OVERWEIGHT DURATION IN OLDER ADULTS AND CANCER RISK: A STUDY OF COHORTS IN EUROPE AND THE UNITED STATES

Running title: Overweight duration in older adults and cancer risk

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ABSTRACT (250 words)

Recent studies have shown that cancer risk related to overweight and obesity is mediated by time and might be better approximated by using life years lived with excess weight. In this study we aimed to assess the impact of overweight duration and intensity in older adults on the risk of developing different forms of cancer. Study participants from seven European and one US cohort study with two or more weight assessments during follow-up were included (n=329,595). Trajectories of body mass index (BMI) across ages were estimated using a quadratic growth model; overweight duration (BMI≥25) and cumulative weighted overweight years were calculated. In multivariate Cox models and random effects analyses, a longer duration of overweight was significantly associated with the incidence of obesity-related cancer (overall Hazard Ratio (HR) per 10-yr increment: 1.39; 95%CI: 1.13-1.64), but also increased the risk of postmenopausal breast and colorectal cancer. Additionally accounting for the degree of overweight further increased the risk of obesity-related cancer. Risks associated with a longer overweight duration were higher in men than in women and were attenuated by smoking. For postmenopausal breast cancer, increased risks were confined to women who never used hormone therapy. Overall, 8.5% of all obesity-related cancers could be attributed to overweight at any age (10.7% in never smokers). These findings provide further insights into the role of overweight duration in the etiology of cancer and indicate that weight control is relevant at all ages. This knowledge is vital for the development of effective and targeted cancer prevention strategies.

INTRODUCTION

Obesity has emerged as one of the most prevalent risk factors for non-communicable diseases and is still on the rise in many populations.(1) Currently about 69% of all US adults are considered overweight or obese (body mass index, BMI ≥25 kg/m^2) and 36% obese (BMI ≥30 kg/m^2), making it one of the countries with the highest prevalence of obesity in the world.(2,3) Even though the level of obesity has been catching up in Western Europe over the past two decades, obesity prevalence is still presently lower than in North America, 20% in 2008.(2) In addition, overweight has become a growing problem specifically in the elderly, the fastest growing population segment in most high-income countries. For example, both in Europe and in the US, women aged 60 and above are more likely to be overweight or obese than any other age group. (3,4)

These developments have come at the cost of parallel rises in obesity-related morbidities, health care expenditures and mortality, most notably from cardio-vascular diseases and cancer.(5) In 2012, nearly half a million cancer cases globally were attributable to high BMI; more than half of this burden occurred in higher-income regions, most notably in Europe and Northern America.(6) These disparities across countries and regions not only reflect varying levels of obesity, but also differences in the strength of the cancer-obesity association between populations and in the prevalence and distribution of other risk factors modifying the association, such as smoking, diabetes and the use of hormone therapy (HT).(7) Although the link between obesity and cancer is well-documented(7), most studies investigating this association are based on single measurements of height and weight at one point in life and evidence on the cumulative effects of overweight during the life course on disease risk remains scarce. Yet recent studies have shown that obesity duration is an important and independent predictor of type 2 diabetes(8), cardio-vascular disease(9) and all-cause mortality(10). Given that a longer exposure to overweight increases the risk and severity of insulin resistance, chronic inflammation, oxidative DNA damage and alterations in endogenous hormone levels (11) – all of which are thought to be cancer promotive – overweight duration may be an important, but also yet understudied, predictor of the risk of cancer development.

In this study, we assessed the impact of overweight duration and intensity on cancer risk in more than 300,000 older adults in a pooled dataset of seven European and one US prospective cohort studies. In secondary analyses, we evaluated the effects of important effect modifiers and confounders including sex, smoking status, diabetes and HT.

MATERIALS AND METHODS

Study design and participants

This study uses repeated anthropometric assessments obtained from seven European (EPIC Elderly Denmark, Greece, Netherlands, and Spain; ESTHER, Germany; PRIME Belfast, Northern Ireland; Tromsø, Norway) and one American cohort study (NIH AARP), pooled as part of the Consortium of Health and Aging: Network of Cohorts in Europe and the United States (CHANCES, www.chancesfp7.eu). A selection of the cohorts' key characteristics is shown in **Table 1**. Additional information on the individual cohorts has been described elsewhere.(12) All CHANCES cohort studies are conducted in accordance with the Declaration of Helsinki. For each study, investigators satisfied the local requirements for ethical research, including obtaining informed consent from participants.

Study participants were required to have at least two valid BMI assessments during follow-up, including baseline and excluding assessments after or in the year preceding cancer diagnosis. For NIH AARP, participants with a retrospective self-reported BMI at age 50 and height and weight assessments at baseline were included. As this study is based on repeated assessments, participants with unknown date of re-contact were excluded (29,667, 4.7% of total). BMI values below 15 kg/m^2 and above 45 kg/m^2 were considered highly unlikely and considered as missing. Patients with a history of cancer and/or missing data on either smoking or physical activity status were excluded (17,894, 2.8% of total). The derivation of the final number of included persons by study is portrayed in **Figure 1**.

Outcomes

Analyses were conducted for specific cancer sites where convincing evidence of a positive association with excess BMI was reported.(7,13) We examined invasive breast cancer (ICD-10 C50) at postmenopausal ages, colorectal cancer (C18-21), as well as a combined obesity-related cancer category that also included cancer of the pancreas (C25), gallbladder (C23), kidney (C64) and endometrium (C54). Small numbers precluded the possibility to perform separate analyses of each obesity-related cancer site.

Exposure variables

Overweight was defined as having a BMI above 25 kg/m^2. For all European studies except ESTHER, where only self-reported BMI was available, BMI was calculated based on measured height and weight. In NIH AARP, height and weight were self-reported at age 50 (retrospectively) and at baseline. While

two BMI assessments were available for study participants from the EPIC, NIH AARP and the PRIME Belfast cohorts, data from up to four time points were available from ESTHER.

Covariates

Baseline information on all covariates except alcohol consumption (continuous, grams/day) were available as categorical variables as follows: (daily) smoking status (never smoker/former smoker/current smoker), (vigorous) physical activity (yes/no), highest level of education (primary or less/more than primary but less than college or university/college or university), HT use (never/ever). Other information on reproductive history and diet were not consistently available in all cohorts and could not be taken into account in our analyses.

