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Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe

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ABSTRACT

Background: We evaluated the associations of anthropometric indicators of general obesity (body mass index, BMI), an established risk factor of various cancer, and body fat distribution (waist circumference, WC; hip circumference, HC; and waist-to-hip ratio, WHR), which may better reflect metabolic complications of obesity, with total obesity-related and site-specific (colorectal and postmenopausal breast) cancer incidence.

Methods: This is a meta-analysis of seven prospective cohort studies participating in the CHANCES consortium including 18,668 men and 24,751 women with a mean age of 62 and 63 years respectively. Harmonized individual participant data from all seven cohorts were analysed separately and alternatively for each anthropometric indicator using multivariable Cox proportional hazards models.

Results: After a median follow-up period of 12 years, 1,656 first incident obesity-related cancers [defined as postmenopausal female breast, colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney] had occurred in men and women. In the meta-analysis of all studies, associations between indicators of adiposity, per standard deviation (SD) increment, and risk for all obesity-related cancers combined yielded the following summary hazard ratios: 1.11 (95 % CI 1.02-1.21) for BMI, 1.13 (95 % CI 1.04-1.23) for WC, 1.09 (95 % CI 0.98-1.21) for HC, and 1.15 (95 % CI 1.00-1.32) for WHR. Increases in risk for colorectal cancer were 16%, 21%, 15%, and 20%, respectively per SD of BMI, WC, HC, and WHR. Effect modification by hormone therapy (HT) use was observed for postmenopausal breast cancer ($P\text{-}_{interaction}<0.001$), where never HT users showed an approximately 20% increased risk per SD of BMI, WC, and HC compared to ever users.

Conclusions: BMI, WC, HC, and WHR show comparable positive associations with obesity-related cancers combined and with colorectal cancer in older adults. For postmenopausal breast cancer we report evidence for effect modification by HT use.

Keywords: CHANCES consortium; Ageing; Cohort; Obesity; Body fat distribution, Cancer; Prevention

INTRODUCTION

The proportion of overweight (body mass index, BMI>25 kg/m^2) or obese (BMI>30 kg/m^2) adults worldwide increased substantially between 1980 and 2013 (NCD Risk Factor Collaboration, 2016), with parallel increases in children and adolescents (Ng *et al*, 2014). Obesity prevalence reaches its peak between age 55 and 60 years in men with ~25% being obese in high-income countries and about 5 years later in women with ~30% being obese (Ng *et al*, 2014). This may have substantial implications for risk of subsequent cancer development, particularly in older adults (60+ years) considering that they are the fastest growing demographic group in most high-income countries.

It is well established that a high BMI is associated with an increased risk of a large number of non-communicable diseases, including cancer. Excess body fatness, as defined by high BMI, has been convincingly linked to an increased risk of eleven different cancer types, including cancer of the oesophagus (adenocarcinoma), gastric cardia, colorectum (CRC, colorectal cancer), gallbladder, pancreas, liver, breast (postmenopausal), ovary, endometrium, kidney and prostate (advanced stage) (World Cancer Research Fund / American Institute for Cancer Research, 2007; Renehan *et al*, 2008; Bhaskaran *et al*, 2014). An up-dated IARC consensus review also judged the strength of evidence sufficient for thyroid, meningioma, and multiple myeloma (Lauby-Secretan *et al*, 2016). These cancers alone comprise about 50% of the total global burden of cancer (based on GLOBOCAN 2012 data) (Arnold *et al*, 2016b).

However, there are uncertainties with regard to how well BMI captures the complex biology underlying associations between adiposity and cancer risk (Renehan *et al*, 2015). This is relevant to the development of cancer prevention strategies because it is increasingly recognized that a proportion of overweight or obese individuals – as defined by a high BMI – might not be at an increased risk for metabolic complications of obesity and its consequences such as cancer (Renehan *et al*, 2015). Waist circumference (WC) and waist-to-hip ratio (WHR) are therefore often used in epidemiological and clinical settings as a means of quantifying body fat distribution indicating central adiposity (National Heart, Lung, 1998; Hu, 2008), and they are thought to be superior predictors of risk of cancer development, at least for the colon and postmenopausal breast (Moore *et al*, 2004; Pischon *et al*, 2006;

White *et al*, 2015). Moreover, a greater hip circumference (HC), after controlling for WC and/or BMI, may be associated with reduced risks of coronary heart disease, type 2 diabetes, and mortality (Heitmann & Lissner, 2011; Cameron *et al*, 2013), but its relation to cancer risk has been fully explored in only a few recent studies (Keimling *et al*, 2013; Steffen *et al*, 2015), where either no association was found for risk of colon cancer with and without adjustment for BMI (Keimling *et al*, 2013) or inverse associations with risk of oesophageal adenocarcinoma after adjustment for WC (Steffen *et al*, 2015). Strictly speaking, HC is not a measure of central adiposity, but of fat accumulated in the lower part of the body (such as the hips and thighs) (Hu, 2008). Together, the evidence that measures of body fat distribution or central adiposity are better predictors of cancer risk than BMI is inconsistent. Also, only a few prospective studies comparing different measures of adiposity were carried out in adults aged 60 years and above.

Our primary objective was to derive standardized risk estimates for anthropometric measures of general adiposity (BMI) and body fat distribution (WC, HC, and WHR) and their association with 'obesity-related' cancers combined (i.e. cancer sites with convincing evidence of a positive association with greater body fatness) as well as CRC and (postmenopausal) breast cancer in a large population of older adults from Europe. Secondary objectives were to examine the shape of the dose–response relationships and to evaluate potential effect modification by sex, smoking status, use of hormone therapy (HT), and interaction between measures of body fat distribution and general adiposity.

METHODS

Study population. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project (www.chancesfp7.eu) is a multi-country study which aims to harmonize data from ongoing prospective cohort studies in Europe and North-America (Boffetta *et al*, 2014).

The following CHANCES cohorts provided data for the current analysis: the study centers in Denmark, Greece, the Netherlands, and Spain of EPIC-Elderly, which is a subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) project that consists of participants aged 60

years or older at recruitment; the Epidemiological Study on Chances for Prevention, Early Detection, and Optimized THERapy of Chronic Diseases at Old Age (ESTHER), a population-based cohort covering the entire federal state of Saarland in Germany, aged 50 or older at recruitment; the PRIME Belfast study, which is a cohort of male residents aged 50-60 years of Belfast and the surrounding area in the United Kingdom; and the Tromsø study, which recruited men and women in Norway between 1994 and 1995 (4^{th} wave) aged 50-84 years. Other CHANCES cohorts either decided not to participate in this analysis or could not provide cancer incidence data. The participating cohorts' key characteristics are summarized in **Table 1**. Additional information on the individual cohorts has been given previously (Boffetta *et al*, 2014). We followed similar inclusion and exclusion criteria, which are displayed in **Figure 1**, as in a companion paper on overweight duration and risk of cancer (Arnold *et al*, 2016a). Further to the exclusions shown in Figure 1, we excluded participants with an implausible BMI below 15 or above 45 kg/m^2 from the analysis.

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.

Outcomes. Incident cancer cases were identified through linkage to cancer registries (EPIC Netherlands, EPIC Denmark, Tromsø) or through self-reports that were confirmed by medical records and/or pathology reports (ESTHER, PRIME Belfast) or both (EPIC Spain, EPIC Greece). All analyses were conducted for cancer sites with convincing evidence of a positive association with greater body fatness (World Cancer Research Fund / American Institute for Cancer Research, 2007; Renehan *et al*, 2008; Lauby-Secretan *et al*, 2016). We examined first invasive breast cancer (ICD-O-3 C50) at postmenopausal ages, CRC (C18-21), and the combination of the two in conjunction with 'other obesity-related cancers' that included cancer of the lower oesophagus (C15.5, as a proxy for oesophageal adenocarcinoma in the absence of histological data), gastric cardia (C16.0), liver (C22), gallbladder (C23), pancreas (C25), endometrium (C54), ovary (C56) and kidney (C64), together labeled as 'obesity-

related cancers'. Advanced prostate cancer was not included because we lacked information on tumor stage. Also, thyroid, meningioma, and multiple myeloma (Lauby-Secretan *et al*, 2016) were not included due to very small numbers of incident cases and inconsistencies in the available data across cohorts. Small numbers precluded the possibility of performing separate analyses of each obesity-related cancer site.

Anthropometric assessment. In all cohorts except ESTHER, height and weight were measured by trained personnel at baseline. In the ESTHER cohort, height and weight were self-reported by the study participants.

Waist and hip circumference were measured by trained personnel in all cohorts except ESTHER, where these measures were not assessed; the narrowest torso circumference (natural waist) or midway between the lowest rib and iliac crest was used for the waist measurement, while the widest circumference or maximum circumference over the buttocks was used for the hip measurement. The majority of cohorts reported that participants were asked to remove any heavy outer garments (light clothing or underwear only allowed) for the anthropometric measurements. In ESTHER, data on WC or HC were not collected at baseline.

