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Pairwise association of key lifestyle factors and risk of solid cancers - A prospective pooled multi-cohort register study

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ABSTRACT

Smoking, alcohol consumption, obesity, and physical inactivity are key lifestyle risk factors for cancer. Previously these have been mostly examined singly or combined as an index, assuming independent and equivalent effects to cancer risk. The aim of our study was to systematically examine the joint pairwise and interactive effects of these lifestyle factors on the risk of a first solid primary cancer in a multi-cohort prospective setting.

We used pooled data from seven Finnish health survey studies during 1972–2015, with 197,551 participants diagnosed with 16,373 solid malignant primary tumors during follow-up. Incidence of any cancer was analyzed separately without and with lung cancers using Poisson regression with main and interaction effects of key lifestyle factors.

When excluding lung cancer, the highest risk of any cancer in men was observed for smokers with a BMI of $\geq$25 kg/m^2 (HR 1.36, 95 % CI 1.25–1.48) and in women for smokers consuming alcohol (HR 1.22, 1.14–1.30). No statistically significant interactions between any studied risk factor pairs were observed. When including lung cancer, the highest HRs among men were observed for smokers who consume alcohol (HR 1.72, 1.57–1.89) and among women for smokers who were physically inactive (HR 1.38, 1.27–1.49).

Smoking combined with other lifestyle factors at any exposure level resulted in highest pairwise risks, both in men and women. These results highlight the importance of smoking prevention, but also the importance of preventing obesity and reducing alcohol consumption.

1. Introduction

Cancers are the leading cause of premature death in most Western countries (Wild et al., 2020). Both cancer incidence and prevalence are on the rise as life expectancy increases and evolving cancer treatments augment cancer survival (Torre et al., 2016). It is estimated that by the year 2040 global cancer burden exceeds 27 million new cancer cases annually, compared with the 18 million new cases worldwide in 2018 (Wild et al., 2020). In addition to human suffering, the economic burden associated with cancer is also rising. The total annual economic cost of cancer worldwide was already around US$1.16 trillion during 2010 (Wild et al., 2020). In future, keeping cancer in remission may require long periods of high-cost treatment and even more health care resources (Howard et al., 2015; Meropol et al., 2009).

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According to the International Agency for Research on Cancer (IARC), 30–50 % of all the cancers could be prevented by influencing modifiable lifestyle factors (Wild et al., 2020). For population cancer burden, tobacco smoking is the most important factor with estimates of population attributable fractions around 20 % in men and 10–15 % (Olsen et al., 1997; Poirier et al., 2019) in women. However, there is evidence of the increasing role of other lifestyle factors for the cancer burden: While smoking is associated with approximately 20 different cancers, including respiratory and gastrointestinal (gi) tract cancers (Wild et al., 2020), alcohol consumption, for instance, is associated with increased risk of gi and urinary tract cancers and breast cancer (Wild et al., 2020). Physical activity is associated with reduced gi-tract and gynecological cancer risks (Wild et al., 2020), while obesity increases the risk of at least 13 different cancers, including gi-tract cancers, postmenopausal breast cancer and kidney cancer (Wild et al., 2020).

In earlier research, the effects of lifestyle factors have been commonly reported for a single factor at a time adjusted for other lifestyle factors with an assumption of their independent effects (Dartois et al., 2014; Parkin et al., 2011; Katzke et al., 2015). Examining joint effects of multiple lifestyle factors would be important from the point of view of cancer prevention programs, but this is challenging due to the required sample sizes needed to achieve sufficient statistical power. This has been circumvented in some studies by focusing on a selected subset of lifestyle factor combinations (Hadrien et al., 2013) or by constructing lifestyle indices wherein the lifestyle factors are encoded as a sum of the component factors (Naudin et al., 2020).

Some interactive effects have been found between certain hazardous exposures and risk of some cancers (Levi, 1999). Considering lifestyle factors, there is some evidence on interaction between smoking and alcohol consumption in relation to specific cancers (Steevens et al., 2010; Maasland et al., 2014; Ramroth et al., 2004; Viner et al., 2019). Alcohol may act as a solvent for tobacco carcinogens thus making tobacco more toxic (IARC, 2012), and as smoking affects central fat distribution (Chiolero et al., 2008), it may influence hormonal activity of the fat tissue thus affecting the cancer risk related with obesity. Regarding body weight and physical exercise, it has been shown that physical activity appears to decrease the risk of pancreatic cancer, especially among those who are overweight (Michaud et al., 2001).

The aim of this study was to systematically examine the joint pairwise and interactive effects of smoking, alcohol consumption, body weight and physical inactivity with the risk of a first solid primary cancer in a multi-cohort prospective setting both excluding and including lung cancers due to the strong known association with smoking.

2. Material and methods

We used data pooled for the METCA consortium (Prospective Meta-Cohort Study of Cancer Burden in Finland, (Pitkäniemi et al., 2020)). The study covers the following survey studies monitoring health behavior in Finland in 1972–2015: The National FINRISK Study conducted at 5-year intervals since 1972 (FINRISK, (Borodulin et al., 2018)), The Adult Health, Wellbeing, and Services Studies from 2010 to 2011 (ATH1) and from 2012 to 2015 (ATH2, (Härkänen et al., 2014)), The Health 2000 Survey (H2000, (Heistaro, 2008)), The Follow-up of the Finnish Mobile Clinic Health Examination from 1972 to 1977 (FMCF, (Knekt et al., 2017)) and the Mini-Finland Health Survey from 1978 to 1980 (MFH, (Knekt et al., 2017)), the Helsinki Health Study from 2000 to 2002 (HHS, (Lahelma et al., 2013)) and The Helsinki Birth Cohort Study (HBCS, (Eriksson, 2006)). Exposure assessment includes both survey data and health examinations.