Statistical analysis

The analysis was carried out in three steps. First, a quadratic growth model with a random intercept and random slope was used to predict individual BMI trajectories for each study participant.(14,15) This model was developed and adjusted in a step-wise manner by adding study, sex, smoking status, physical activity and an interaction term for study and contact age to the fixed effects part of the model. The obtained predicted BMI values for all ages between study entry and study exit were then used to estimate overweight (BMI≥25) duration in years. Weighted cumulative overweight years (OWY) were computed by multiplying the duration of overweight in years by the difference (in BMI units) above normal BMI (BMI≥25) for each increment of age. This measure takes into account the degree of overweight over time and is comparable to pack-years in relation to tobacco smoking. Overweight duration was assessed per 10-year increment and cumulative OWY per 100 units.

Secondly, Cox proportional hazard models with age as time metric were used to estimate hazard ratios (HR) and 95% confidence limits (CI) to describe the relation between overweight duration, cumulative OWY and the risk of developing cancer. Overweight duration and cumulative OWY were treated as continuous, time-dependent covariates in the model. Subjects were censored at death, lost to follow-up, any cancer excluding non-melanoma skin cancer (C44) diagnosis other than the site of interest and end of follow-up, whichever occurred first. For all outcomes, three models with different sets of adjustments were fitted. In model 1, adjustments were made for age and sex. Model 2 was additionally adjusted for smoking status and physical activity. In model 3, further adjustments were made for education and alcohol consumption. All analyses were carried out for each study separately and the results were then combined using random-effects meta-analysis. (16) We used three-knot cubic splines

to model non-linear relations between obesity duration, OWY and cancer risk. In secondary analyses, data from all cohorts were pooled to assess interactions in stratified analyses by sex, smoking status, HT use and diabetes history.

Lastly, and based on the assumption that the association between overweight and the cancer sites included in our study is causal (17), population attributable fractions (PAF) and their 95% CIs were calculated (18,19) using the maximum likelihood method (20) and the 'punaf' command in Stata. PAFs represent the proportion of obesity-related cancer cases that could have been avoided if participants were never overweight during follow-up.

All statistical analyses were performed using Stata 12.

RESULTS

In total, 329 595 participants were included in this study, with 14 998 obesity-related cancer cases occurring during follow-up (**Table 1**). Study participants were recruited between 1991 and 2003, with a mean age at study entry ranging from 54 years in Northern Ireland (PRIME Belfast) cohort to 67 years in Greece (EPIC elderly). Education level (highest attained degree) was particularly high in the US (NIH AARP) (75% with college or university degree), while more than 85% of the Spanish participants (EPIC elderly) had only primary education or less. Mean BMI at baseline ranged between 25.8 kg/m^2 in the Netherlands to 29.5 kg/m^2 in Spain, where 42% of the study participants were classified as obese (BMI≥30). While 75% of all participants from Denmark (EPIC elderly) reported to be physically active, this applied to only 5% in Spain. Alcohol intake was highest in Denmark (20.2 g/d) and lowest in Norway (Tromsø – 3.6 g/d), in contrast with smoking, where Norway had the highest and Greece the lowest proportion of current daily smokers (31% and 12% respectively). Median follow-up ranged between 10.4 years in Germany (ESTHER) and 18.0 years in Northern Ireland (PRIME Belfast). Age-standardized incidence rates of obesity-related cancers ranged between 319 per 100 000 person-years in the US to 29 per 100 000 in Greece.

In the meta-analysis of all studies, a longer duration of overweight was significantly associated with an increased risk of obesity-related cancer combined (Hazard Ratio (HR) per 10-yr increment: 1.39; 95%CI: 1.13 to 1.64) and was most pronounced in the German ESTHER cohort (HR: 2.52, 95%CI: 1.80 to 3.52), but not statistically significant in the Spanish and Danish EPIC cohorts (**Figure 2**). When taking the degree of overweight over time into account, risks tended to be slightly more pronounced, especially in the US NIH AARP cohort (**Figure 2**), but also overall (HR per 100-unit increment in OWY: 1.47; 95%CI: 1.15 to 1.80). While results were similar for postmenopausal breast and colorectal cancer, higher risks were found for other obesity-related sites, comprising cancer of the pancreas, kidney, gallbladder and endometrium. HRs for the association between overweight duration and cumulative OWY by cancer site and cohort, for the different models are presented in **Supplementary Table 1**. As adjustments for alcohol consumption and education level in model 3 only marginally altered the results of model 2, the latter simpler model was used when exploring dose-response relationships between increasing overweight duration, intensity and cancer risk. Clear associations were found for all obesity-related cancer sites combined, but also for breast cancer in HT non-users (**Figure 3, panel A**). When taking into account the degree of overweight over time, the risk increase became more pronounced, especially for other obesity-related cancers (**Figure 3, panel B**). This relationship was mainly driven by kidney and

endometrial cancer, showing exponential associations with the combination of overweight duration and intensity over time (**Supplementary Figure 1**).

The population attributable fraction (PAF) for ever being overweight during follow-up was 8.5% (95%CI: 6.2 to 10.7%) for obesity-related cancers combined (**Table 2**). PAFs were considerably higher in men than in women (18.7% vs 5.4%), in never smokers relative to current and past smokers and in those with a history of diabetes type 2. In women who never used HT, 17.9% (12.6 to 22.8%) of all breast cancers were attributable to ever being overweight during follow-up.

In secondary analyses, we investigated the potential confounding effects of sex, smoking status, HT use and diabetes history in the pooled dataset (**Supplementary Table 2**). Generally, the risks associated with both overweight duration and cumulative OWY were higher in men than in women. After stratification for sex, the risk of colorectal cancer associated with a longer overweight duration and intensity (OWY) reached statistical significance in both men and women. Clear gradients in risk were found across smoking categories, indicating that the risk of obesity-related cancer due to overweight duration and/or cumulative OWY was highest among never smokers, intermediate among former smokers and low or negligible in current smokers. For breast cancer, significant effects were limited to never smokers and those who never used HT, with similar effect sizes for both overweight duration (HR: 1.41, 95%CI: 1.25 to 2.58) and cumulative OWY (HR: 1.33, 95%CI: 1.15 to 1.53). Risks of obesity-related cancers were higher in study participants who ever reported type 2 diabetes relative to those who had no diabetes history, especially when the degree of overweight over time was taken into account.