Covariate assessment. Age, sex, smoking status, physical activity, alcohol consumption, and HT use in women were collected in all cohorts following standardized procedures and *a posteriori* harmonized within the CHANCES project (Boffetta *et al*, 2014). All covariates except alcohol consumption (continuous, g/day) were modelled categorically: (daily) smoking status (never daily smoker; former daily smoker; current daily smoker; unknown), (vigorous) physical activity (yes; no; unknown) defined according to the CHANCES harmonization rules as 'performing intense exercise at least once a week', level of education attained (primary or less; more than primary but less than college or university; college or university; unknown), current use (or history) of HT in women (ever; never; unknown).

105 *Statistical analysis.* Cox proportional hazard models with age as the time metric were used to
106 estimate hazard ratios (HR) and 95% confidence intervals (CI) for the relation between four obesity
107 indicators and the risk of developing (1) 'obesity-related cancers', (2) CRC, (3) postmenopausal breast
108 cancer, and (4) 'other obesity-related cancers' in each of the included cohorts. All obesity indicators were
109 treated as continuous covariates; BMI was examined as a measure of overall adiposity, whereas WC, HC,
110 and WHR were examined as measures of body fat distribution. For comparability between the four
111 obesity indicators, we calculated the HR and their CI per 1-standard deviation (SD) increment of each
112 indicator (Keimling *et al*, 2013). The relationships between anthropometric measures were evaluated
113 using Pearson correlation coefficients (Supplementary **Table S1**).
114 Subjects were censored at age of study exit (death, lost to follow-up, any cancer diagnosis other
115 than cancers considered as outcomes in this study, and end of follow-up), whichever occurred first.
116 For all outcomes, three models with different sets of adjustments were fitted. Model 1 included
117 each of the anthropometric measures alternatively, stratified by age (1-y categories) and sex, and adjusted
118 for height (except the model for BMI). Model 2 (main model) extended Model 1 by further adjusting for
119 smoking status, alcohol consumption, level of educational attainment, physical activity, and recruitment
120 year. Missing values in any of the categorical covariates were included as a separate category. Model 3
121 was based as model 2, but with mutual adjustment for all anthropometric measures using residuals of
122 WC, HC, and WHR (Roswall *et al*, 2014).
123 All Cox models were fitted for each study separately (EPIC-Elderly was sub-divided into study-
124 centers/countries) giving a study-level risk per 1-SD increment and the results of models 2 and 3 were
125 then combined using DerSimonian and Laird random-effect meta-analysis (Harris *et al*, 2008). The
126 heterogeneity of associations across studies was expressed by I^2 (Higgins & Thompson, 2002).
127 The proportional hazard assumptions in the study-specific analysis were assessed by visual
128 inspection of log-log plots and by statistical tests using Schoenfeld residuals. Because the proportional
129 hazards were unlikely for sex and age, we stratified Cox models by sex and age (in 1-y categories).

Exclusion of individuals with missing data on smoking, education or physical activity gave virtually the same results.

To directly compare cancer risk discrimination between the four obesity indicators, we used respective predictions from Cox models (model 2, pooling all cohorts) to assess discrimination by Harrell's C-index (Collaboration TFS, 2009).

For analyses addressing the impact of effect modification, we pooled all cohorts into one dataset, and additionally stratified all Cox models by study. To investigate potential non-linear dose-response associations between the four obesity indicators and cancer risks, we used three-knot restricted cubic spline models at Harrell's default percentiles (i.e. 10^{th}, 50^{th}, and 90^{th}) in combination with a Wald-type test to evaluate the linearity hypothesis (Orsini & Greenland, 2011).

We tested *a priori* for potential interactions between the four adiposity indicators and for effect modification of the studied associations by smoking status and HT use using likelihood ratio tests. Since Cox-models were stratified by sex and age, no formal tests for interaction by sex or age were performed.

All statistical tests were two-sided and *P*-values were considered statistically significant at the 0.05 level. All statistical analyses were performed using Stata 12.1 (College Station, Texas, USA).

RESULTS

In total, 43,419 participants were included in this study, with 1,656 obesity-related cancer cases occurring during a median follow-up time of 12 years, which ranged between 10.4 years in Germany (ESTHER) and 18.0 years in Northern Ireland (PRIME Belfast) (**Table 1**). Study participants were recruited between 1991 and 2003, with a mean age at study entry ranging from 54 years in Northern Ireland to 67 years in Greece (EPIC-Greece). The prevalence of obesity (BMI>30 kg/m^2) at recruitment was lowest in Northern Ireland with 11% and highest in participants from Spain with 42%.

Meta-analysis of adiposity measures and risk of cancer. In the meta-analysis of all studies, BMI, WC, and WHR were significantly associated with an increased risk of 'obesity-related cancers'; the HRs

per 1-SD increment in BMI, WC, and WHR were 1.11 (95% CI: 1.02-1.21), 1.13 (95% CI: 1.04-1.23), and 1.15 (95% CI: 1.00-1.32), respectively. For BMI, the risk was most pronounced in the PRIME Belfast study (HR=1.50, 95% CI: 1.08-2.07) and a statistically non-significant inverse association was observed in the EPIC-Spain cohort (HR=0.88, 95% CI: 0.74-1.04) (**Figure 2**). After adjusting for HC and WC (Model 3 – Supplementary **Figure S1**), the HR for EPIC-Spain per 1-SD increase in BMI changed to 1.14 (95% CI: 0.82-1.60) and heterogeneity across studies for BMI decreased from 59% (P-$_{heterogeneity}$=0.02) to <1% (P-$_{heterogeneity}$=0.58). Omitting EPIC-Spain from the meta-analysis also reduced heterogeneity for BMI (to 25%, P-$_{heterogeneity}$=0.25) and for HC (61% to 7%, P-$_{heterogeneity}$=0.369). HC was positively associated with risk of 'obesity-related cancers' with a comparable effect size ($HR_{1\text{-}SD\ increase}$=1.09, 95% CI: 0.98-1.21) but did not reach formal statistical significance (Figure 2). Mutual adjustment for adiposity measures attenuated risk estimates for all measures of body fat distribution, i.e. WC, WHR, and HC. In contrast, the HR for BMI increased to 1.15 per 1-SD increment and remained statistically significant (95% CI: 1.09-1.22) (Model 3 – Figure S1).

For CRC, findings were more consistent across the four adiposity measures with little evidence for heterogeneity across studies (all I^2<36%, all P-$_{heterogeneity}$>0.17), although the risk estimates for EPIC-Spain followed a similar pattern as for 'obesity-related cancers' (**Figure 3**) including reduced heterogeneity after omitting EPIC-Spain (data not shown). Effect sizes for CRC were in general higher with strongest associations observed for WC ($HR_{1\text{-}SD\ increase}$=1.21, 95% CI: 1.08-1.35) and the weakest for HC ($HR_{1\text{-}SD\ increase}$=1.15, 95% CI: 1.01-1.32). After mutual adjustment for adiposity measures, only BMI remained a significant risk factor of CRC ($HR_{1\text{-}SD\ increase}$=1.19, 95% CI: 1.08-1.31) (Figure S1).

For postmenopausal breast cancer, a significant positive association was observed with BMI but only after additional adjustment for HC and WC (model 3) with a HR per 1-SD increase in BMI of 1.15 (95% CI: 1.03-1.27) (Figure S1). Associations with other measures of adiposity were non-significant although effect sizes were comparable, except for WHR (**Figure 4**). In addition, heterogeneity across studies was high for relative risks associated with WHR (I^2 = 66%, P-$_{heterogeneity}$=0.02) and did not change after excluding EPIC-Spain.

WHR was strongest and most consistently associated with 'other obesity-related cancers' (i.e. lower oesophagus, gastric cardia, liver, gallbladder, pancreas, endometrium, ovary, and kidney) with a HR per 1-SD increase of 1.20 (95% CI: 1.04-1.38) (**Figure 5**). All other obesity-measures were non-significant. After mutual adjustment for adiposity measures, WC was also independently associated with 'other obesity-related cancers' ($HR_{1\text{-}SD\ increase}$=1.15, 95% CI: 1.03-1.28) (Figure S1), while the association with WHR was marginally attenuated.

All estimates for the association between the four adiposity measures by cancer site and cohort, and the pooled estimates for the different models are presented in Supplementary **Table S2**.

Dose-response associations. After pooling all cohorts into one dataset, clear linear dose-response associations were found between all adiposity measures and 'obesity-related cancers', except for WHR ($P\text{-}_{non\text{-}linear}$=0.02), where an increased cancer risk became apparent only at values >0.96 of the WHR (Supplementary **Figure S2**). For CRC, linear dose-response associations were observed for all four adiposity measures (Figure S2). For postmenopausal breast and 'other obesity-related cancers', dose-response relationships were inconsistent across the four obesity measures and linearity largely statistically insignificant (Supplementary **Figure S3**). These findings were confirmed when analyzing BMI and WC in pre-defined categories (Supplementary **Table S6**)

Direct comparisons between anthropometric indicators. C-indices for WC, HC, and WHR were marginally and non-significantly lower than for BMI in predicting risk of 'obesity-related cancers', CRC, postmenopausal breast cancer (range of C-index differences to BMI: -0.01 to -0.02) and vice versa for 'other obesity-related cancers'(range of C-index differences to BMI: 0.02 to 0.03) (**Table 2**). Compared to a null model including all confounding variables but none of the four anthropometric indicators, adding BMI, WC, HC, and WHR separately or jointly resulted in virtually similar model fit as evaluated by AIC (Table 2).

