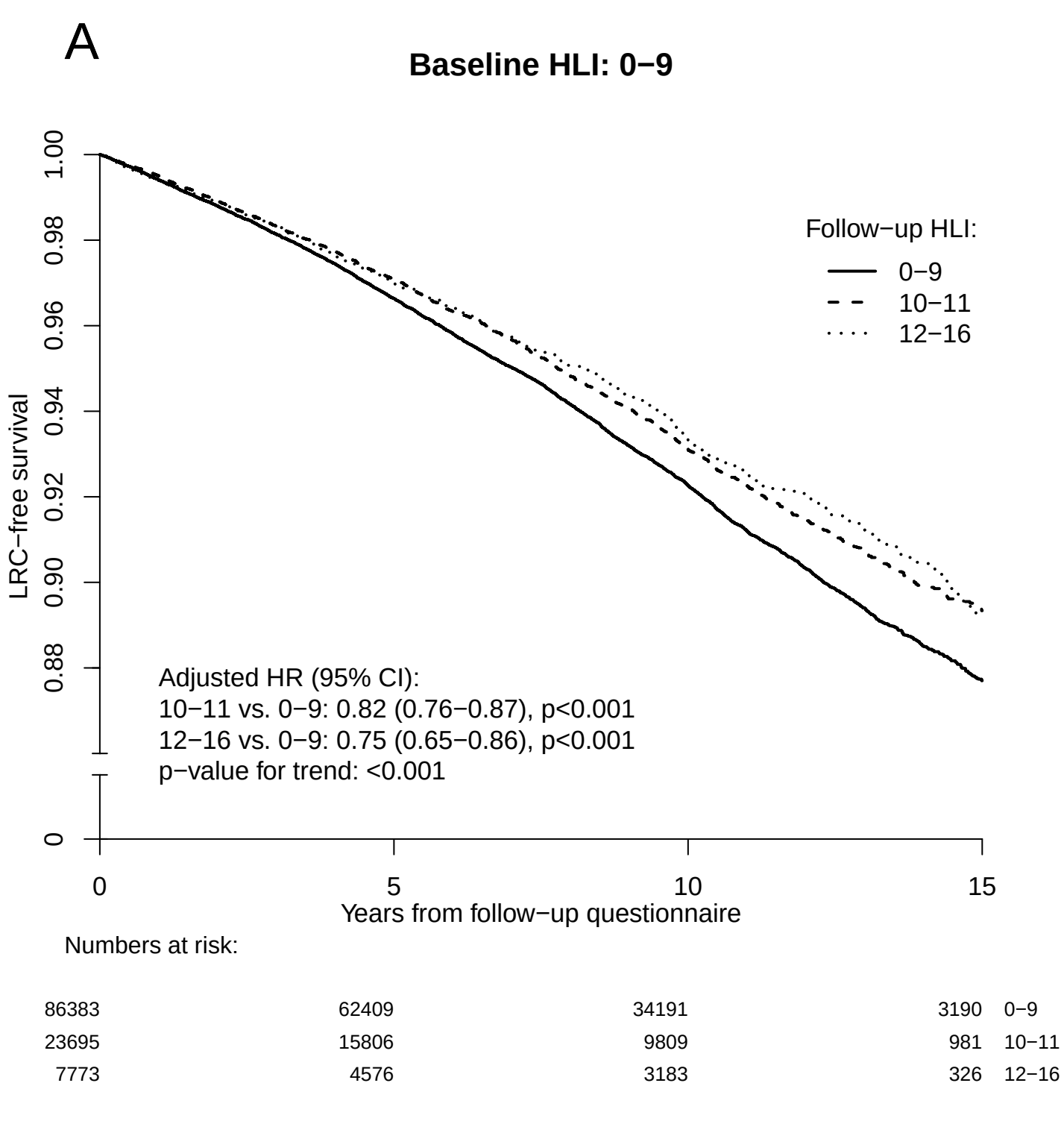
BMI score

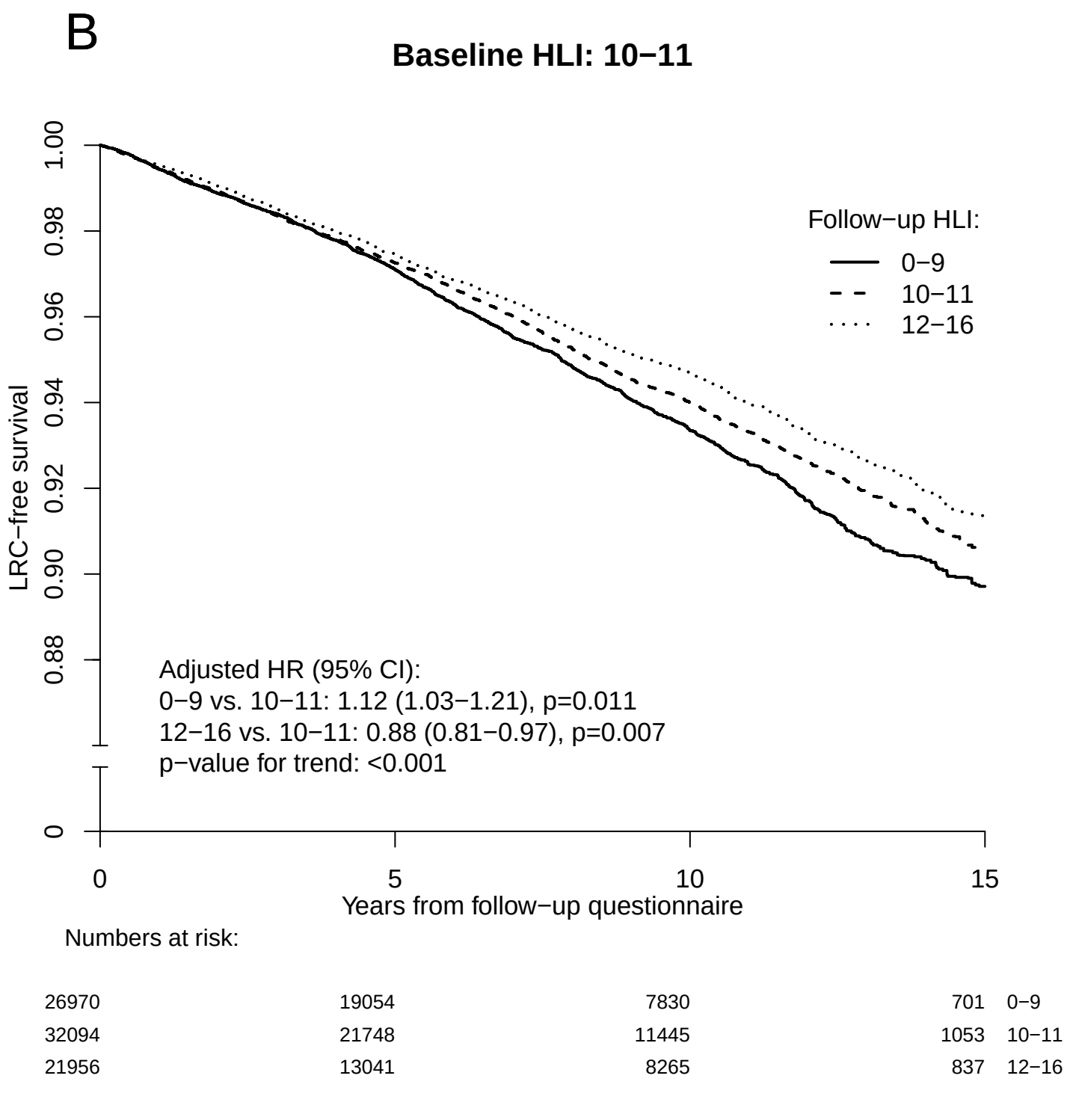

4
3
2
1
0
4
3
2
1
0
Baseline questionnaire
Follow−up questionnaire

Physical activity score



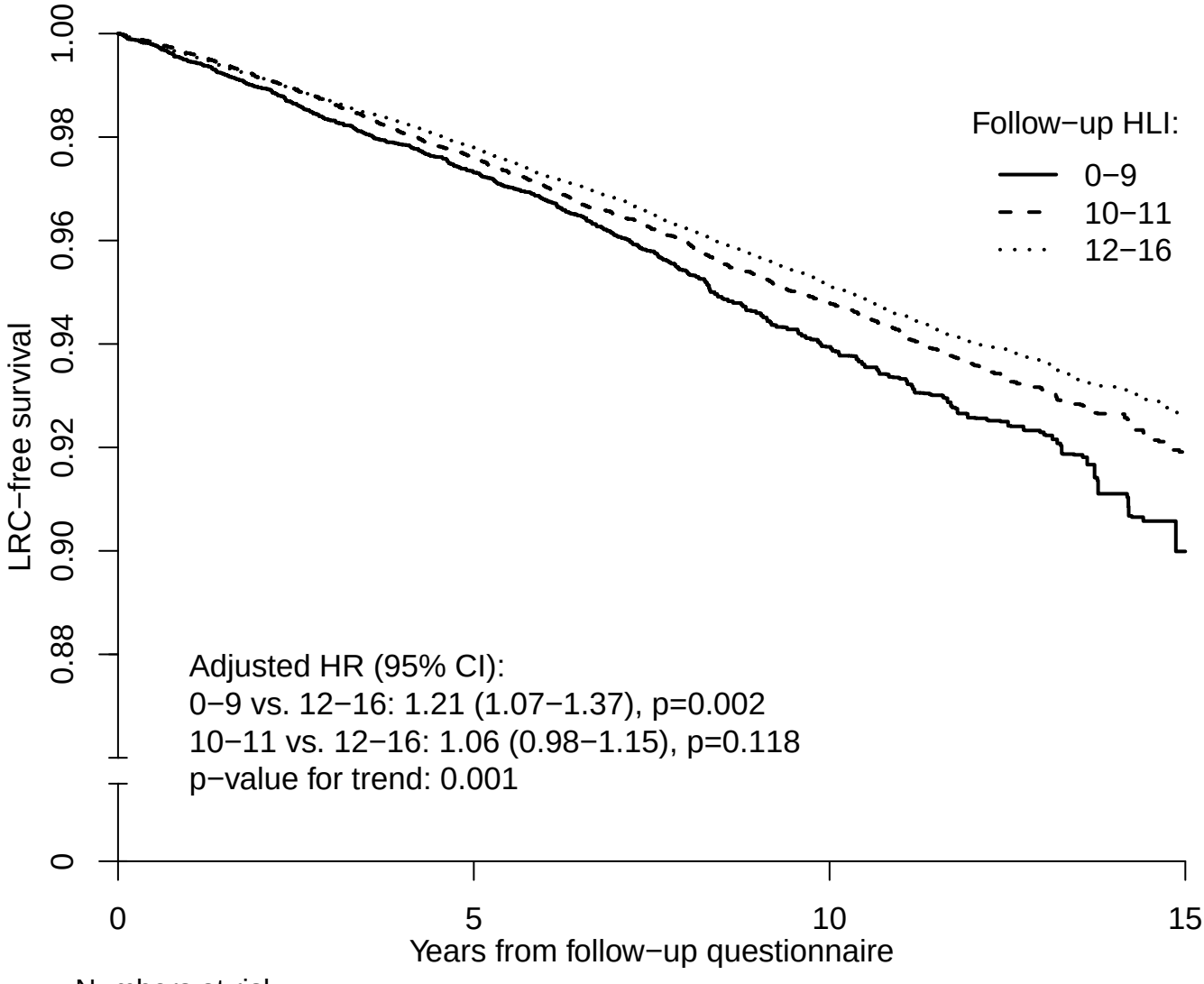

HR (95% CI)
p-value
HR (95% CI)
Overall
0.96 (0.95-0.97)
Sex
Females
0.97 (0.96-0.98)
0.007
Males
0.94 (0.93-0.96)
Age at recruitment
≤ 55 years
0.96 (0.95-0.97)
0.869
> 55 years
0.96 (0.95-0.98)
Education
None or primary
0.95 (0.94-0.97)
0.386
Secondary
0.97 (0.95-0.98)
University or higher
0.95 (0.93-0.98)
Country
France
0.97 (0.91-1.02)
0.556
United Kingdom
0.96 (0.94-0.98)
Germany
0.96 (0.93-0.98)
Denmark
0.97 (0.95-0.99)
Spain
0.95 (0.92-0.97)
Italy
0.94 (0.90-0.99)