DISCUSSION

Based on a pooling of eight cohort studies, 300 000 participants and more than 15 000 obesity-related cancers, this is the first study to assess the impact of overweight duration on cancer risk in older populations. Overall, we found that a longer duration of overweight was significantly associated with a higher risk of postmenopausal breast and colorectal cancer, as well as for obesity-related cancers combined. Risks associated with a longer overweight duration were higher in men than in women and among non-smokers than in current smokers. For post-menopausal breast cancer, increased risks were confined to women who never used HT. When additionally taking the degree of overweight over time into account, risks increased even further. Overall, 8.5% of obesity-related cancers could be attributed to being overweight at any time point after age 50 (10.7% in never smokers).

These findings are consistent with studies reporting associations between high BMI at one point in time and cancer risk (7,21) and are in line with evidence on the impact of obesity duration on other health outcomes, including type 2 diabetes, cardiovascular disease and all-cause mortality.(8-10) One of the putative underlying biological mechanisms involves changes in the metabolism of sex-steroid hormones, namely oestrogen, which is mainly produced by fat tissue in postmenopausal women.(22) Hence, a longer overweight duration increases the exposure time to elevated hormone levels, which may in turn increase the risk of developing cancer. In our study, we found that the increased risk of postmenopausal breast cancer related to a longer overweight duration was confined to women who never used HT and risks were similar for overweight duration and OWY. This finding suggests that exogenous oestrogen and hormone levels modify the association between overweight duration and postmenopausal breast cancer, as noted in previous studies.(23,24)

We also noted important sex differences in the risk of developing obesity-related cancer associated with increasing overweight duration. Higher risks in men were mainly evident for colorectal cancer and all obesity-related cancers combined. This is consistent with previous studies pointing towards a stronger link between different measures of obesity and colorectal cancer in men, with the association much weaker or absent in women.(25,26) Increased waist circumference has been suggested to be a better predictor of colorectal cancer risk than BMI that varies markedly by sex.(26,27) Waist circumference is a proxy for visceral adipose tissue, where leptin and adiponectin are predominantly secreted. Adiponectin is inversely correlated with body fatness, is anti-inflammatory and inhibits tumour growth in animals.(28) As circulating levels of adiponectin have been found to be higher in women than men, this

may offer an explanation for sex differences in colorectal cancer risk associated with overweight and obesity.(25)

Another important confounder was smoking. We found that never smokers were at a higher risk of obesity-related cancer with increasing overweight duration relative to current smokers. This association was more pronounced when the degree of overweight was taken into account, and is supported by previous findings on the role of smoking in the obesity-cancer pathway. (7,29) Other factors such as hormones and circulating levels of DNA adducts have been suggested to contribute to lower risks of obesity-related cancers observed in smokers. (7,30-32) In contrast, history of type 2 diabetes modified the overweight-cancer association in our study in a way that participants with a positive history had the greatest risk. This finding confirms previous findings on the interaction between overweight duration, diabetes and pancreatic cancer.(33)

While our findings were largely consistent across studies, we generally found weaker associations in the US cohort when compared to the European cohorts. This may be partly explained by differences in the baseline characteristics between European and US study participants as well as the relative study sizes. In comparison with the combined European cohorts, comprising 38 563 study participants, the US NIH AARP cohort was much larger (291 032 participants), and hence better powered. Additionally, the majority of the US NIH AARP participants were highly educated and less likely to be current smokers or physically inactive than participants of the European cohorts, limiting the generalizability of the findings to the general US population. Yet, given the similar associations found across the studies and the general notion that the effect of obesity on cancer development should not differ between Europeans and North Americans, we believe that our results are valid and most likely a conservative estimate of the true effect.

In this pooled analysis, we were able to include a large number of study participants from several European countries and the US, which enabled an assessment of the dose-response relationship between overweight duration and cancer risk, as well as related sensitivity analyses. However, some methodological considerations and limitations should be noted. In the first step of our analysis, we used repeated measurements and self-reports of height and weight to model BMI across ages using a growth curve approach. With this approach, we were able to estimate each study participant's overweight trajectory and duration during follow-up. As the results from the German ESTHER study (where only self-reported height and weight were available) were consistent with those from the other European cohorts (where BMI was calculated based on measured height and weight), we believe that the type of BMI

information has not unduly affected our overall findings. When we repeated the analyses with obesity (BMI≥30) duration, the associations became slightly stronger. It is however important to note that BMI may not be an ideal measure of body fatness since it can reflect both adiposity and muscularity and is limited in its ability to predict body fatness across ethnic groups and age.(34) Age-related decreases in height might falsely lead to an increase in BMI and with advancing age fat tissue tends to be redistributed towards the abdominal region.(34) Hence, it might have been more appropriate to use one of the measures of central obesity as a surrogate for overweight and obesity as these have been suggested to better predict obesity-related health outcomes when compared to BMI.(35,36) These measures were however not available longitudinally from the cohorts included in this study. Yet, in a companion paper using data from the same cohorts (except NIH-AARP), we found that the risk associated with a standard deviation increase in baseline BMI and waist circumference were similar for post-menopausal breast, colorectal and obesity-related cancers combined (Heinz Freisling, personal communication).

Further limitations of our study are related to differences in study design between cohorts, including differences in length of follow-up, anthropometric assessment methods and their frequency, as well as the comparability of several variables. In order to harmonize the data and variable definitions across cohorts, some variables such as physical activity were only available in binary form (yes/no). Despite adjustment for the main confounding factors, namely smoking and physical activity, we cannot rule out confounding by other unmeasured factors, most importantly reproductive risk factors and diet. As these were not consistently available from all cohorts, we were not able to take these into account in our analyses.