The cohort participants were individually followed-up with personal identity codes through register linkage to the nation-wide population-based Finnish Cancer Registry for cancers and the Population Register Centre for deaths. Cancer data cover the entire target population and have been validated with high coverage of solid cancers (96 %), i.e., it is unlikely that incident cancers are missed (Leinonen et al., 2017). The follow-up started from the date of baseline survey or the date when the person turned 30 years, which ever occurred latest, and continued until the end of 2013 or 2015 (depending on the cohort), death or emigration, which ever earliest (Pitkäniemi et al., 2020).

Total of 16,373 solid malignant primary tumors (excluding skin non-melanoma but including benign central nervous system tumors) among 197,551 persons were diagnosed during the follow-up of 2,305,658 person years (Table 1). The largest numbers of cases were observed for cancers of the prostate (N = 2904), breast (N = 2825), lung (N = 1914), colorectum (N = 1650) and bladder and urinary tract (N = 702). All the analyses of pairwise effects were done separately without and with lung cancers. The largest individual study cohorts were ATH1 and ATH2 (n = 70,043, see Appendix I) and FINRISK (n = 51,415), but longest follow-up times and substantial number of person-years were obtained from the FMCF (369,451 person-years), MFH (133,825) and FINRISK (795,228).

Smoking, alcohol consumption, body mass index (BMI), and physical inactivity measures were harmonized between the study cohorts and categorized into those exposed and those not exposed. Smoking was grouped into never-smokers (reference, not exposed) and smokers (ex- and current smokers). Regarding alcohol use, subjects reporting using 0 g of alcohol per week (MFH, HHS), per month (FMCF), never use of alcohol (FINRISK, H2000, HBCS), or not using alcohol within the past year (ATH) were categorized as non-exposed. Accordingly, subjects reporting any, ever, or current use of alcohol were considered as exposed. Applicable information on alcohol use was not available in the FINRISK 1982 survey. Body mass index was divided into those with BMI < 25 kg/m^2 (reference; not exposed) and having overweight (BMI ≥ 25 kg/m^2, exposed). Physically inactive (no leisure time physical activity) were categorized into exposed and physically active into not exposed (reference, those with any leisure time activity). Missing item values of a covariate were handled as a separate category in the analysis.

For each pair of lifestyle factors we calculated the sum of person years, the number of first primary solid malignant tumors, and the incidence rate standardized to the age structure of the World 1966 population. The hazard ratios (HRs) of lifestyle factors for solid malignant tumor were estimated using Poisson regression models based on multiplicative hazard functions as described in the following paragraph. As sensitivity analyses, we estimated the HRs by excluding the first two years of follow-up.

Let C_{apsx} be the number of cancer cases among persons in age group a, calendar period p (five-year periods) and survey study s with vector $x = (x(1), x(2), x(3), x(4))$ of values of four lifestyle factors. The number of cases is described by the Poisson distribution C_{apsx} Poisson$\left(\lambda_{apsx} y_{apsx}\right)$ where λ_{apsx} is the cancer incidence rate and y_{apsx} is the number of persons years in the stratum. In the first model, we included only the main effects of the lifestyle factors:

$$\log\left(\lambda_{apsx}\right) = \alpha_{aps} + \beta^1_{x(1)} + \beta^2_{x(2)} + \beta^3_{x(3)} + \beta^4_{x(4)} \quad (1)$$

Table 1
Descriptive statistics of the METCA consortium, adult cohort, 1972–2015, Finland.

Population characteristics	Total	Men	Women
Years of baseline of harmonized cohort	1972–2015		
N of subjects in harmonized cohort	197,551	88,963	108,588
Person years (in thousands)	2306	1046	1260
Solid malignant tumors	16,373	8469	7904
Lung cancers	1914	1514	400
Age distribution of tumors (incl. lung)			
30–49	959	266	693
50–69	7950	4029	3921
70+	7464	4174	3290
Follow-up years (median (SD))	6 (12)	6 (12)	6 (13)
Age at baseline (mean (SD))	53 (16)	52 (16)	53 (17)
Proportion of men/women (%)	45/55		

where $\exp(\alpha_{aps})$ is the baseline hazard, $\beta^{i}_{x(i)} = 0$ is the reference level of factor i, and $\exp\left(\beta^{i}_{x(i)}\right)$ is the multiplicative main effect of factor i with value $x(i)$. The baseline hazard was stratified by age (5-year groups of attained age) and calendar time (5-year periods) to account for variation in the hazard by age and period, and variation in the baseline hazard between studies was modelled by multiplicative study-specific effects: $\alpha_{aps} = \alpha_{ap} + \delta_s$. In model M1, we assumed the main effects model for the lifestyle factors, i.e., the HR of two factors was the product of the HRs of each lifestyle factor, and made the common statistical assumption of proportional hazards, i.e., the HRs were constant in time. In an alternative model, M2 for each pair (i,j) of lifestyle factors separately, the interaction term $\gamma^{ij}_{x(i),x(j)}$ of the factors with values $(x(i),x(j))$ was added to model M1:

$$\log(\lambda_{apsx}) = \alpha_{aps} + \beta^{1}_{x(1)} + \beta^{2}_{x(2)} + \beta^{3}_{x(3)} + \beta^{4}_{x(4)} + \gamma^{ij}_{x(i),x(j)} \quad (2)$$

where $\beta^{i}_{x(i)} = 0$ is the reference level of factor i, and if $x(i)$ or $x(j)$ is the reference level or missing, then $\gamma^{ij}_{x(i),x(j)} = 0$. HRs of main effects $\exp\left(\beta^{i}_{x(i)}\right)$ and $\exp\left(\beta^{j}_{x(j)}\right)$, pairwise effect $\exp\left(\beta^{i}_{x(i)} + \beta^{j}_{x(j)} + \gamma^{ij}_{x(i),x(j)}\right)$ and multiplicative interaction $\exp\left(\gamma^{ij}_{x(i),x(j)}\right)$ are reported with their 95 % confidence intervals (CI). To test interaction for pairs of lifestyle factors, we compared the fit of models M1 and M2 by using the likelihood ratio test. Models M1 and M2 were fitted separately for men and women. P-values were adjusted for multiple testing using the method of Benjamini and Hochberg (Benjamini and Hochberg, 1995). Statistical analyses were conducted in statistical program R version 4.0.5 using popEpi package version 0.4.10.