Effect modification by sex, smoking, HT use, and weight status. After stratification by sex, the risks for 'obesity-related cancers' associated with BMI and WC were comparable between men and women (Supplementary **Table S3**). However, HC yielded higher risk estimates in women for 'obesity-related cancers' and CRC. On the other hand, WHR yielded higher risk estimates in men compared to women for 'obesity-related cancers', CRC, and 'other obesity-related cancers'. Some of these sex-specific differences became more pronounced or only apparent after mutual adjustment for adiposity measures (Model 3) (Table S3).

Some variability in risk estimates was observed across smoking categories (Supplementary **Table S4**). However, formal tests for effect modification were only significant for associations between HC and CRC (P-$_{interaction}$=0.02) with a significantly increased risk observed in never smokers ($HR_{1\text{-SD increase}}$=1.33, 95% CI: 1.16-1.54).

For postmenopausal breast cancer, significantly increased risks were observed in women who never used HT, with similar effect sizes of ~20% increased risk per 1-SD increase of BMI, WC, and HC (P-$_{interaction}$<0.001) (Model 2, Supplementary **Table S5**).

No significant interactions between measures of body fat distribution (i.e. WC, HC, and WHR) and World Health Organizations' BMI categories (normal weight: BMI <25 kg/m^2, overweight: BMI ≥25 to <30 kg/m^2, obesity: BMI ≥30 kg/m^2) in relation to 'obesity-related cancers' and CRC or postmenopausal breast cancer were observed (data not shown). A borderline significant interaction for associations between WC and CRC across categories of BMI was observed (P-$_{interaction}$=0.07) showing a significantly increased risk of CRC ($HR_{1\text{-SD increase}}$=1.52, 95% CI: 1.20-1.92) in the overweight category.

DISCUSSION

In this pooled analysis of seven prospective cohort studies, we observed increased risks of 'obesity-related cancers', overall and of CRC and postmenopausal breast cancer associated with equivalent increments of general adiposity (BMI) and measures of body fat distribution (WC, HC, and WHR). Relative risk estimates were comparable across the different adiposity indices. For

postmenopausal breast cancer, there was indication that increased risks were confined to women who never used HT. When mutually adjusting for all four anthropometric measures, which may be linked to different underlying biological mechanisms, BMI appeared to be an independent risk factor of 'obesity-related cancers', CRC, and postmenopausal breast cancer. In contrast, WC and WHR appeared to be independent risk factors of 'other obesity-related cancers', which we could not analyse separately due to low number of cases. To our knowledge, this is the first study of older adults to comprehensively compare anthropometric measures of general adiposity and body fat distribution, to examine and quantify the respective independent effects of these measures and to examine the shape of the dose–response relationship for cancers known to be obesity-related.

Our analysis does not corroborate the hypothesis that central adiposity is a superior predictor of CRC or postmenopausal breast cancer among older adults, as proposed by some previous studies (Pischon *et al*, 2006; Stolzenberg-Solomon *et al*, 2013; White *et al*, 2015). In contrast, and in line with our results, is an analysis of the NIH-AARP Diet and Health Study, where BMI, WC, and WHR were found to be equally discriminatory for colon cancer risk (Keimling *et al*, 2013). HC was not associated with risk of colon cancer in Keimling et al., while in our analysis HC virtually mirrored results for BMI, albeit effect sizes were slightly lower as compared to BMI. HC in disease models that do not account for BMI and/or WC is probably more indicative of general adiposity rather than an indicator of fat accumulation in the lower extremities reflected by a high correlation between HC and BMI (Pearson correlation ~0.8 in our data). Mutual adjustment of obesity indicators may reduce heterogeneity across studies as observed in our data. This could indicate that BMI does not capture general adiposity equally well in all White Caucasians and that holding WC and HC constant, improves the interpretation of BMI as a measure of general adiposity.

Furthermore, in the Cancer Prevention Study-II Nutrition Cohort, positive associations between WC and BMI and postmenopausal breast cancer risk were reported, but only the association with BMI remained significant after mutual adjustment (Gaudet *et al*, 2014).

For postmenopausal breast cancer, early results from the Iowa Women Health Study suggested a statistically significant multiplicative interaction between BMI and WHR (Folsom *et al*, 2000). However, in subsequent reports that specifically tested interactions between BMI and indicators of central adiposity in relation to risk of CRC (Keimling *et al*, 2013) and breast cancer (Gaudet *et al*, 2015), no statistically significant associations were found. Our findings are in line with these more recent reports in that we did not find statistically significant multiplicative interactions between BMI and any of the three measures of body fat distribution.

For most of the cancer sites that we grouped into 'other obesity-related cancers' due to the small number of cases, previous studies reported somewhat stronger associations with regard to measures of central adiposity as compared to BMI, which is in line with our findings. For example, in the meta-analysis of Aune et al. on pancreatic cancer, WHR yielded an overall RR of 1.19 (95% CI: 1.09-1.31), while that for BMI was 1.10 (95% CI: 1.07-1.14) (Aune *et al*, 2012). Slightly stronger associations for WC and WHR, as compared to BMI, were also reported in the most recent WCRF/AICR pooled analyses for advanced prostate cancer (World Cancer Research Fund / American Institute for Cancer Research., 2014). We were not able to include prostate cancer in our analysis because of lack of data by stage.

In an analysis using data from the large EPIC prospective cohort, we reported previously that abdominal obesity, rather than general obesity, is a risk factor for the development of oesophageal adenocarcinoma and gastric cardia cancer (Steffen *et al*, 2015). In the prospective NIH-AARP cohort both overall adiposity (BMI) and abdominal adiposity (WC, WHR) were associated with a higher risk of oesophageal adenocarcinoma, but only BMI was associated with a higher risk of gastric cardia adenocarcinoma (O'Doherty *et al*, 2012). In an updated WCRF/AICR meta-analysis, BMI was more strongly associated with an increased risk of endometrial cancer compared to WC or WHR, although WC was also associated with an increased risk (Aune *et al*, 2015b). Similarly, an increased risk of ovarian cancer was reported with greater BMI and a marginally significant positive association with WC, but no association was found for HC or WHR (Aune *et al*, 2015a). We are not aware of studies investigating the role of body fat distribution and risk of cancers of the liver and gallbladder. The evidence with regard to

BMI was judged convincing for both of these cancer sites by the most recent WCRF/AICR pooled analyses (World Cancer Research Fund / American Institute for Cancer Research., 2015a, 2015b). For these last two cancer sites, further assessment of the impact of body fat distribution in future studies is warranted.

Although WC and WHR (and HC as noted above) have been interpreted as measures of body fat distribution, they may well also be markers of general adiposity (Anderson *et al*, 2014). In the current study, we saw that these measures have associations with cancer that are similar to those for BMI, but mostly when used in separate models. However, few studies have conducted mutual adjustments between BMI and measures of body fat distribution to try to clarify their independent roles. This is a limitation, which needs further assessment in future studies because it may provide insight into the biologic mechanisms underlying observed associations between adiposity and cancer risk (Keimling *et al*, 2013). Ideally, for mutual adjustment of BMI and measures of body fat distribution, residuals of measures of WC and/or HC should be used in order to retain the interpretability of BMI as an indicator of general adiposity and to avoid potential problems of multi-collinearity. Otherwise, BMI is not easily interpretable or becomes an indicator of muscularity rather than adiposity (Hu, 2008). It is also of note that WC, HC, and WHR have larger measurement errors compared with measurement of BMI, which may affect the reliability of respective risk estimates and calls for additional caution when comparing results between these indicators.

Links between greater adiposity and increased risk of many cancers are biologically plausible considering that obesity is related to a vast array of metabolic and physiological dysfunctions (Park *et al*, 2014). A number of these altered processes have specifically been implicated in cancer development; notably (1) abnormalities of insulin resistance and the IGF-I system; described as the insulin-IGF-I-insulin pathway, which may promote tumor development at many anatomic sites (Park *et al*, 2014; Renehan *et al*, 2015); 2) the impact of adiposity on the biosynthesis and bioavailability of endogenous sex steroids (e.g., oestradiol) which applies predominantly, but not exclusively, to postmenopausal breast, endometrial and ovarian cancers (Park *et al*, 2014; Renehan *et al*, 2015); our findings that obesity-

associated risk of postmenopausal breast cancer was strongest in women, who never used HT support that hypothesis 3) obesity induced low-grade chronic systemic inflammation; and 4) alterations in the levels of adipocyte-derived factors, known as adipokines (Lee *et al*, 2015). All of these proposed pathways have been extensively investigated in mechanistic studies and tested in epidemiological settings. For example, adiponectin, one of the most abundant adipokines, has been shown to be a key mediator in the development of several types of obesity-related cancers including endometrial, breast, advanced prostate, CRC, renal, and pancreatic (Dalamaga *et al*, 2012). Unlike most of the other adipose tissue derived adipokines, serum adiponectin is reduced in obesity and correlates inversely with BMI, WC, HC, and WHR, independently of age and menopausal status (Dalamaga *et al*, 2012). Migrating adipose progenitor cells, which can be found in high concentration in white adipose tissue and may acquire a tumor-promoting function, and the gut microbiome are two emerging mechanistic hypotheses linking obesity with cancer risk (Renehan *et al*, 2015).