Lastly, it is important to acknowledge a number of methodological limitations, which we hope will prompt further research. In the same way that we have estimated cumulative exposure for our main independent variable, overweight duration, it may be surmised that the nature of the confounding or moderating effects of other exposures (such as smoking, alcohol intake or physical activity) might, in uncertain ways, depend on how their own cumulative effects have been modelled. Related to this is the fact that methodologists have recently debated about the correct way to model cumulative effects, when their effects on absolute rather than relative risk scales might differ and when more complex temporal patterns of exposure may not be modelled well on a proportional hazards scale. (37-39)

Implications and conclusions

We report that longer overweight duration increases the risk of cancer in older adults, in both Europe and the US, with 8.5% of obesity-related cancers attributable to overweight at any time point after age 50. Previous studies suggest that avoidance of weight gain, engaging in physical activity, and even small amounts of weight loss in the elderly may prevent adverse health consequences of obesity.(34,40) Our findings provide further insights into the role of overweight duration on the aetiology of cancer in older adults and indicate that weight control is relevant at all ages. This knowledge is vital for the development of effective and targeted cancer prevention strategies. Future studies should further investigate the specific roles of age at onset of overweight and different BMI trajectories on cancer risk.

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FIGURE LEGENDS

Figure 1. Flowchart of participant inclusion

* information on history of cancer and cancer sequence was not available from the NIH AARP cohort

Figure 2. Hazard ratios (HR)* and their 95% confidence intervals (95% CI) for overweight (BMI≥25) duration and weighted cumulative overweight years (OWY), by cohort and cancer site, men and women combined.

[*] results from random-effects meta-analysis with adjustments for age, sex, smoking status, physical activity (yes/no), alcohol consumption and education level (Model 3)
[a] breast, colorectum, pancreas, kidney, gallbladder, endometrium; [b]pancreas, kidney, gallbladder, endometrium

Figure 3. Hazard ratios (HR) and their 95% confidence intervals (95%CI) for the association between (A) overweight (BMI≥25) duration, (B) weighted cumulative overweight years (OWY) and cancer risk, men and women combined

[a]breast, colorectum, pancreas, kidney, gallbladder, endometrium; [b]pancreas, kidney, gallbladder, endometrium
The figure shows a 3-knot spline of the relation between overweight duration and cancer risk, allowing for non-linear effects and adjusted for age, sex, smoking status and physical activity (Model 2). P-values are for non-linearity.

Table 1. Selected cohort characteristics

	EPIC-Elderly								Germany (ESTHER)		Northern Ireland (PRIME Belfast)		Norway (Tromsø)		USA (NIH AARP)	
	Denmark		Greece		Netherlands		Spain									
Baseline characteristics	(n=6,871)		(n=6,877)		(n=4,149)		(n=4,550)		(n=8347)		(n=1,920)		(n=5,849)		(n=291,032)	
Recruitment year (range)	1993-1997		1994-1999		1993-1997		1992-1996		2000-2003		1991-1994		1994-1995		1995-1997	
Mean age, in years (SD)	62.5	1.5	67.0	4.4	64.3	2.8	62.5	1.7	61.8	6.6	54.2	2.8	59.4	6.9	62.2	5.3
Sex																
Men	3521	51.2%	2693	39.2%	154	3.7%	1931	42.4%	3784	45.3%	1920	100.0%	2736	46.8%	173065	59.5%
Women	3350	48.8%	4184	60.8%	3995	96.3%	2619	57.6%	4563	54.7%	0	0.0%	3113	53.2%	117967	40.5%
Education																
Low (primary or less)	2451	35.7%	6281	91.3%	1279	30.8%	3899	85.7%	6025	72.2%	15	0.8%	2999	51.3%	1391	0.5%
Medium (more than primary but less than college)	3040	44.2%	379	5.5%	2364	57.0%	317	7.0%	1736	20.8%	1655	86.2%	1710	29.2%	64972	22.3%
High (college or university)	1366	19.9%	200	2.9%	503	12.1%	284	6.2%	412	4.9%	250	13.0%	1108	18.9%	218582	75.1%
Missing	14	0.2%	17	0.2%	3	0.1%	50	1.1%	174	2.1%	0	0.0%	32	0.5%	6087	2.1%
Mean BMI at baseline (SD)	26.1	3.8	29.3	4.3	25.8	3.9	29.5	4.0	27.6	4.2	26.1	3.2	26.1	3.7	26.8	4.5
Underweight (BMI < 18.5)	35	0.5%	18	0.3%	45	1.1%	4	0.1%	33	0.4%	8	0.4%	43	0.7%	2448	0.8%
Normal weight (BMI ≥ 18.5 & BMI < 25)	2819	41.0%	1062	15.4%	1891	45.6%	491	10.8%	2268	27.2%	717	37.3%	2352	40.2%	105200	36.1%
Overweight (BMI ≥ 25 & BMI < 30)	3096	45.1%	2997	43.6%	1674	40.3%	2151	47.3%	3953	47.4%	980	51.0%	2634	45.0%	123553	42.5%
Obese (BMI ≥ 30)	921	13.4%	2800	40.7%	539	13.0%	1904	41.8%	2093	25.1%	215	11.2%	820	14.0%	59831	20.6%
Vigorous physical activity[a]																
No	1742	25.4%	5418	78.8%	1669	40.2%	4308	94.7%	4678	56.0%	1668	86.9%	3526	60.3%	150884	51.8%
Yes	5129	74.6%	1459	21.2%	2480	59.8%	242	5.3%	3669	44.0%	252	13.1%	2323	39.7%	140148	48.2%
Alcohol intake																
(average daily consumption in grams)	20.2		7.4		7.8		13.0		6.8		20		3.6		13.3	
N missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	664	8.0%	0	0.0%	1082	18.5%	0	0.0%
Smoking status[a]																
Never daily smoker	2293	33.4%	4830	70.2%	2002	48.3%	3095	68.0%	4188	50.2%	792	41.3%	1935	33.1%	106553	36.6%
Former daily smoker	2650	38.6%	1257	18.3%	1482	35.7%	722	15.9%	2771	33.2%	637	33.2%	2107	36.0%	151257	52.0%
Current daily smoker	1928	28.1%	790	11.5%	665	16.0%	733	16.1%	1388	16.6%	491	25.6%	1807	30.9%	33222	11.4%
Hormone therapy use[b]																
Ever	1686	50.3%	0	0.0%	3299	82.6%	2310	88.2%	1965	43.1%	n/a		1475	47.4%	52024	44.1%
Never	1564	46.7%	0	0.0%	692	17.3%	288	11.0%	2287	50.1%	n/a		873	28.0%	65943	55.9%
Missing	100	3.0%	4184	100.0%	4	0.1%	21	0.8%	311	6.8%	n/a		765	24.6%	0	0.0%
Self-reported or documented diabetes type 2																
No	6429	93.6%	5924	86.1%	3986	96.1%	4026	88.5%	n/a		n/a		n/a		266620	91.6%
Yes	143	2.1%	944	13.7%	159	3.8%	515	11.3%	n/a		n/a		n/a		24412	8.4%
Missing	299	4.4%	9	0.1%	4	0.1%	9	0.2%	n/a		n/a		n/a		0	0.0%
Median follow-up time (years)	11.9		11.5		13.2		13.4		10.4		18.0		15.9		10.5	
N cancers cases (N/incidence rate[c] per 100 000)	734		340		403		483		845		256		722		53108	
N breast cancer (age>50, women only)	110	42.4	21	9.3	109	57.0	42	21.4	120	86.0	0	0.0	64	39.1	5905	152.9
N colorectal cancer	94	37.4	37	10.1	77	39.3	66	35.1	110	67.8	40	75.3	112	53.9	4470	93.5
N obesity-related[d]	253	99.2	86	29.2	226	116.6	153	78.8	313	208.0	52	93.6	205	107.6	13710	318.8