The study was approved by The Finnish Institute for Health and Welfare (Permits no. THL/1091/6.02.00/2015 and THL/679/6.02.00/2018), which include evaluation of informed consent of each participating study cohort. Cancer data was obtained according to national legislation of secondary use of health and social data (Act on the Secondary Use of Health and Social Data, 552/2019 and Act on the National Institute for Health and Welfare, 668/2008).

3. Results

The prevalence of the risk factors in all study subjects and in subjects diagnosed with cancer are presented in Table 2A. About half of the survey respondents were never smokers and half former or current smokers (47 % and 51 %, respectively). One fifth reported no use of alcohol (22 %), 41 % had a BMI < 25 kg/m^2 and 71 % reported being active during leisure time. Prevalence of all pairwise-categorized lifestyle factors for men and women and separately for subjects diagnosed with cancer are shown in Table 2B. The proportion of subjects with non-exposed lifestyle factor pairs varied from 9 % (N = 17,022) for non-alcohol users with BMI < 25 kg/m^2 to 35 % (N = 66,727) for physically active never smokers.

3.1 Single effects of lifestyle factors

Former or current smokers had the highest HR for any solid cancer (HR 1.20, 95 % CI 1.13–1.26 for men and 1.15, 1.09–1.21 for women, Table 3), when compared to never-smokers. Both high alcohol consumption and overweight/obesity were associated with an increased risk in men (HR 1.13, 1.05–1.21 and 1.12, 1.07–1.18, respectively). For women, after adjusting for other lifestyle factors, alcohol consumption and overweight/obesity resulted in a small increased risk of any solid cancer (HR 1.06, 1.00–1.12 and 1.06, 1.01–1.11, respectively). Lack of physical activity increased the risk of any solid cancer by 4 % among men and women, with a borderline statistical significance (HR 1.04, 0.99–1.10 in both groups).

In men and women, single factor HRs for current or former smoking were significantly higher when lung cancer was included in the analyses. For men, smoking increased the risk of any solid cancer by 48 % (95 % CI 1.40–1.56), when lung cancer was included in the analyses, in contrast to the observed 20 % increase when lung cancer was excluded. Including lung cancers resulted in lower cancer risk for overweight/obesity in men, as compared to analyses without lung cancers (HR 0.99, 0.95–1.04 vs. HR 1.12, 1.07–1.18, respectively). Regarding alcohol consumption and physical inactivity, including lung cancer in the analyses resulted in minor changes only. For women, the differences in the HRs were small between the two analyses. The biggest difference was for smoking, with HR 1.15, 1.09–1.21 when lung cancers were excluded and HR 1.27, 1.21–1.34 when lung cancers were included.

3.2 The pairwise effects of lifestyle factors

The number of solid cancers (excluding and including lung cancer), person-years, incidence rates and adjusted HRs for all lifestyle factor pairs are shown in Table 4. The ordered age-standardized incidence rates for all lifestyle factor pairs are plotted in Fig. 1 by sex. Men who were former or current smokers and had overweight/obesity had the highest age standardized rate of cancer (460 per 100 000, 95 % CI 443/10^5-479/10^5, Table 4). For women, the highest age standardized cancer rates were in physically inactive former or current smokers (469/10^5, 434/10^5-507/10^5). High cancer rates were observed also when smoking was combined with alcohol consumption, for both men (445/10^5, 431/10^5-459/10^5) and women (463/10^5, 442/10^5-485/10^5).

Both men and women exposed to any two of the four studied lifestyle factors had significantly elevated HRs compared to those not exposed to either of the factors in the studied pair (Tables 4 and 5 and Supplementary Fig. 1). Former or current smokers with a BMI of ≥ 25 kg/m^2

Table 2A
Prevalence of risk factors in all study subjects and in subjects diagnosed with cancer. METCA consortium, adult cohort, 1972–2015, Finland.

Risk factors		All study subjects						Subjects diagnosed with cancer					
		Total		Men		Women		Total		Men		Women	
		N	%	N	%	N	%	N	%	N	%	N	%
Smoking	Never smoker	93,433	47	28,013	31	65,420	60	7722	47	1803	25	5919	64
	Ex or current smoker	99,882	51	59,181	67	40,701	37	8354	51	5192	73	3162	34
	Missing	4236	2	1769	2	2467	2	297	2	110	2	187	2
Alcohol	No use of alcohol	43,692	22	12,541	14	31,151	29	3798	23	921	13	2877	31
	Use alcohol	148,293	75	74,353	84	73,940	68	12,250	75	6070	85	6180	67
	Missing	5566	3	2069	2	3497	3	325	2	114	2	211	2
Body mass index	Normal weight	81,186	41	32,294	36	48,892	45	7400	45	2910	41	4490	48
	Overweight or obese	108,926	55	53,518	60	55,408	51	8672	53	4056	57	4616	50
	Missing	7439	4	3151	4	4288	4	301	2	139	2	162	2
Physical inactivity	Any leisure time exercise	139,799	71	64,240	72	75,559	70	11,280	69	5016	71	6264	68
	No leisure time exercise	52,459	27	22,336	25	30,123	28	4706	29	1889	27	2817	30
	Missing	5293	3	2387	3	2906	3	387	2	200	3	187	2

Table 2B
Prevalence of risk factor pairs in all study subjects and in subjects diagnosed with cancer. METCA consortium, adult cohort, 1972–2015, Finland.