Our study has some limitations that may affect the interpretation of the results. Despite the pooling of seven cohorts, we were not able to compare adiposity measures across all anatomical cancer sites with strong evidence of an association with obesity because of low numbers of cases. These cancer sites were therefore combined in 'other obesity-related cancers'. For this reason, we could not investigate whether one or several of these cancers may have driven the observed associations with WC and WHR. Also related to the low number of cases, we were not able to sub-divide CRC in its anatomical sub-sites – knowing that effects sizes are more pronounced for cancers of the colon as compared to the rectum (World Cancer Research Fund / American Institute for Cancer Research., 2011) – or to sub-divide breast cancer by receptor status. However, associations with BMI appear to be unrelated to receptor status in postmenopausal women who have never used HT (Renehan *et al*, 2015).

Further limitations of our study are related to differences in study design between cohorts, including differences in length of follow-up and assessment of several covariates. In order to harmonize the data and variable definitions across cohorts, some covariates 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 factors and diet. As these were not consistently available from all cohorts, we were not able to take these into account in our analyses. However, we don't expect risk estimates being noticeably confounded by diet as has been shown previously (Renehan *et al*, 2012). In the ESTHER study, BMI based on self-reported height and weight was the only adiposity indicator available. Although self-reported BMI may grossly under-estimate prevalence of adiposity at the population level, ranking of individuals according to their BMI is less affected (Hu, 2008). Furthermore, study-specific risk estimates for ESTHER were consistent with the other cohorts and the summary estimates; excluding ESTHER from the meta-analysis had virtually no effect on the summary estimates (data not shown). Keeping ESTHER in our analysis also facilitates comparison of results with our companion paper, where we investigated the impact of overweight duration on obesity-related cancers (Arnold *et al*, 2016a). Finally, we did not *a priori* stratify our analysis by sex, mainly due to sample size considerations. However, in secondary analysis, largely similarly increased risks among men and women were observed for the investigated adiposity indicators (Table S3).

Strengths of our study include the availability of harmonized individual-level data for the estimation of cohort-specific risk estimates. This allowed us to use the same exposure definitions, disease endpoints, and multivariate models in all included studies. Our investigation included only prospective cohort studies, which reduces the potential of biases that are often reason for concern in retrospective studies, e.g. recall and selection bias. Individuals within each of our cohorts were largely White Caucasian, which adds further validity to our results because the effects of a given WC in a White population may be very different to the same WC in an Asian or African-American population. However, these potential ethic differences need to be evaluated in future studies. Further, we explored and compared, to our knowledge for the first time in a pooled analysis of cohorts consisting of middle-aged and older adults, non-linear associations between BMI, WC, HC, and WHR for cancer-sites known to be adiposity-related.

Conclusions

General adiposity as measured by BMI and body fat distribution as measured by WC, HC or WHR show comparable positive associations with obesity-related cancers combined, with CRC, and with postmenopausal breast cancer. For postmenopausal breast cancer there was evidence for effect modification by HT use which needs further exploration in other cohorts and populations. Avoiding abdominal fatness may also be important for specific cancer sites, but requires further investigation. Overall, our results underscore the importance of avoiding excess body fatness for cancer prevention irrespective of age and gender.

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Supplementary Material- British Journal of Cancer

Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe

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Text S1. Residual models.

Table S1. Correlation matrix of anthropometric measures in the CHANCES cohorts.

Table S2. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures for men and women, *by cohort and cancer site.*

Table S3. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, *by sex and cancer site.*

Table S4. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, *by smoking status and cancer site.*

Table S5. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident breast cancer (postmenopausal) per 1 standard deviation (SD) increment of anthropometric measures, *by hormone therapy (HT) use.*

Table S6. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per categories of Body mass index (BMI) and waist circumference (WC), *by sex*.

Figure S1. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) 'obesity-related cancers', (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) 'other obesity-related cancers' *after mutual adjustment for each obesity-indicator.*

Figure S2. Association of different obesity indicators with 'obesity-related cancers' and with colorectal cancer, *allowing for non-linear effects.*

Figure S3. Association of different obesity indicators with postmenopausal breast cancer and with 'other obesity-related cancers', *allowing for non-linear effects.*

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Text S1. Residual models.

Residuals of waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) were calculated with separate sex-specific linear regression models with body mass index (BMI) as the independent variable and WC, HC, and WHR as the dependent variables. These residuals are by definition independent of BMI and they facilitate model fitting and interpretation, where BMI and measures of central adiposity are included in the same model (Hu, 2008; Roswall et al, 2014). In such models, BMI retains its interpretation as a measure of overall adiposity, while the residuals of WC and WHR retain their interpretation as measures of central adiposity that are independent of overall adiposity. On the other hand, relative risk associated with higher HC adjusted for BMI, WC, or both can be interpreted as an indicator of the combination of the bone structure of the pelvis (which is mostly genetically determined), gluteofemoral muscle mass, and gluteofemoral fat accumulation (Hu, 2008).

Table S1. Correlation matrix of anthropometric measures in the CHANCES cohorts.

	BMI	WC	HC	WHR	Height	WC-residuals	HC-residuals	WHR-residuals
Men and Women								
BMI	1.00							
WC	0.75	1.00						
HC	0.82	0.61	1.00					
WHR	0.30	0.78	-0.02	1.00				
Height	-0.19	0.18	-0.15	0.34	1.00			
WC-residuals	0.00	0.48	0.13	0.49	0.20	1.00		
HC-residuals	0.00	0.12	0.51	-0.26	0.29	0.25	1.00	
WHR-residuals	0.00	0.37	-0.21	0.64	0.00	0.77	-0.40	1.00
Men								
BMI	1.00							
WC	0.85	1.00						
HC	0.76	0.79	1.00					
WHR	0.53	0.74	0.18	1.00				
Height	-0.16	0.00	0.09	-0.10	1.00			
WC-residuals	0.00	0.51	0.24	0.55	0.34	1.00		
HC-residuals	0.00	0.20	0.60	-0.33	0.42	0.40	1.00	
WHR-residuals	0.00	0.34	-0.24	0.82	0.01	0.68	-0.40	1.00
Women								
BMI	1.00							
WC	0.84	1.00						
HC	0.87	0.78	1.00					
WHR	0.41	0.75	0.17	1.00				
Height	-0.29	-0.21	-0.09	-0.23	1.00			
WC-residuals	0.00	0.53	0.08	0.74	0.21	1.00		
HC-residuals	0.00	0.09	0.48	-0.37	0.36	0.17	1.00	
WHR-residuals	0.00	0.44	-0.20	0.90	-0.01	0.82	-0.41	1.00

All values are Pearson correlation coefficients.

Residuals of WC, HC, and WHR were calculated with separate sex-specific linear regression models with BMI as the independent variable and WC, HC, and WHR as the dependent variables in each of the three models; all models were adjusted for cohort.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

Table S2. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures for men and women, *by cohort and cancer site*