[a]participants with missing information on physical activity and smoking status were excluded
[b]women only
[c]age-standardized to the World standard population
[d]breast, colorectal, pancreas, kidney, gallbladder, endometrium

Table 2. Population attributable fractions (PAF) of ever being overweight (body mass index >= 25kg/m2) and cancer risk

		Obesity-related cancers[a]		Breast cancer		Colorectal cancer		Other obesity-related cancers[b]	
	% ever overweight	PAF (95% CI)		PAF (95% CI)		PAF (95% CI)		PAF (95% CI)	
Overall	68.6%	8.5%	(6.2-10.7)			9.6%	(5.3-13.8)	23.9%	(19.4-28.2)
Men	75.0%	18.7%	(14.1-23.1)			13.3%	(7.3-18.9)	28.3%	(20.9-35.1)
Women	60.0%	5.4%	(2.9-7.8)	*	*	*	*	20.4%	(14.8-25.7)
Current daily smoker	59.1%	*	*	*	*	*	*	*	*
Former daily smoker	72.2%	8.6%	(5.1-12.0)	*	*	8.7%	(2.2-14.8)	27.0%	(20.0-33.3)
Never daily smoker	67.1%	10.7%	(7.2-14.1)	*	*	15.2%	(8.0-21.8)	25.7%	(18.5-32.2)
Diabetes ever	85.8%	17.2%	(3.7-28.7)	*	*	*	*	52.8%	(31.8-67.3)
Diabetes never	66.7%	7.0%	(4.7-9.3)	*	*	8.6%	(4.0-13.0)	20.5%	(15.7-25.0)
HRT ever users	54.7%	*	*	*	*	*	*	*	*
HRT never users	63.7%	17.1%	(13.2-20.8)	17.9%	(12.6-22.8)	*	*	32.3%	(24.3-39.5)

[a]breast, colorectum, pancreas, kidney, gallbladder, endometrium; [b]pancreas, kidney, gallbladder, endometrium

* PAF not calculated because HR statistically non-significant.