		All study subjects						Subjects diagnosed with cancer					
		Total		Men		Women		Total		Men		Women	
Risk factor pair		N	%	N	%	N	%	N	%	N	%	N	%
Smoking	*Alcohol*												
Never-smoker	No use of alcohol	31,564	17	5991	7	25,573	25	2903	18	416	6	2487	28
	Use alcohol	59,752	31	21,560	25	38,192	37	4678	30	1359	20	3319	37
Ex- or current smoker	No use of alcohol	11,472	6	6315	7	5157	5	852	5	490	7	362	4
	Use alcohol	87,133	46	52,158	61	34,975	34	7418	47	4657	67	2761	31
Smoking	*Body mass index*												
Never-smoker	Normal	39,441	21	10,855	13	28,586	28	3441	22	755	11	2686	30
	Overweight or obese	50,657	27	16,246	19	34,411	34	4155	26	1019	15	3136	35
Ex- or current smoker	Normal	40,414	22	20,937	25	19,477	19	3851	24	2120	31	1731	19
	Overweight or obese	56,391	30	36,454	43	19,937	19	4385	28	2992	43	1393	16
Smoking	*Physical inactivity*												
Never-smoker	Any leisure time exercise	66,727	35	21,566	25	45,161	43	5185	33	1364	20	3821	43
	No leisure time exercise	24,622	13	5876	7	18,746	18	2372	15	394	6	1978	22
Ex- or current smoker	Any leisure time exercise	71,152	38	41,877	49	29,275	28	5907	37	3593	53	2314	26
	No leisure time exercise	27,014	14	16,171	19	10,843	10	2292	15	1481	22	811	9
Alcohol	*Body mass index*												
No use of alcohol	Normal	17,022	9	5157	6	11,865	12	1440	9	400	6	1040	12
	Overweight or obese	24,946	13	6990	8	17,956	18	2275	14	500	7	1775	20
Use alcohol	Normal	62,639	34	26,645	32	35,994	35	5848	37	2478	36	3370	38
	Overweight or obese	81,646	44	45,713	54	35,933	35	6248	40	3505	51	2743	31
Alcohol	*Physical inactivity*												
No use of alcohol	Any leisure time exercise	26,531	14	8295	10	18,236	18	2021	13	593	9	1428	16
	No leisure time exercise	15,864	8	3866	5	11,998	12	1655	11	287	4	1368	15
Use alcohol	Any leisure time exercise	110,994	59	55,185	65	55,809	54	9087	58	4363	64	4724	53
	No leisure time exercise	35,398	19	18,142	21	17,256	17	2966	19	1583	23	1383	16
Body mass index	*Physical inactivity*												
Normal	Any leisure time exercise	61,772	33	24,312	29	37,460	37	5440	34	2103	31	3337	37
	No leisure time exercise	18,139	10	7474	9	10,665	10	1868	12	765	11	1103	12
Overweight or obese	Any leisure time exercise	74,473	40	38,401	46	36,072	35	5726	36	2865	42	2861	32
	No leisure time exercise	32,204	17	14,115	17	18,089	18	2757	17	1098	16	1659	19

Table 3
Adjusted hazard ratios (HR) and 95% confidence intervals (CI) of any solid malignant tumors (excluding and including lung cancers) for lifestyle risk factors. METCA consortium, adult cohort, 1972–2015, Finland.

	Men (lung cancer excl.)	Men (lung cancer incl.)	Women (lung cancer excl.)	Women (lung cancer incl.)
	HR 95 % CI	HR 95 % CI	HR 95 % CI	HR 95 % CI
Ex- or current smoker vs never smoker	1.20 (1.13–1.26)	1.48 (1.40–1.56)	1.15 (1.09–1.21)	1.27 (1.21–1.34)
Use alcohol vs. no use of alcohol	1.13 (1.05–1.21)	1.14 (1.07–1.21)	1.06 (1.00–1.12)	1.05 (0.99–1.11)
Overweight or obese vs normal weight	1.12 (1.07–1.18)	0.99 (0.95–1.04)	1.06 (1.01–1.11)	1.04 (0.99–1.09)
No leisure time exercise vs any leisure time exercise	1.04 (0.99–1.10)	1.08 (1.03–1.13)	1.04 (0.99–1.10)	1.06 (1.00–1.11)

[#] adjusted for study, age, calendar time, and other lifestyle risk factors.

had the highest risk of any cancer (HR 1.36, 1.25–1.48), compared to never-smoker men with BMI < 25 kg/m^2. Men who smoked and consumed alcohol had an almost similar increase in cancer risk as smoking men with overweight/obesity (HR 1.35, 1.23–1.48). For women, the highest HRs were observed for former or current smokers who also consumed alcohol (HR 1.22, 1.14–1.30) or were physically inactive (HR 1.22, 1.12–1.33). In general, when including lung cancer in the pairwise inspection, the effect of smoking was larger and the effect of overweight/obesity smaller (Table 5). For men, the highest HR was observed for smokers who also consumed alcohol (HR 1.72, 1.57–1.89). For women, smoking combined with alcohol consumption resulted in HR 1.33 (95 % CI 1.24–1.42). The highest HR, however, was seen for physically inactive smoking women (1.38, 1.27–1.49). Results of the sensitivity analyses excluding the first two years of follow-up are shown in Supplementary Tables 1-3.