	Obesity-related cancers[a]						Breast cancer						Colorectal cancer						Other obesity-related cancers[b]					
	Model 2			Model 3			Model 2			Model 3			Model 2			Model 3			Model 2			Model 3		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Body mass index																								
EPIC_DK	1.06	0.96	1.16	1.06	0.96	1.16	0.98	0.84	1.13	1.00	0.87	1.17	1.19	1.00	1.42	1.18	0.98	1.41	1.05	0.87	1.26	1.03	0.85	1.24
EPIC_GR	1.09	0.92	1.31	1.08	0.90	1.29	1.13	0.76	1.67	1.11	0.74	1.65	1.23	0.88	1.71	1.22	0.88	1.70	1.02	0.79	1.31	1.02	0.79	1.31
EPIC_NL	1.17	1.03	1.33	1.16	1.02	1.33	1.32	1.09	1.60	1.32	1.08	1.60	1.11	0.89	1.40	1.10	0.87	1.40	1.01	0.76	1.34	0.97	0.73	1.29
EPIC_SP	0.88	0.74	1.04	1.14	0.82	1.60	0.86	0.63	1.18	0.92	0.47	1.80	0.84	0.64	1.11	0.86	0.65	1.15	0.95	0.71	1.27	0.99	0.74	1.33
ESTHER[c]	1.20	1.09	1.33	1.2	1.09	1.33	1.16	0.99	1.36	1.16	0.99	1.36	1.17	0.97	1.43	1.18	0.97	1.43	1.28	1.08	1.53	1.28	1.08	1.53
PRIME Belfast[d]	1.50	1.08	2.07	1.51	1.09	2.10							1.60	1.10	2.33	1.67	1.14	2.44	1.12	0.58	2.17	1.14	0.59	2.23
TROMSO	1.13	0.98	1.30	1.14	0.97	1.33	1.23	0.97	1.57	1.31	0.98	1.76	1.23	1.00	1.52	1.19	0.95	1.49	0.85	0.64	1.14	0.92	0.67	1.25
Waist circumference																								
EPIC_DK	1.06	0.95	1.17	1.00	0.90	1.11	0.94	0.80	1.10	0.91	0.77	1.06	1.19	0.98	1.45	1.04	0.86	1.27	1.12	0.92	1.36	1.14	0.94	1.39
EPIC_GR	1.09	0.89	1.33	1.00	0.85	1.17	0.97	0.61	1.55	0.84	0.60	1.17	1.20	0.83	1.74	0.97	0.72	1.31	1.10	0.83	1.46	1.11	0.88	1.39
EPIC_NL	1.17	1.00	1.36	0.99	0.86	1.15	1.26	1.00	1.58	0.91	0.73	1.14	1.18	0.90	1.54	1.09	0.84	1.42	1.04	0.76	1.42	1.05	0.77	1.42
EPIC_SP	1.01	0.83	1.22	1.24	1.07	1.45	1.05	0.72	1.51	1.30	0.97	1.76	0.94	0.69	1.28	1.21	0.94	1.55	1.09	0.79	1.51	1.26	0.97	1.64
ESTHER[c]																								
PRIME Belfast[d]	1.45	1.03	2.04	1.06	0.73	1.54							1.52	1.02	2.26	0.94	0.61	1.45	1.26	0.64	2.50	1.45	0.72	2.94
TROMSO	1.28	1.08	1.51	1.23	1.04	1.46	1.51	1.09	2.10	1.28	0.93	1.76	1.35	1.06	1.72	1.26	0.98	1.61	1.01	0.72	1.41	1.15	0.84	1.59
Hip circumference																								
EPIC_DK	1.05	0.95	1.16	1.00	0.90	1.11	1.02	0.88	1.18	1.05	0.89	1.24	1.16	0.96	1.40	0.98	0.80	1.20	0.99	0.81	1.21	0.91	0.74	1.11
EPIC_GR	1.22	1.02	1.46	1.24	1.04	1.48	1.23	0.84	1.81	1.25	0.84	1.85	1.40	1.00	1.95	1.29	0.93	1.79	1.15	0.89	1.49	1.22	0.94	1.58
EPIC_NL	1.17	1.03	1.33	1.06	0.91	1.24	1.29	1.07	1.56	1.05	0.83	1.32	1.12	0.90	1.40	1.07	0.82	1.41	1.02	0.78	1.35	1.07	0.77	1.48
EPIC_SP	0.86	0.73	1.02	0.87	0.74	1.03	0.92	0.68	1.23	0.96	0.70	1.33	0.85	0.65	1.12	0.90	0.69	1.17	0.86	0.65	1.13	0.77	0.58	1.02
ESTHER[c]																								
PRIME Belfast[d]	1.36	0.95	1.95	0.90	0.62	1.29							1.51	1.00	2.27	0.96	0.62	1.46	1.00	0.48	2.11	0.73	0.37	1.44
TROMSO	1.12	0.95	1.32	0.91	0.78	1.07	1.26	0.92	1.73	0.87	0.64	1.18	1.20	0.93	1.54	0.92	0.73	1.17	0.91	0.66	1.26	0.94	0.69	1.28
Waist-to-hip ratio																								
EPIC_DK	1.04	0.92	1.18	1.00	0.92	1.10	0.87	0.72	1.05	0.90	0.79	1.03	1.16	0.92	1.46	1.04	0.88	1.23	1.24	0.99	1.56	1.16	0.98	1.37
EPIC_GR	0.91	0.72	1.15	0.93	0.80	1.09	0.72	0.42	1.25	0.79	0.55	1.13	0.91	0.59	1.40	0.89	0.66	1.20	1.01	0.73	1.39	1.02	0.82	1.27
EPIC_NL	1.05	0.86	1.27	0.96	0.84	1.10	1.04	0.77	1.39	0.91	0.74	1.12	1.12	0.80	1.58	1.02	0.80	1.30	1.03	0.70	1.54	1.00	0.76	1.33
EPIC_SP	1.33	1.05	1.68	1.25	1.07	1.45	1.33	0.83	2.12	1.23	0.91	1.67	1.2	0.82	1.75	1.21	0.96	1.54	1.52	1.02	2.25	1.31	1.01	1.7
ESTHER[c]																								
PRIME Belfast[d]	1.52	0.97	2.38	1.12	0.79	1.58							1.44	0.85	2.44	0.99	0.66	1.49	1.74	0.73	4.15	1.52	0.81	2.85
TROMSO	1.36	1.14	1.61	1.20	1.06	1.36	1.47	1.10	1.97	1.24	1.00	1.53	1.40	1.08	1.82	1.21	1.00	1.47	1.17	0.81	1.68	1.15	0.91	1.46
All cohorts pooled																								
BMI	1.11	1.06	1.17	1.12	1.02	1.24	1.11	1.01	1.21	1.10	0.99	1.23	1.16	1.07	1.27	1.16	1.05	1.28	1.06	0.97	1.16	0.99	0.89	1.11
WC	1.12	1.04	1.19	1.06	1.00	1.13	1.07	0.96	1.19	0.96	0.86	1.08	1.20	1.08	1.34	1.09	0.98	1.21	1.08	0.96	1.22	1.14	1.02	1.27
HC	1.08	1.01	1.14	1.01	0.94	1.07	1.11	1.00	1.24	1.05	0.94	1.18	1.14	1.03	1.27	0.99	0.89	1.10	0.98	0.88	1.10	0.96	0.85	1.07
WHR	1.11	1.03	1.20	1.05	0.99	1.11	0.98	0.89	1.09	0.95	0.85	1.05	1.19	1.04	1.36	1.08	0.98	1.18	1.18	1.03	1.36	1.13	1.03	1.25

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum; [c] No data available on WC, HC, and WHR; [d] No breast cancer cases because men only.

Model 2: stratified for age (1-y categories), and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; in the pooled analysis, models were additionally stratified by cohort.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

Note: Results of Model 1 are not shown due to space limitations, but results were similar to Model 2.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

Table S3. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1-standard deviation (SD) increment of anthropometric measures, *by sex and cancer site*

	Model 1				Model 2				Model 3			
	Cases	HR	95% CI		Cases	HR	95% CI		Cases	HR	95% CI	
MEN												
Body mass index (1 SD=3.6 kg/m^2)												
Obesity-related cancers[a]	524	1.13	1.04	1.24	524	1.14	1.05	1.25	389	1.17	1.00	1.38
Colorectal cancer	318	1.13	1.01	1.26	318	1.16	1.01	1.33	243	1.15	0.98	1.34
Other obesity-related cancers[b]	206	1.14	0.99	1.31	206	1.15	1.01	1.33	146	1.10	0.85	1.43
Waist circumference (1 SD=10.1 cm)												
Obesity-related cancers[a]	389	1.15	1.03	1.28	389	1.15	1.03	1.28	389	1.14	1.01	1.27
Colorectal cancer	243	1.13	0.98	1.29	243	1.15	0.98	1.36	243	1.06	0.90	1.25
Other obesity-related cancers[b]	146	1.20	1.01	1.42	146	1.19	1.00	1.42	146	1.31	1.09	1.56
Hip circumference (1 SD=7.2 cm)												
Obesity-related cancers[a]	389	1.02	0.91	1.14	389	1.04	0.93	1.17	389	0.90	0.80	1.02
Colorectal cancer	243	1.04	0.90	1.20	243	1.07	0.89	1.28	243	0.91	0.78	1.06
Other obesity-related cancers[b]	146	1.01	0.84	1.21	146	1.03	0.85	1.24	146	0.90	0.74	1.09
Waist-to-hip ratio (1 SD=0.06)												
Obesity-related cancers[a]	389	1.20	1.09	1.33	389	1.19	1.07	1.31	389	1.15	1.04	1.27
Colorectal cancer	243	1.18	1.03	1.35	243	1.21	0.99	1.47	243	1.09	0.94	1.27
Other obesity-related cancers[b]	146	1.28	1.10	1.50	146	1.26	1.07	1.48	146	1.25	1.08	1.45
WOMEN												
Body mass index (1 SD=4.6 kg/m^2)												
Obesity-related cancers[a]	1132	1.08	1.01	1.15	1132	1.10	1.03	1.17	867	1.07	1.00	1.16
Colorectal cancer	273	1.17	1.03	1.32	273	1.17	1.04	1.32	222	1.15	1.00	1.31
Breast cancer	555	1.09	0.99	1.19	555	1.12	1.02	1.22	409	1.10	0.99	1.23
Other obesity-related cancers[b]	304	0.99	0.87	1.12	304	1.00	0.88	1.13	236	1.16	0.89	1.50
Waist circumference (1 SD=11.6 cm)												
Obesity-related cancers[a]	867	1.08	1.01	1.16	867	1.09	1.01	1.17	867	1.04	0.96	1.12
Colorectal cancer	222	1.23	1.07	1.42	222	1.24	1.07	1.44	222	1.13	0.98	1.29
Breast cancer	409	1.05	0.95	1.17	409	1.07	0.96	1.19	409	0.96	0.86	1.08
Other obesity-related cancers[b]	236	1.01	0.87	1.16	236	1.00	0.87	1.16	236	1.07	0.93	1.23
Hip circumference (1 SD=9.3 cm)												
Obesity-related cancers[a]	867	1.08	1.00	1.16	867	1.09	1.01	1.17	867	1.04	0.96	1.13
Colorectal cancer	222	1.20	1.04	1.38	222	1.18	1.04	1.34	222	1.08	0.93	1.25
Breast cancer	409	1.09	0.99	1.21	409	1.11	1.00	1.24	409	1.05	0.94	1.18
Other obesity-related cancers[b]	236	0.95	0.82	1.09	236	0.96	0.83	1.10	236	0.98	0.84	1.13
Waist-to-hip ratio (1 SD=0.07)												
Obesity-related cancers[a]	867	1.04	0.97	1.12	867	1.04	0.97	1.12	867	1.01	0.94	1.09
Colorectal cancer	222	1.16	1.00	1.35	222	1.17	0.98	1.40	222	1.06	0.94	1.20
Breast cancer	409	0.98	0.89	1.09	409	0.98	0.9	1.1	409	0.95	0.85	1.05
Other obesity-related cancers[b]	236	1.08	0.94	1.23	236	1.06	0.9	1.2	236	1.07	0.94	1.22