Figure 1

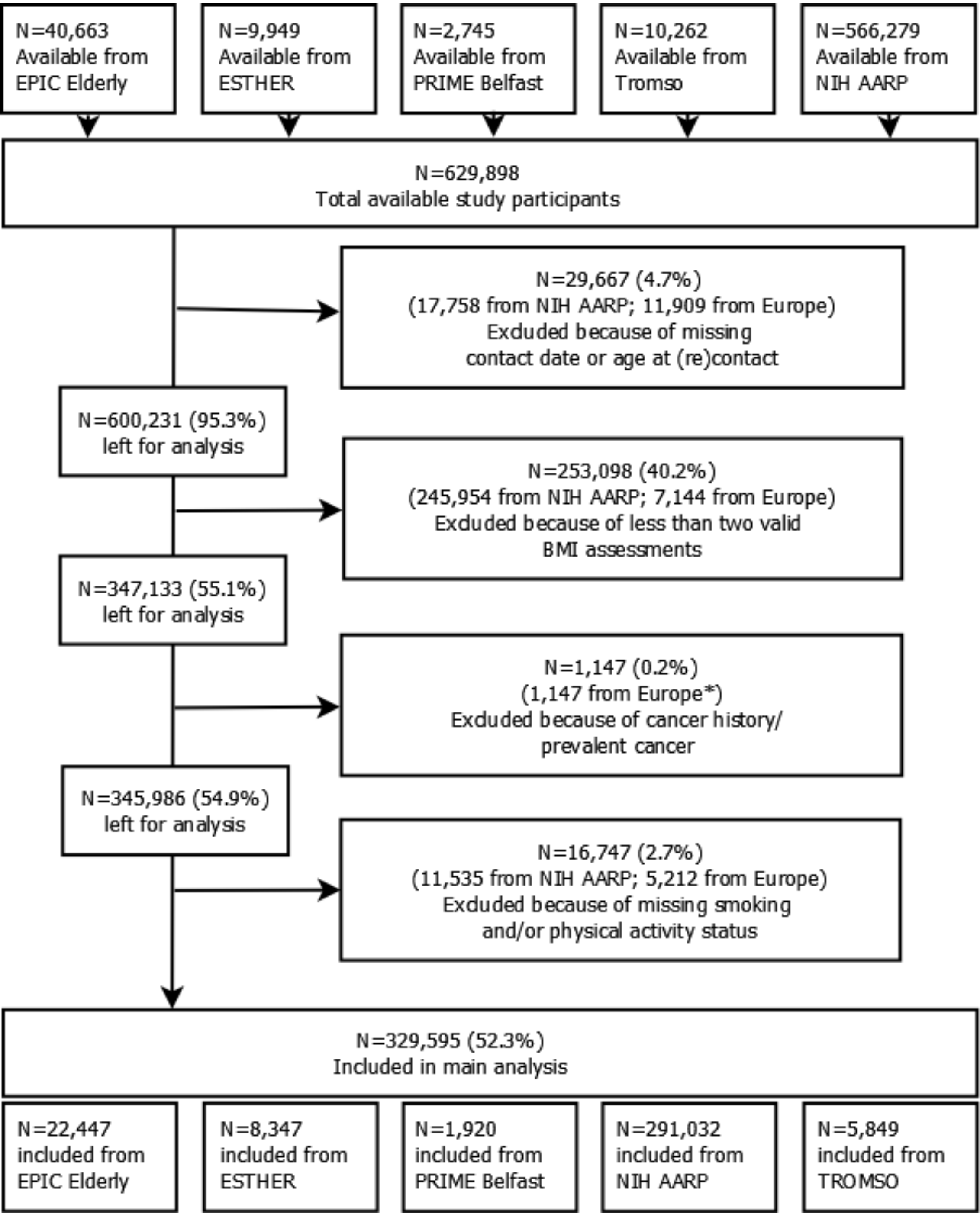
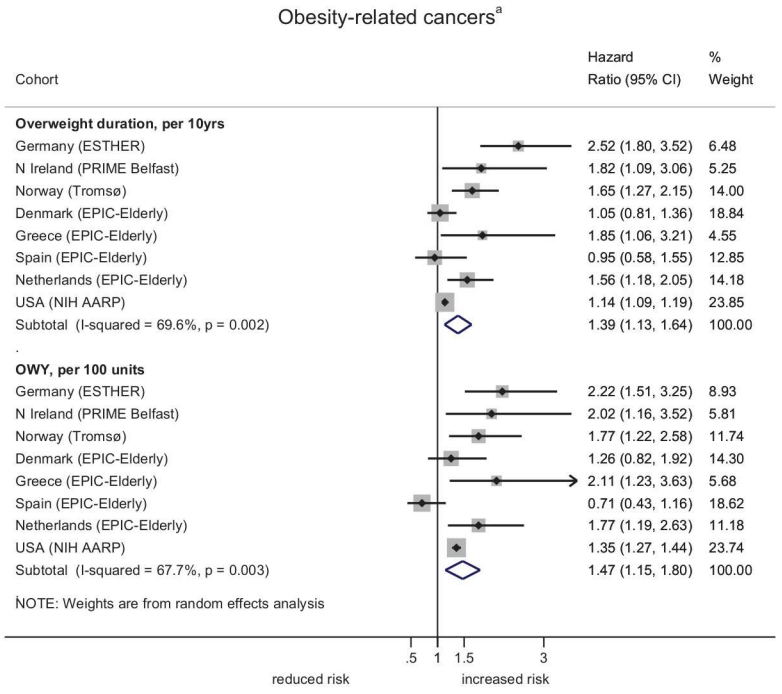
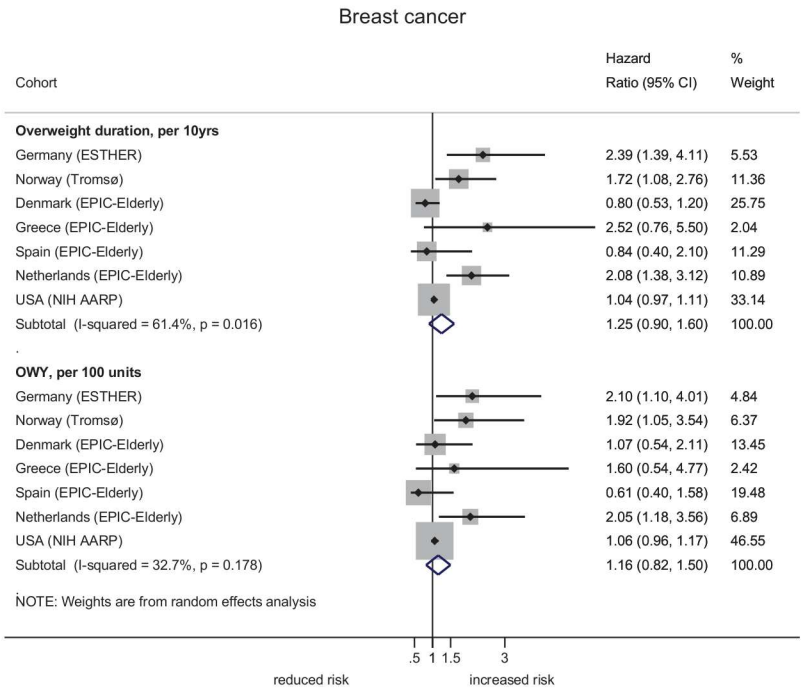
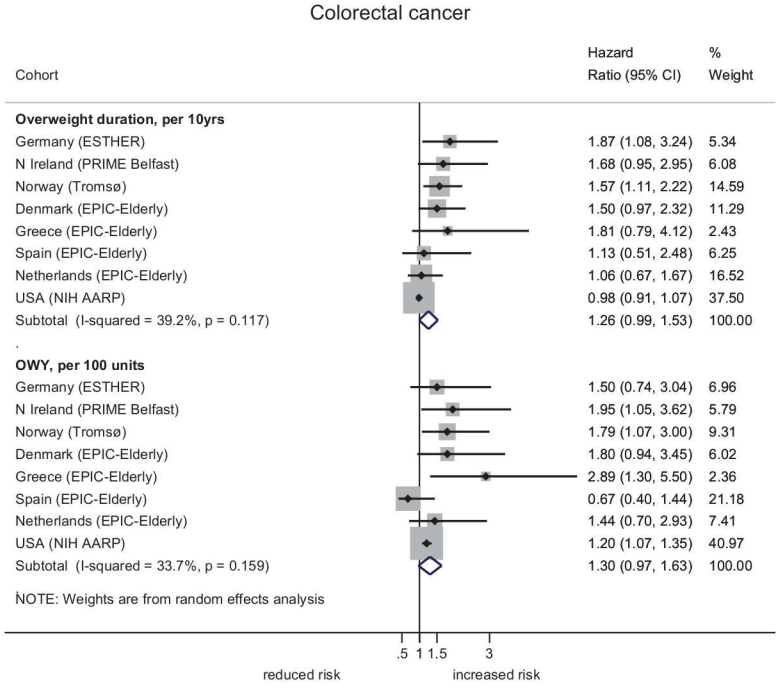