3.3 Interactions of effects

Measures of interactions on a multiplicative scale between pairwise lifestyle factors are shown in Table 4. No statistically significant interactions were detected, when adjusting for multiple comparison. When lung cancer was included in the analyses, significant negative interactions between smoking and BMI were found: the joint effect of smoking and BMI together was smaller (15 % in men and 12 % in women) than the product of the estimated effects of smoking and BMI alone (Table 5).

4. Discussion

Both men and women exposed to any two of the four studied lifestyle factors had a significantly elevated risk of solid malignant tumors when lung cancer was excluded from the analysis. For men, the highest risk

Table 4
Number of solid malignant tumors (Cancers) and person-years (kPY: person-years in thousands), age standardized incidence rate (Rate) and adjusted hazard ratios (HR) of solid malignant tumors for lifestyle risk factor pairs in men (excluding and including lung cancer). METCA consortium, adult cohort, 1972–2015, Finland.

		Excluding lung cancer			Including lung cancer		
Risk factor pair		Cancers/kPY	Rate	HR (95 % CI)	Cancers/kPY	Rate	HR (95 % CI)
Smoking	Alcohol						
Never smoker	No use of alcohol	501/75	314 (284, 351)	1.00	510/75	321 (291, 359)	1.00
	Use alcohol	1300/224	385 (363, 408)	1.13 (1.02, 1.26)	1330/224	395 (373, 419)	1.18 (1.07, 1.31)
Ex- or current smoker	No use of alcohol	556/67	366 (328, 416)	1.20 (1.07, 1.35)	751/66	507 (464, 563)	1.55 (1.39, 1.73)
	Use alcohol	4481/666	445 (431, 459)	1.35 (1.23, 1.48)	5687/663	566 (550, 582)	1.72 (1.57, 1.89)
Interaction				0.99 (0.87, 1.13)			0.94 (0.83, 1.06)
p-interaction[1]				0.915			0.449
Smoking	Body mass index						
Never smoker	Normal	641/134	331 (305, 359)	1.00	656/134	339 (313, 368)	1.00
	Overweight or obese	1145/160	388 (364, 417)	1.15 (1.05, 1.27)	1169/160	397 (372, 426)	1.12 (1.03, 1.23)
Ex- or current smoker	Normal	1758/306	404 (385, 424)	1.22 (1.12, 1.34)	2458/305	567 (544, 591)	1.63 (1.50, 1.77)
	Overweight or obese	3220/413	460 (443, 479)	1.36 (1.25, 1.48)	3894/411	557 (538, 577)	1.56 (1.44, 1.69)
Interaction				0.96 (0.86, 1.07)			0.85 (0.77, 0.95)
p-interaction[1]				0.735			0.029
Smoking	Physical inactivity						
Never smoker	Any exercise	1395/233	371 (350, 393)	1.00	1429/233	381 (361, 404)	1.00
	No exercise	392/66	351 (315, 394)	0.97 (0.87, 1.09)	398/66	357 (321, 401)	0.97 (0.87, 1.08)
Ex- or current smoker	Any exercise	3625/530	431 (416, 447)	1.17 (1.10, 1.25)	4559/528	545 (528, 562)	1.43 (1.35, 1.52)
	No exercise	1384/199	454 (429, 481)	1.25 (1.16, 1.35)	1831/198	599 (571, 630)	1.58 (1.48, 1.70)
Interaction				1.10 (0.97, 1.24)			1.14 (1.01, 1.29)
p-interaction[1]				0.534			0.084
Alcohol	Body mass index						
No use of alcohol	Normal	401/68	300 (267, 340)	1.00	513/67	387 (350, 431)	1.00
	Overweight or obese	647/73	364 (332, 412)	1.18 (1.05, 1.33)	736/73	428 (393, 478)	1.04 (0.93, 1.16)
Use alcohol	Normal	1995/373	400 (382, 419)	1.17 (1.06, 1.30)	2599/372	523 (502, 544)	1.17 (1.07, 1.29)
	Overweight or obese	3706/499	450 (434, 467)	1.30 (1.17, 1.44)	4316/498	524 (507, 542)	1.15 (1.05, 1.26)
Interaction				0.94 (0.82, 1.07)			0.95 (0.84, 1.06)
p-interaction[1]				0.647			0.468
Alcohol	Physical inactivity						
No use of alcohol	Any exercise	705/100	325 (298, 357)	1.00	839/100	396 (367, 432)	1.00
	No exercise	333/41	366 (319, 431)	1.03 (0.91, 1.17)	400/41	444 (393, 513)	1.04 (0.92, 1.16)
Use alcohol	Any exercise	4307/663	426 (413, 440)	1.12 (1.04, 1.22)	5141/662	510 (496, 526)	1.12 (1.04, 1.21)
	No exercise	1436/223	444 (420, 469)	1.18 (1.07, 1.29)	1823/222	563 (536, 591)	1.22 (1.12, 1.32)
Interaction				1.01 (0.88, 1.16)			1.05 (0.92, 1.19)
p-interaction[1]				0.915			0.497
Body mass index	Physical inactivity						
Normal	Any exercise	1794/333	379 (361, 398)	1.00	2254/331	478 (458, 499)	1.00
	No exercise	598/107	391 (359, 426)	1.06 (0.97, 1.16)	849/107	560 (522, 601)	1.16 (1.07, 1.25)
Overweight or obese	Any exercise	3185/419	434 (418, 452)	1.13 (1.06, 1.19)	3680/418	505 (487, 524)	1.02 (0.97, 1.08)
	No exercise	1143/151	452 (424, 485)	1.17 (1.08, 1.26)	1338/150	527 (497, 561)	1.06 (0.99, 1.13)
Interaction				0.97 (0.87, 1.09)			0.89 (0.81, 0.98)
p-interaction[1]				0.869			0.070