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 1: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for height.

Model 2: as model 1 and further adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), and recruitment year.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the model for WHR was further adjusted for BMI using WHR-residuals.

Notes: no formal test for interaction by sex was performed because Cox models were stratified by sex to meet the proportionality of hazards assumption; SDs for anthropometric measure shown within brackets are the pooled average across all 7 cohorts by sex.

Table S4. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, *by smoking status and cancer site*

	Obesity-related cancers[a]				Breast cancer				Colorectal cancer				Other obesity-related cancers[b]			
	Model 2		Model 3		Model 2		Model 3		Model 2		Model 3		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Body mass index (1 SD=4.2 kg/m^2)																
Current daily smoker	1.09	0.98 - 1.21	1.06	0.94 - 1.19	1.26	1.03 - 1.55	1.28	1.00 - 1.63	1.11	0.93 - 1.32	1.03	0.85 - 1.25	0.92	0.75 - 1.13	0.93	0.76 - 1.14
Former daily smoker	1.10	1.00 - 1.20	1.08	0.97 - 1.21	1.02	0.85 - 1.22	1.05	0.85 - 1.28	1.17	1.01 - 1.35	1.16	0.97 - 1.38	1.13	0.94 - 1.37	1.08	0.87 - 1.33
Never daily smoker	1.12	1.04 - 1.20	1.08	1.00 - 1.18	1.11	0.99 - 1.25	1.08	0.93 - 1.25	1.20	1.05 - 1.37	1.23	1.06 - 1.43	1.10	0.95 - 1.28	0.98	0.84 - 1.16
Waist circumference (1 SD=12.1 cm)																
Current daily smoker	1.14	1.02 - 1.28	1.07	0.95 - 1.20	1.13	0.89 - 1.44	0.88	0.68 - 1.13	1.19	0.99 - 1.43	1.19	0.97 - 1.44	1.05	0.86 - 1.27	1.12	0.91 - 1.37
Former daily smoker	1.09	0.98 - 1.22	1.00	0.89 - 1.11	0.97	0.79 - 1.19	0.87	0.72 - 1.07	1.14	0.96 - 1.35	0.94	0.79 - 1.12	1.23	1.01 - 1.50	1.25	1.03 - 1.53
Never daily smoker	1.11	1.02 - 1.22	1.10	1.01 - 1.19	1.10	0.95 - 1.27	1.05	0.90 - 1.21	1.27	1.08 - 1.49	1.16	1.00 - 1.35	1.02	0.86 - 1.21	1.10	0.94 - 1.28
Hip circumference (1 SD= 8.6 cm)																
Current daily smoker	0.99	0.87 - 1.12	0.93	0.83 - 1.04	1.26	0.99 - 1.60	1.07	0.84 - 1.36	0.91	0.74 - 1.12	0.88	0.73 - 1.05	0.89	0.72 - 1.10	0.89	0.73 - 1.08
Former daily smoker	1.04	0.93 - 1.16	0.95	0.86 - 1.06	1.02	0.84 - 1.24	0.97	0.80 - 1.17	1.08	0.90 - 1.29	0.92	0.78 - 1.09	1.03	0.84 1.28	0.95	0.78 - 1.16
Never daily smoker	1.14	1.05 - 1.24	1.09	0.99 - 1.19	1.12	0.97 - 1.29	1.10	0.95 - 1.27	1.33	1.16 - 1.54	1.14	0.97 - 1.33	1.00	0.85 - 1.17	1.00	0.85. - 1.18
Waist-to-hip ratio (1 SD=0.1)																
Current daily smoker	1.22	1.08 - 1.37	1.09	0.99 - 1.21	0.96	0.76 - 1.21	0.87	0.68 - 1.10	1.36	1.13 - 1.64	1.22	1.04 - 1.42	1.19	0.98 - 1.46	1.14	0.96 - 1.35
Former daily smoker	1.11	0.99 - 1.25	1.03	0.93 - 1.14	0.94	0.77 - 1.13	0.91	0.76 - 1.10	1.15	0.95 - 1.38	0.98	0.83 - 1.17	1.36	1.10 - 1.68	1.25	1.04 - 1.50
Never daily smoker	1.04	0.94 - 1.16	1.04	0.96 - 1.13	1.03	0.89 - 1.19	1.00	0.87 - 1.16	1.08	0.89 - 1.29	1.05	0.90 - 1.22	1.08	0.89 - 1.32	1.07	0.92 - 1.25

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 2: stratified for age (1-y categories), sex, and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

All P-values for interaction (LR test) >0.10, except for HC vs. CRC in model 2 (P=0.02).

Note: SDs for anthropometric measure shown within brackets are the pooled average across all 7 cohorts and men and women combined.

Table S5. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident breast cancer (postmenopausal) per 1 standard deviation (SD) increment of anthropometric measures, *by hormone therapy (HT) use*

		Breast cancer (postmenopausal)			
		Model 2		Model 3	
	Cases	HR	95% CI	HR	95% CI
Body mass index (1 SD=4.6 kg/m^2)					
never HT user	263	1.22	1.08 - 1.38	1.28	1.11 - 1.47
ever HT user	245	0.99	0.86 - 1.14	0.91	0.76 - 1.10
unknown	47	1.26	0.95 - 1.67	1.02	0.73 - 1.43
Waist circumference (1 SD=11.6 cm)					
never HT user	205	1.21	1.05 - 1.40	0.95	0.81 - 1.11
ever HT user	167	0.93	0.78 - 1.11	0.99	0.83 - 1.18
unknown	37	1.00	0.71 - 1.41	1.01	0.75 - 1.35
Hip circumference (1 SD=9.3 cm)					
never HT user	205	1.24	1.08 - 1.42	1.00	0.86 - 1.16
ever HT user	167	0.96	0.80 - 1.14	1.08	0.91 - 1.28
unknown	37	1.13	0.82 - 1.55	1.25	0.92 - 1.68
Waist-to-hip ratio (1 SD=0.07)					
never HT user	205	1.06	0.91 - 1.23	0.96	0.83 - 1.12
ever HT user	167	0.94	0.80 - 1.11	0.95	0.81 - 1.11
unknown	37	0.89	0.64 - 1.24	0.91	0.67 - 1.24

Model 2: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.
Model 3: as model 2, but models for BMI, WC, and HC mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.
All P-values for interaction (LR test) <0.001.
Note: SDs for anthropometric measure shown within brackets are the pooled average across all cohorts in women.