N=40,663
Available from
EPIC Elderly
N=9,949
Available from
ESTHER
N=2,745
Available from
PRIME Belfast
N=10,262
Available from
Tromso
N=566,279
Available from
NIH AARP
N=629,898
Total available study participants
N=29,667 (4.7%)
(17,758 from NIH AARP; 11,909 from Europe)
Excluded because of missing
contact date or age at (re)contact
N=600,231 (95.3%)
left for analysis
N=253,098 (40.2%)
(245,954 from NIH AARP; 7,144 from Europe)
Excluded because of less than two valid
BMI assessments
N=347,133 (55.1%)
left for analysis
N=1,147 (0.2%)
(1,147 from Europe*)
Excluded because of cancer history/
prevalent cancer
N=345,986 (54.9%)
left for analysis
N=16,747 (2.7%)
(11,535 from NIH AARP; 5,212 from Europe)
Excluded because of missing smoking
and/or physical activity status
N=329,595 (52.3%)
Included in main analysis
N=22,447
included from
EPIC Elderly
N=8,347
included from
ESTHER
N=1,920
included from
PRIME Belfast
N=291,032
included from
NIH AARP
N=5,849
included from
TROMSO

Figure 2


Obesity-related cancers[a]
Cohort
Hazard Ratio (95% CI)
% Weight
Overweight duration, per 10yrs
Germany (ESTHER) 2.52 (1.80, 3.52) 6.48
N Ireland (PRIME Belfast) 1.82 (1.09, 3.06) 5.25
Norway (Tromsø) 1.65 (1.27, 2.15) 14.00
Denmark (EPIC-Elderly) 1.05 (0.81, 1.36) 18.84
Greece (EPIC-Elderly) 1.85 (1.06, 3.21) 4.55
Spain (EPIC-Elderly) 0.95 (0.58, 1.55) 12.85
Netherlands (EPIC-Elderly) 1.56 (1.18, 2.05) 14.18
USA (NIH AARP) 1.14 (1.09, 1.19) 23.85
Subtotal (I-squared = 69.6%, p = 0.002) 1.39 (1.13, 1.64) 100.00
OWY, per 100 units
Germany (ESTHER) 2.22 (1.51, 3.25) 8.93
N Ireland (PRIME Belfast) 2.02 (1.16, 3.52) 5.81
Norway (Tromsø) 1.77 (1.22, 2.58) 11.74
Denmark (EPIC-Elderly) 1.26 (0.82, 1.92) 14.30
Greece (EPIC-Elderly) 2.11 (1.23, 3.63) 5.68
Spain (EPIC-Elderly) 0.71 (0.43, 1.16) 18.62
Netherlands (EPIC-Elderly) 1.77 (1.19, 2.63) 11.18
USA (NIH AARP) 1.35 (1.27, 1.44) 23.74
Subtotal (I-squared = 67.7%, p = 0.003) 1.47 (1.15, 1.80) 100.00
NOTE: Weights are from random effects analysis
.5 1 1.5 3
reduced risk
increased risk


Breast cancer
Cohort
Hazard Ratio (95% CI)
% Weight
Overweight duration, per 10yrs
Germany (ESTHER) 2.39 (1.39, 4.11) 5.53
Norway (Tromsø) 1.72 (1.08, 2.76) 11.36
Denmark (EPIC-Elderly) 0.80 (0.53, 1.20) 25.75
Greece (EPIC-Elderly) 2.52 (0.76, 5.50) 2.04
Spain (EPIC-Elderly) 0.84 (0.40, 2.10) 11.29
Netherlands (EPIC-Elderly) 2.08 (1.38, 3.12) 10.89
USA (NIH AARP) 1.04 (0.97, 1.11) 33.14
Subtotal (I-squared = 61.4%, p = 0.016) 1.25 (0.90, 1.60) 100.00
OWY, per 100 units
Germany (ESTHER) 2.10 (1.10, 4.01) 4.84
Norway (Tromsø) 1.92 (1.05, 3.54) 6.37
Denmark (EPIC-Elderly) 1.07 (0.54, 2.11) 13.45
Greece (EPIC-Elderly) 1.60 (0.54, 4.77) 2.42
Spain (EPIC-Elderly) 0.61 (0.40, 1.58) 19.48
Netherlands (EPIC-Elderly) 2.05 (1.18, 3.56) 6.89
USA (NIH AARP) 1.06 (0.96, 1.17) 46.55
Subtotal (I-squared = 32.7%, p = 0.178) 1.16 (0.82, 1.50) 100.00
NOTE: Weights are from random effects analysis
.5 1 1.5 3
reduced risk
increased risk


Colorectal cancer
Cohort
Hazard Ratio (95% CI)
% Weight
Overweight duration, per 10yrs
Germany (ESTHER) 1.87 (1.08, 3.24) 5.34
N Ireland (PRIME Belfast) 1.68 (0.95, 2.95) 6.08
Norway (Tromsø) 1.57 (1.11, 2.22) 14.59
Denmark (EPIC-Elderly) 1.50 (0.97, 2.32) 11.29
Greece (EPIC-Elderly) 1.81 (0.79, 4.12) 2.43
Spain (EPIC-Elderly) 1.13 (0.51, 2.48) 6.25
Netherlands (EPIC-Elderly) 1.06 (0.67, 1.67) 16.52
USA (NIH AARP) 0.98 (0.91, 1.07) 37.50
Subtotal (I-squared = 39.2%, p = 0.117) 1.26 (0.99, 1.53) 100.00
OWY, per 100 units
Germany (ESTHER) 1.50 (0.74, 3.04) 6.96
N Ireland (PRIME Belfast) 1.95 (1.05, 3.62) 5.79
Norway (Tromsø) 1.79 (1.07, 3.00) 9.31
Denmark (EPIC-Elderly) 1.80 (0.94, 3.45) 6.02
Greece (EPIC-Elderly) 2.89 (1.30, 5.50) 2.36
Spain (EPIC-Elderly) 0.67 (0.40, 1.44) 21.18
Netherlands (EPIC-Elderly) 1.44 (0.70, 2.93) 7.41
USA (NIH AARP) 1.20 (1.07, 1.35) 40.97
Subtotal (I-squared = 33.7%, p = 0.159) 1.30 (0.97, 1.63) 100.00
NOTE: Weights are from random effects analysis
.5 1 1.5 3
reduced risk
increased risk