[1]P-interaction: p-value for H_0: HR (interaction) = 1.00, corrected for multiple comparisons (Benjamini-Hochberg)

was observed for smokers with a BMI of $\geq$25 kg/m^2 (HR 1.36, 95 % CI 1.25–1.48), followed by smokers consuming alcohol (HR 1.35, 1.23–1.48). For women, the highest risk was observed for smokers consuming alcohol (HR 1.22, 1.14–1.30) or being physically inactive (HR 1.22, 1.12–1.33). When including lung cancer, the highest HRs among men were observed for smokers who also consumed alcohol (HR 1.72, 1.57–1.89) and among women for smokers who were physically inactive (HR 1.38, 1.27–1.49). No statistically significant interactions were observed between any studied lifestyle pairs, except for smoking and BMI in the analyses including lung cancer.

We examined the risk of any solid cancer both with and without lung cancer cases. This was done because smoking is so strongly associated with lung cancer that it could dominate the results and obscure other significant associations. When lung cancer cases were excluded from the analysis, the cancer risk among those who smoked or consumed alcohol appeared somewhat smaller than when lung cancer cases were included. Overweight/obesity increased the cancer risk among men who were ex- or current smokers or who consumed alcohol. When lung cancer cases were included, we found an interaction between smoking and overweight/obesity: ex- or current smokers with overweight/obesity had lower risk of any cancer compared to smokers with normal weight, implying that overweight/obesity may be protective against cancer among smokers. Similarly, the risk of cancer among men who consumed alcohol and were overweight/obese appeared lower compared to those with normal weight, although no statistically significant interaction was found. However, the confidence intervals of these HRs were clearly overlapping and the confidence intervals for interaction term were close to 1.00, so no strong conclusions can be made. It is probable that the difference is affected by heavy smokers typically having lower body weight, especially if already with an undiagnosed lung cancer. This would result in a misleading pairwise hazard ratio when examining body weight and smoking together.

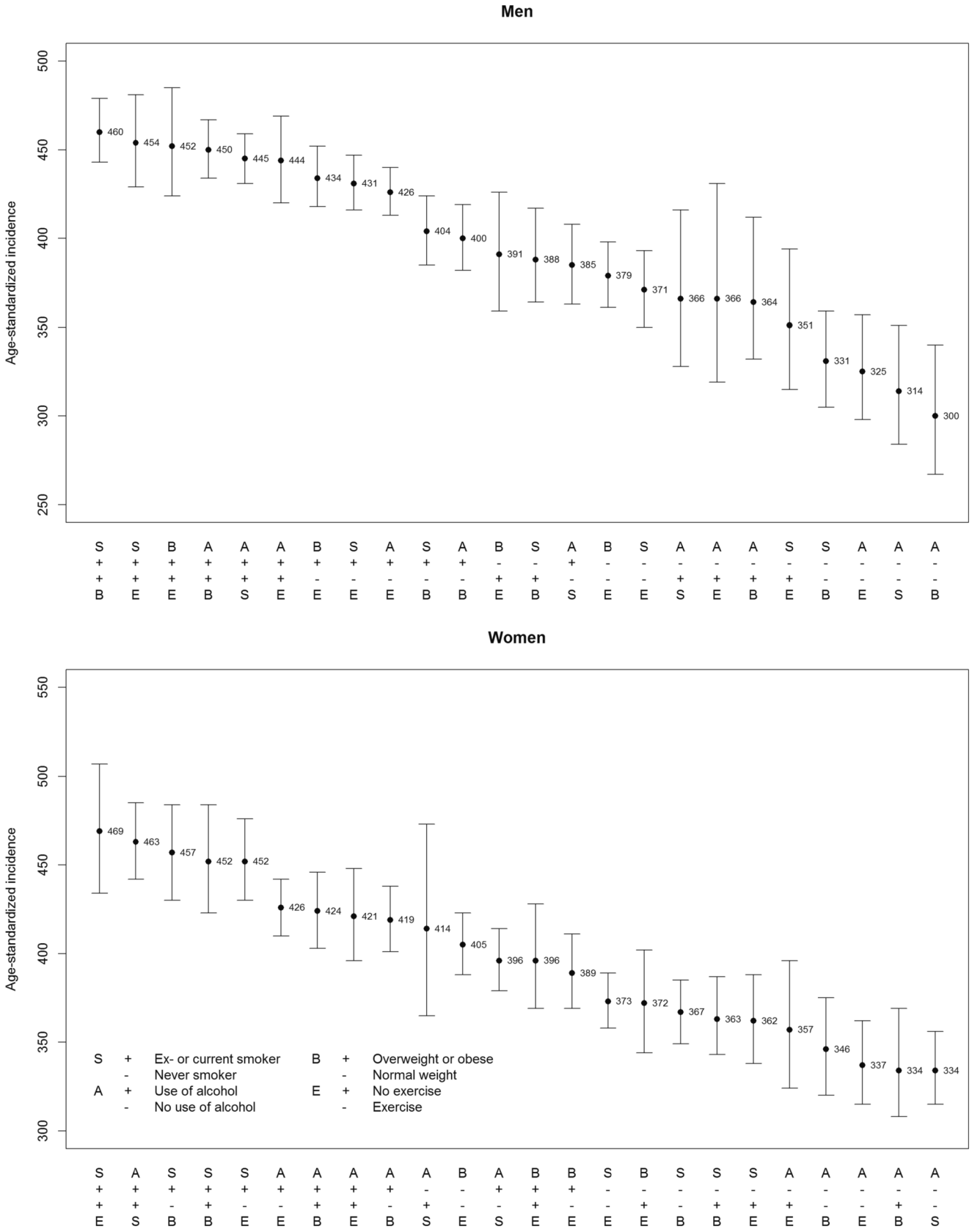

Fig. 1. Age-standardized incidence rate (per 100,000 person years) of solid malignant tumors (excluding lung cancer) with 95% confidence intervals for lifestyle risk factor pairs by sex. METCA consortium, adult cohort, 1972–2015, Finland.