Table S6. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per categories of Body mass index (BMI) and waist circumference (WC), *by sex*

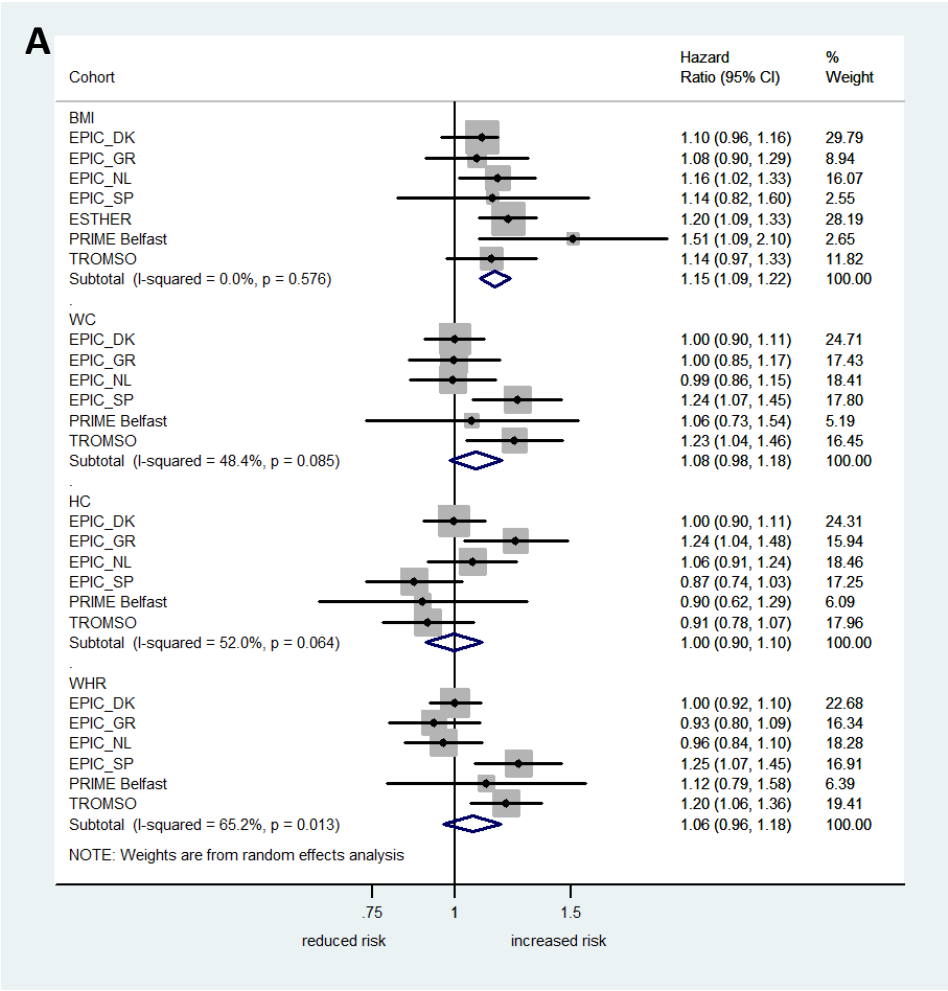
		Obesity-related cancers[a]				Breast cancer				Colorectal cancer				Other obesity-related cancers[b]			
	n	Cases	HR	95 % CI	p-trend	Cases	HR	95 % CI	p-trend	Cases	HR	95 % CI	p-trend	Cases	HR	95 % CI	p-trend
MEN																	
BMI categories																	
<25 kg/m^2	5,192	127	1 (ref.)							81	1 (ref.)			46	1 (ref.)		
25-29.9 kg/m^2	9,733	285	1.25	1.01 - 1.55						173	1.23	0.94 - 1.62		112	1.29	0.91 - 1.83	
>30 kg/m^2	3,743	112	1.36	1.04 - 1.78	0.023					64	1.33	0.94 - 1.88	0.113	48	1.44	0.94 - 2.19	0.095
WC categories																	
<102 cm	9,677	254	1 (ref.)							170	1 (ref.)			84	1 (ref.)		
>102 cm	4,348	135	1.25	1.00 - 1.57						73	1.07	0.80 - 1.44		62	1.60	1.13 - 2.28	
WOMEN																	
BMI categories																	
<25 kg/m^2	8,422	418	1 (ref.)			207	1 (ref.)			95	1 (ref.)			116	1 (ref.)		
25-29.9 kg/m^2	9,888	442	1.02	0.89 - 1.17		224	1.11	0.92 - 1.35		102	1.02	0.77 - 1.36		116	0.86	0.66 - 1.13	
>30 kg/m^2	6,441	272	1.17	1.00 - 1.39	0.057	124	1.22	0.96 - 1.55	0.098	76	1.44	1.04 - 2.00	0.029	72	0.90	0.65 - 1.24	0.517
WC categories																	
<88 cm	10,482	502	1 (ref.)			249	1 (ref.)			119	1 (ref.)			134	1 (ref.)		
>88 cm	8,566	365	1.14	0.99 - 1.32		160	1.13	0.91 - 1.39		103	1.33	1.00 - 1.76		102	1.01	0.77 - 1.34	

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 2: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Notes: BMI categories according to World Health Organization; category <25 kg/m^2 includes 47 men and 169 women with a BMI <18.5 kg/m^2, respectively; WC categories according to American Heart Association/National Heart, Lung and Blood Institute.



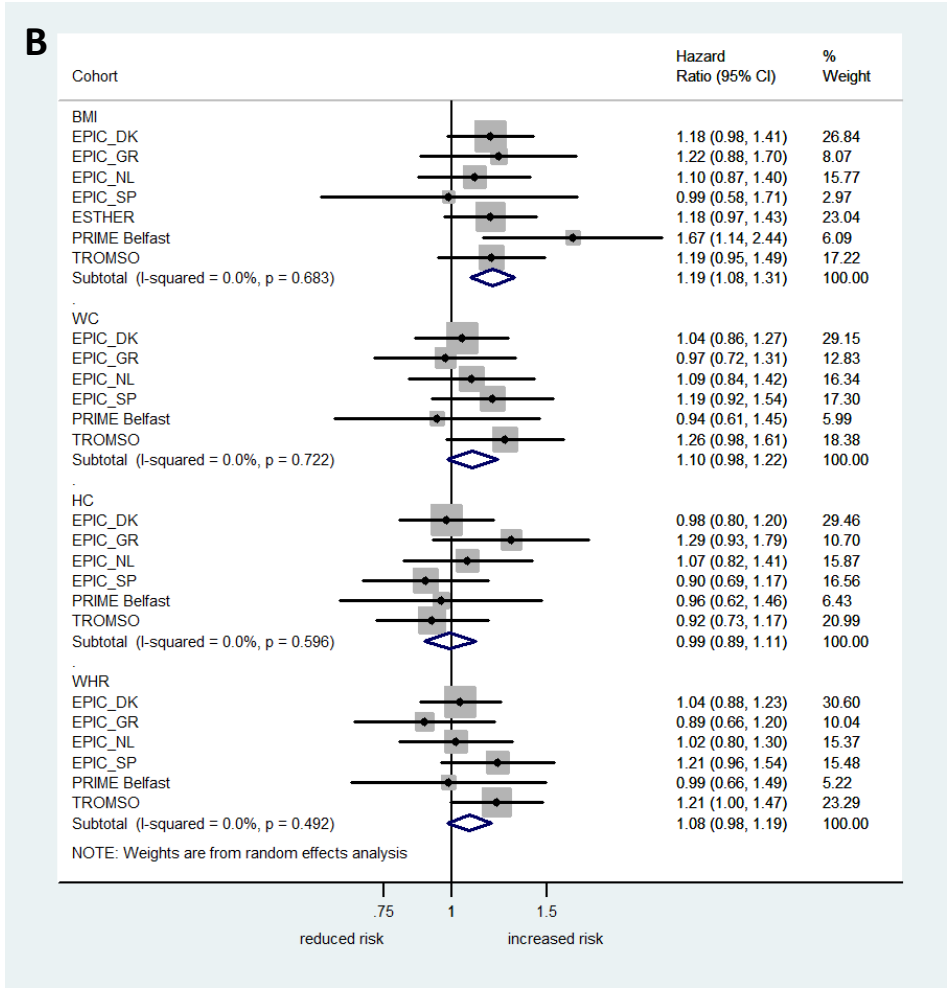


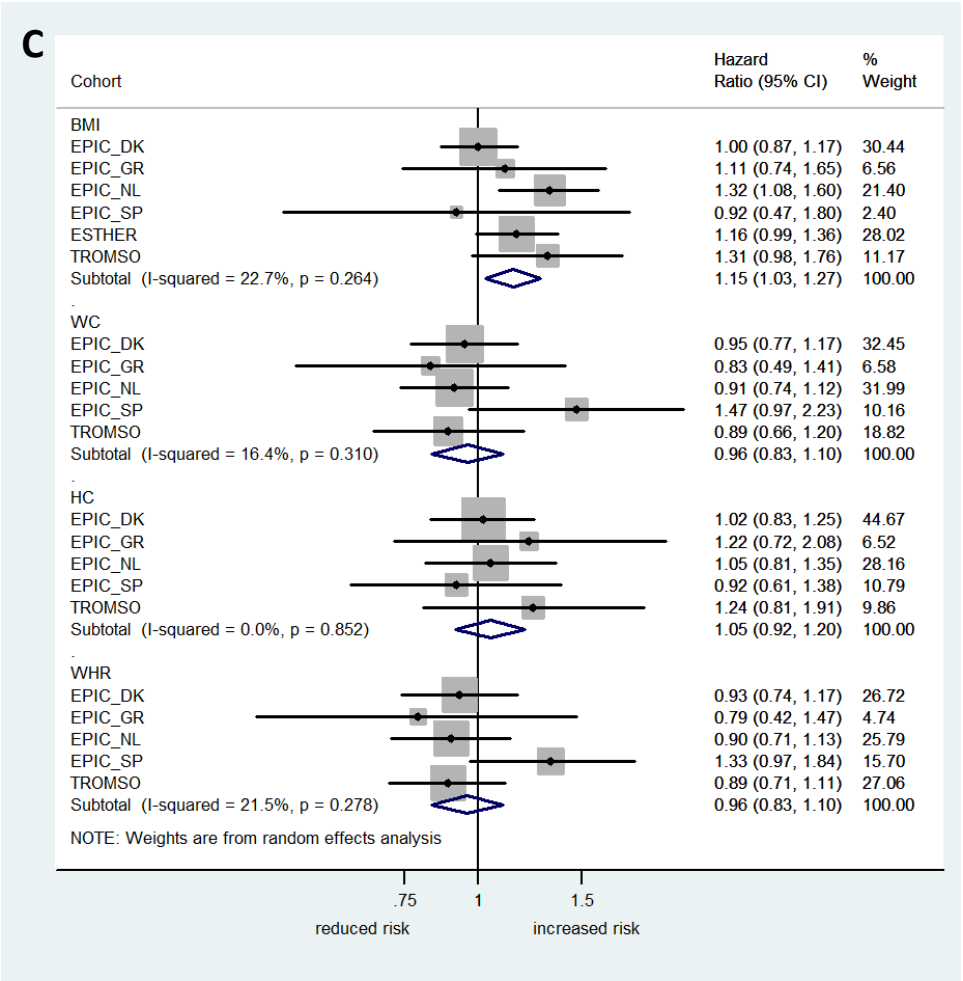
Figure S1. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) 'obesity-related cancers'[a], (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) 'other obesity-related cancers'[b] *after mutual adjustment for each obesity-indicator.*