Norway
0.98 (0.94-1.02)
Sweden
0.96 (0.93-0.99)
The Netherlands
1.03 (0.96-1.10)
Time between questionnaires
≤ 5.7 years
0.96 (0.95-0.97)
0.971
> 5.7 years
0.96 (0.94-0.98)
Removing one component
Smoking
0.98 (0.97-0.99)
Alcohol
0.95 (0.94-0.96)
Body mass index
0.96 (0.95-0.97)
Physical activity
0.97 (0.96-0.98)
Excluding first follow-up years
1 year
0.96 (0.95-0.97)
2 years
0.96 (0.95-0.97)
3 years
0.96 (0.95-0.97)
4 years
0.96 (0.95-0.97)
5 years
0.96 (0.94-0.97)
0.90
0.95
1.00
1.05
1.10


A
Baseline HLI: 0−9
LRC−free survival
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0
Follow−up HLI:
0−9
10−11
12−16
Adjusted HR (95% CI):
10−11 vs. 0−9: 0.82 (0.76−0.87), p<0.001
12−16 vs. 0−9: 0.75 (0.65−0.86), p<0.001
p−value for trend: <0.001
0
5
10
15
Years from follow−up questionnaire
Numbers at risk:
86383 62409 34191 3190 0−9
23695 15806 9809 981 10−11
7773 4576 3183 326 12−16


B
Baseline HLI: 10−11
LRC−free survival
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0
Follow−up HLI:
0−9
10−11
12−16
Adjusted HR (95% CI):
0−9 vs. 10−11: 1.12 (1.03−1.21), p=0.011
12−16 vs. 10−11: 0.88 (0.81−0.97), p=0.007
p−value for trend: <0.001
0
5
10
15
Years from follow−up questionnaire
Numbers at risk:
26970 19054 7830 701 0−9
32094 21748 11445 1053 10−11
21956 13041 8265 837 12−16

C

Baseline HLI: 12−16



Numbers at risk:

9876	7077	2344	147	0−9
27465	19371	8588	603	10−11
59653	39769	22172	1816	12−16