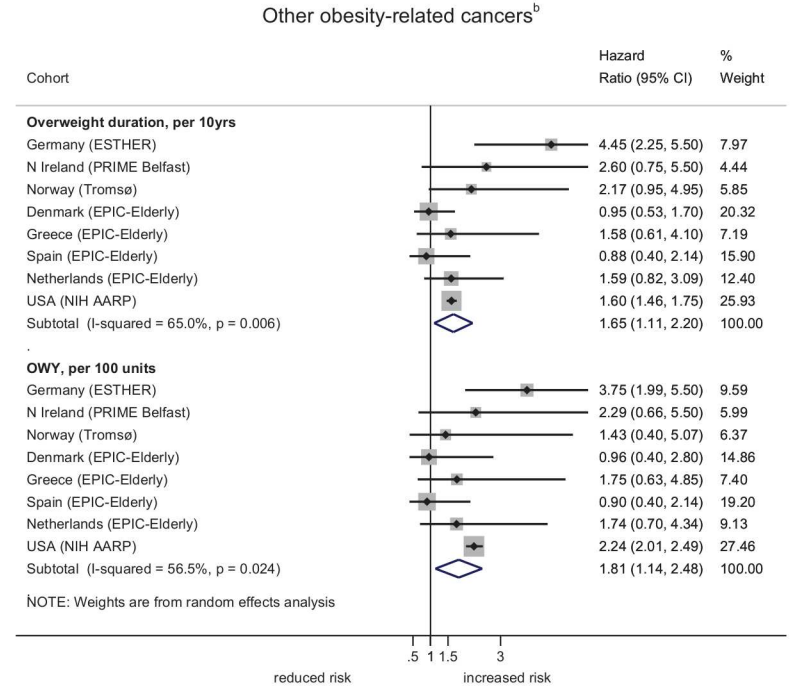
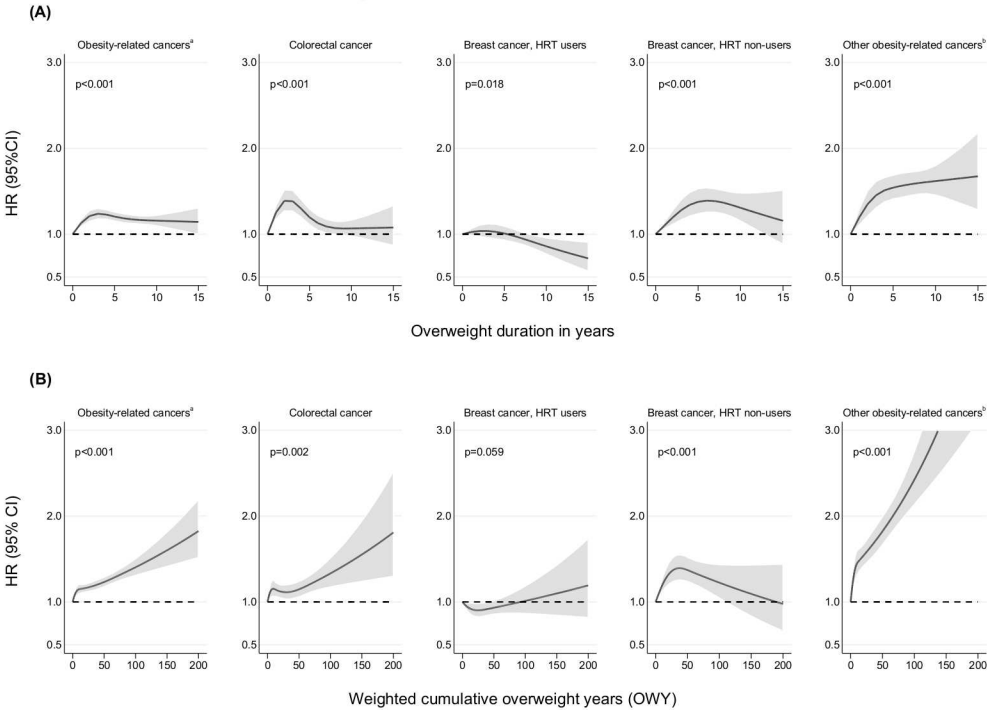

Other obesity-related cancers[b]
Cohort
Hazard Ratio (95% CI)
% Weight
Overweight duration, per 10yrs
Germany (ESTHER) 4.45 (2.25, 5.50) 7.97
N Ireland (PRIME Belfast) 2.60 (0.75, 5.50) 4.44
Norway (Tromsø) 2.17 (0.95, 4.95) 5.85
Denmark (EPIC-Elderly) 0.95 (0.53, 1.70) 20.32
Greece (EPIC-Elderly) 1.58 (0.61, 4.10) 7.19
Spain (EPIC-Elderly) 0.88 (0.40, 2.14) 15.90
Netherlands (EPIC-Elderly) 1.59 (0.82, 3.09) 12.40
USA (NIH AARP) 1.60 (1.46, 1.75) 25.93
Subtotal (I-squared = 65.0%, p = 0.006) 1.65 (1.11, 2.20) 100.00
OWY, per 100 units
Germany (ESTHER) 3.75 (1.99, 5.50) 9.59
N Ireland (PRIME Belfast) 2.29 (0.66, 5.50) 5.99
Norway (Tromsø) 1.43 (0.40, 5.07) 6.37
Denmark (EPIC-Elderly) 0.96 (0.40, 2.80) 14.86
Greece (EPIC-Elderly) 1.75 (0.63, 4.85) 7.40
Spain (EPIC-Elderly) 0.90 (0.40, 2.14) 19.20
Netherlands (EPIC-Elderly) 1.74 (0.70, 4.34) 9.13
USA (NIH AARP) 2.24 (2.01, 2.49) 27.46
Subtotal (I-squared = 56.5%, p = 0.024) 1.81 (1.14, 2.48) 100.00
NOTE: Weights are from random effects analysis
.5 1 1.5 3
reduced risk
increased risk

Figure 3


(A)
Obesity-related cancers[a]
p<0.001
Colorectal cancer
p<0.001
Breast cancer, HRT users
p=0.018
Breast cancer, HRT non-users
p<0.001
Other obesity-related cancers[b]
p<0.001
HR (95%CI)
Overweight duration in years
(B)
Obesity-related cancers[a]
p<0.001
Colorectal cancer
p=0.002
Breast cancer, HRT users
p=0.059
Breast cancer, HRT non-users
p<0.001
Other obesity-related cancers[b]
p<0.001
HR (95% CI)
Weighted cumulative overweight years (OWY)