Table 5
Number of solid malignant tumors (Cancers) and person-years (kPY: person-years in thousands), age standardized incidence rate (Rate) and adjusted hazard ratios (HR) of solid malignant tumors for lifestyle risk factor pairs in women (excluding and including lung cancer). METCA consortium, adult cohort, 1972–2015, Finland.

		Excluding lung cancer			Including lung cancer		
Risk factor pair		Cancers/kPY	Rate	HR (95 % CI)	Cancers/kPY	Rate	HR (95 % CI)
Smoking	Alcohol						
Never smoker	No use of alcohol	2518/383	334 (315, 356)	1.00	2596/382	342 (323, 364)	1.00
	Use alcohol	2454/432	396 (379, 414)	1.06 (1.00, 1.13)	2499/432	403 (386, 422)	1.06 (1.00, 1.12)
Ex- or current smoker	No use of alcohol	362/55	414 (365, 473)	1.17 (1.05, 1.30)	415/55	462 (411, 524)	1.32 (1.19, 1.46)
	Use alcohol	1972/365	463 (442, 485)	1.22 (1.14, 1.30)	2171/364	510 (488, 533)	1.33 (1.24, 1.42)
Interaction				0.98 (0.87, 1.11)			0.95 (0.85, 1.07)
p-interaction[1]				0.881			0.468
Smoking	Body mass index						
Never smoker	Normal	1965/383	367 (349, 385)	1.00	2008/382	374 (356, 393)	1.00
	Overweight or obese	2945/422	363 (343, 387)	1.09 (1.03, 1.15)	3023/422	372 (352, 395)	1.08 (1.02, 1.15)
Ex- or current smoker	Normal	1179/233	457 (430, 484)	1.21 (1.12, 1.30)	1326/233	516 (488, 546)	1.35 (1.26, 1.45)
	Overweight or obese	1114/178	452 (423, 484)	1.20 (1.11, 1.29)	1217/177	490 (460, 522)	1.29 (1.20, 1.39)
Interaction				0.91 (0.82, 1.00)			0.88 (0.80, 0.97)
p-interaction[1]				0.353			0.043
Smoking	Physical inactivity						
Never smoker	Any exercise	3300/554	373 (358, 389)	1.00	3374/554	381 (365, 397)	1.00
	No exercise	1656/258	362 (338, 388)	1.03 (0.97, 1.09)	1701/257	369 (345, 396)	1.03 (0.97, 1.09)
Ex- or current smoker	Any exercise	1617/296	452 (430, 476)	1.14 (1.07, 1.21)	1774/295	495 (471, 520)	1.24 (1.17, 1.32)
	No exercise	715/123	469 (434, 507)	1.22 (1.12, 1.33)	811/123	528 (491, 568)	1.38 (1.27, 1.49)
Interaction				1.05 (0.94, 1.16)			1.08 (0.98, 1.19)
p-interaction[1]				0.674			0.240
Alcohol	Body mass index						
No use of alcohol	Normal	1007/180	346 (320, 375)	1.00	1055/180	359 (333, 388)	1.00
	Overweight or obese	1815/250	334 (308, 369)	1.10 (1.02, 1.19)	1900/250	347 (320, 382)	1.09 (1.02, 1.18)
Use alcohol	Normal	2140/436	419 (401, 438)	1.10 (1.02, 1.19)	2282/435	446 (428, 465)	1.10 (1.02, 1.19)
	Overweight or obese	2238/348	424 (403, 446)	1.13 (1.05, 1.22)	2336/347	441 (420, 464)	1.10 (1.02, 1.19)
Interaction				0.94 (0.85, 1.03)			0.92 (0.84, 1.01)
p-interaction[1]				0.534			0.128
Alcohol	Physical inactivity						
No use of alcohol	Any exercise	1644/263	337 (315, 362)	1.00	1723/263	350 (328, 375)	1.00
	No exercise	1205/170	357 (324, 396)	1.07 (1.00, 1.16)	1258/170	368 (336, 408)	1.07 (1.00, 1.15)
Use alcohol	Any exercise	3269/587	426 (410, 442)	1.08 (1.01, 1.15)	3423/586	444 (429, 461)	1.06 (0.99, 1.13)
	No exercise	1156/209	421 (396, 448)	1.09 (1.01, 1.19)	1243/209	451 (425, 479)	1.10 (1.02, 1.19)
Interaction				0.95 (0.86, 1.04)			0.97 (0.88, 1.07)
p-interaction[1]				0.644			0.572
Body mass index	Physical inactivity						
Normal	Any exercise	2353/455	405 (388, 423)	1.00	2483/455	426 (409, 444)	1.00
	No exercise	789/161	372 (344, 402)	0.97 (0.90, 1.05)	849/161	398 (369, 429)	0.98 (0.91, 1.06)
Overweight or obese	Any exercise	2528/384	389 (369, 411)	1.02 (0.96, 1.08)	2631/384	403 (383, 426)	1.00 (0.95, 1.06)
	No exercise	1516/212	396 (369, 428)	1.11 (1.04, 1.19)	1594/212	415 (387, 448)	1.11 (1.04, 1.19)
Interaction				1.13 (1.02, 1.25)			1.13 (1.02, 1.24)
p-interaction[1]				0.185			0.058

[1]P-interaction: p-value for H_0: HR (interaction) = 1.00, corrected for multiple comparisons (Benjamini-Hochberg)

Although physical inactivity is associated with an increased cancer risk (Wild et al., 2020), in our study physical inactivity appeared to have only a minor effect on the pairwise associations. This may be since the METCA cohort studies surveyed only leisure time physical activity and did not include physical activity during the working day. Especially during earlier METCA substudies in the 1970 s working days were more physically strenuous and leisure time physical activity was not common. Hence physical inactivity variable in our study might not describe the 24-hour physical activity correctly.

Our results are in accordance with previous studies. It has been shown that smoking combined with high alcohol use is associated with especially high risk of laryngeal and gi-tract cancers (Steevens et al., 2010; Maasland et al., 2014; Ramroth et al., 2004) and colon and prostate cancers (Viner et al., 2019). These studies found a significant interaction between current smoking and high alcohol use. However, we did not find any interaction between smoking and alcohol use when all solid cancers (excl non-melanoma skin) were analysed together, but our previous study (Roos et al., 2022) has found a positive interaction between smoking and alcohol use when only colon cancer risk was analyzed.

The strengths of the study include large sample size as the data include seven different national cohort studies. This improves statistical power to detect possible interactive effect. The follow-up period is long and enables reliable evaluation of exposure effects with long latency. Cancer diagnoses are based on reliable and conclusive register data on practically all diagnosed cancers in Finland (Leinonen et al., 2017). We adjusted for study cohort effect in the baseline hazard. According to the earlier study with the same dataset no significant heterogeneity was observed between the cohort-specific risk factor effects (Pitkäniemi et al., 2020).

We chose to examine any solid cancer (excluding non-melanoma skin cancer) as the primary outcome, although risk factors and their pairwise

effects are likely to vary between cancers. This may attenuate reported associations somewhat. Among the weaknesses of our study was that exposure information was available only from the baseline. Exposure status may have changed during the follow-up and for example yet undiagnosed cancer may cause substantial changes in behavior. Results of the sensitivity analyses suggested that reverse causation does not play a major role in these associations, since the exclusion of the first two years of follow up did not much affect the estimates. As another limitation, some of the gathered health survey data is based on face-to-face health examination which might cause participation bias. It is known that for example feeling sick prohibits participation in face-to-face health examination, especially among older participants (Tolonen et al., 2017) and overall, the participants tend to be healthier than non-participants (Strandhagen et al., 2010). Instead of considering all possible combinations of exposures simultaneously, we analyzed one pair of exposures at a time, including interaction terms of the pair and assuming multiplicative effects for the other risk factors. The binary categorization into exposed and non-exposed does not allow the assessment of the dose–response of the exposure. Our analyses do hence not consider more complex combinatory effects. The number of those simultaneously exposed to several risk factors would become very small even with the large sample size of our current study, leading to very little statistical power to detect any higher order associations.

In previous research cancer risk has been studied using lifestyle indexes, combining different lifestyle factors together (Naudin et al., 2020). In our study the effect of lifestyle factors on overall cancer risk appeared independent and hence combining these factors may be done. However, it should be noted that different lifestyle factors do not have the same value regarding cancer risk. For example, physical inactivity and smoking are not equivalent risk factors. The approach based on lifestyle indexes is quite different than what we have done here and should be considered in a separate study.

Our results suggest that since lifestyle effects appeared largely independent, it is useful to focus preventive strategies on those lifestyle factors that have the largest impact on cancer risk on an individual, but also on community level and on those sub-populations that have multiple risk factors. Not long ago an editorial in JNCI (Samet, 2018) discussed the complicated relationship between smoking, obesity and lung cancer as research has shown that while BMI is inversely associated with lung cancer risk, central obesity appears to increase the risk (GBD 2015 Tobacco Collaborators et al., 2017). The editorial raised the concern that smoking is still highly prevalent, and the obesity epidemic shows no evidence of declining, and both are powerful risk factors for cancer. In our study, current smokers who were also obese had the highest risk of any solid cancer (when excluding lung cancer). A recent Australian study estimated that a notable number of cancers attributable to obesity, smoking and alcohol consumption and their combinations are preventable (Arriaga et al., 2017). For these reasons, the interplay of these risk factors needs to be better understood.

In conclusion, the main finding was that for almost all pairs of lifestyle factors, the relative risk of any cancer increases multiplicatively in relation to the respective relative risks generated by either exposure in the absence of the other. Especially current smoking combined with other lifestyle factors at any exposure level resulted in highest pairwise risks, both in men and women. These results highlight the importance of smoking prevention, but also the importance of preventing obesity and reducing alcohol consumption.

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CRediT authorship contribution statement

Eira Roos: Writing – original draft, Investigation, Conceptualization. **Sanna Heikkinen:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Karri Seppä:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Olli Pietiläinen:** Investigation, Conceptualization. **Heidi Ryynänen:** Writing – original draft, Investigation, Formal analysis, Data curation. **Maarit Laaksonen:** Writing – review & editing. **Teemu Roos:** Writing – review & editing, Methodology, Investigation. **Paul Knekt:** Writing – review & editing. **Satu Männistö:** Writing – review & editing. **Tommi Härkänen:** Writing – review & editing. **Pekka Jousilahti:** Writing – review & editing. **Seppo Koskinen:** Writing – review & editing. **Johan G. Eriksson:** Writing – review & editing. **Nea Malila:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Ossi Rahkonen:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Janne Pitkäniemi:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102607.

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