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 3: stratified for age (1-y categories) and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; and models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; and the models for WHR were further adjusted for BMI using WHR-residuals.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.



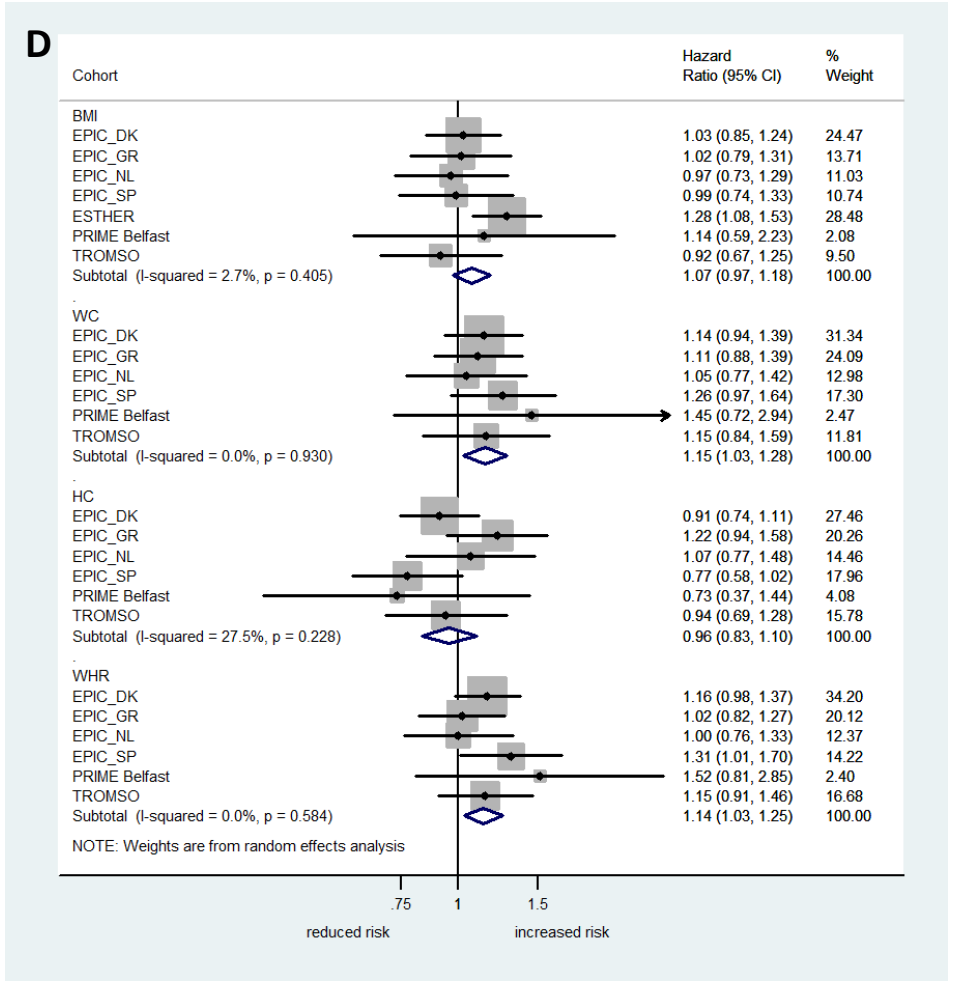


Figure S1 continued. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) 'obesity-related cancers'[a], (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) 'other obesity-related cancers'[b] *after mutual adjustment for each obesity-indicator.*

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 3: stratified for age (1-y categories) and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; and models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; and the models for WHR were further adjusted for BMI using WHR-residuals.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

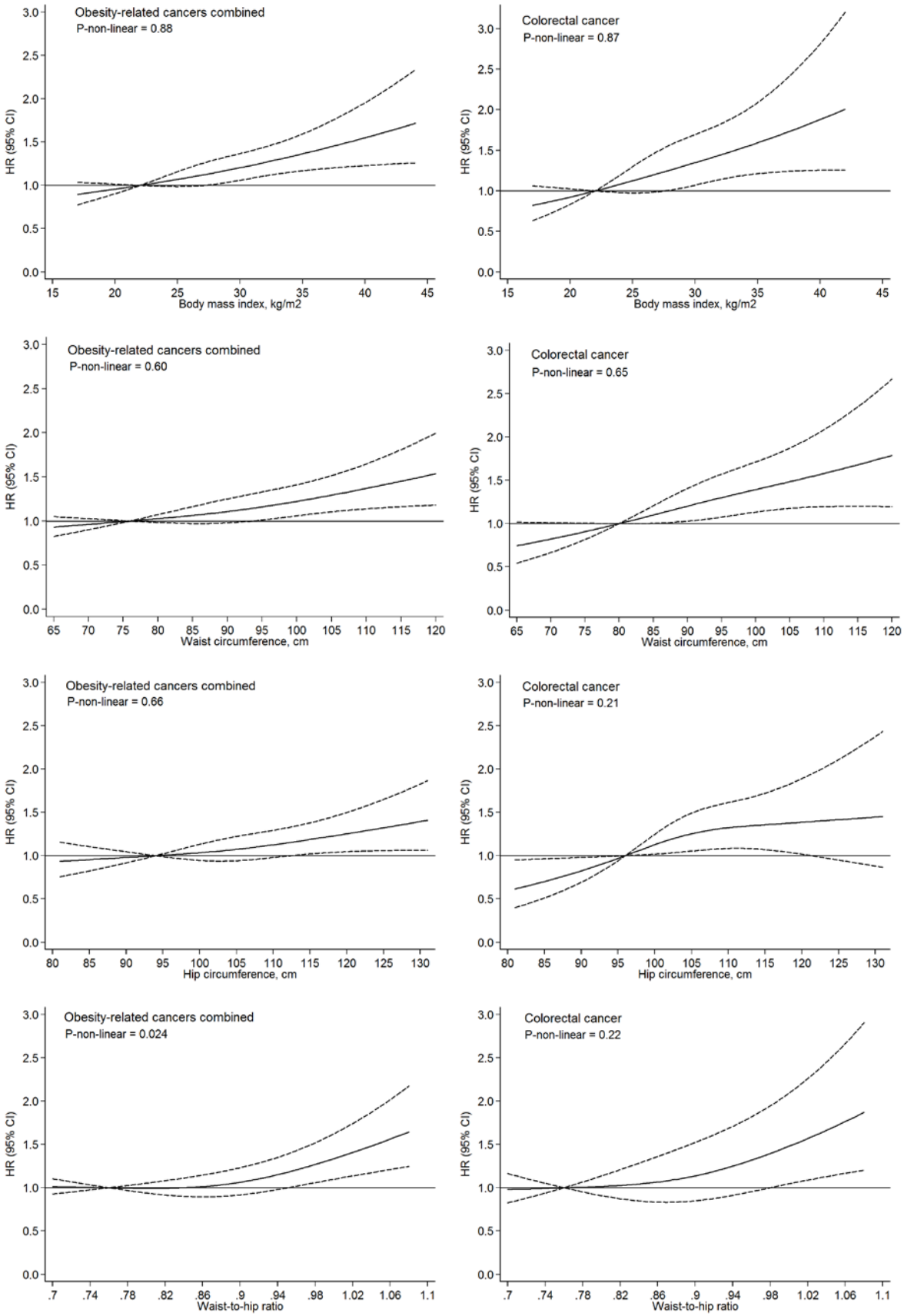


Figure S2. Association of different obesity indicators with 'obesity-related cancers'[a] and with colorectal cancer, allowing for non-linear effects.

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

The figures show a 3-knot restricted cubic spline model at Harrell's default percentiles (i.e. 10th [reference point], 50th, and 90th) allowing for non-linear effects and are stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height. *P*-values are from Wald-test evaluating the linearity hypothesis.

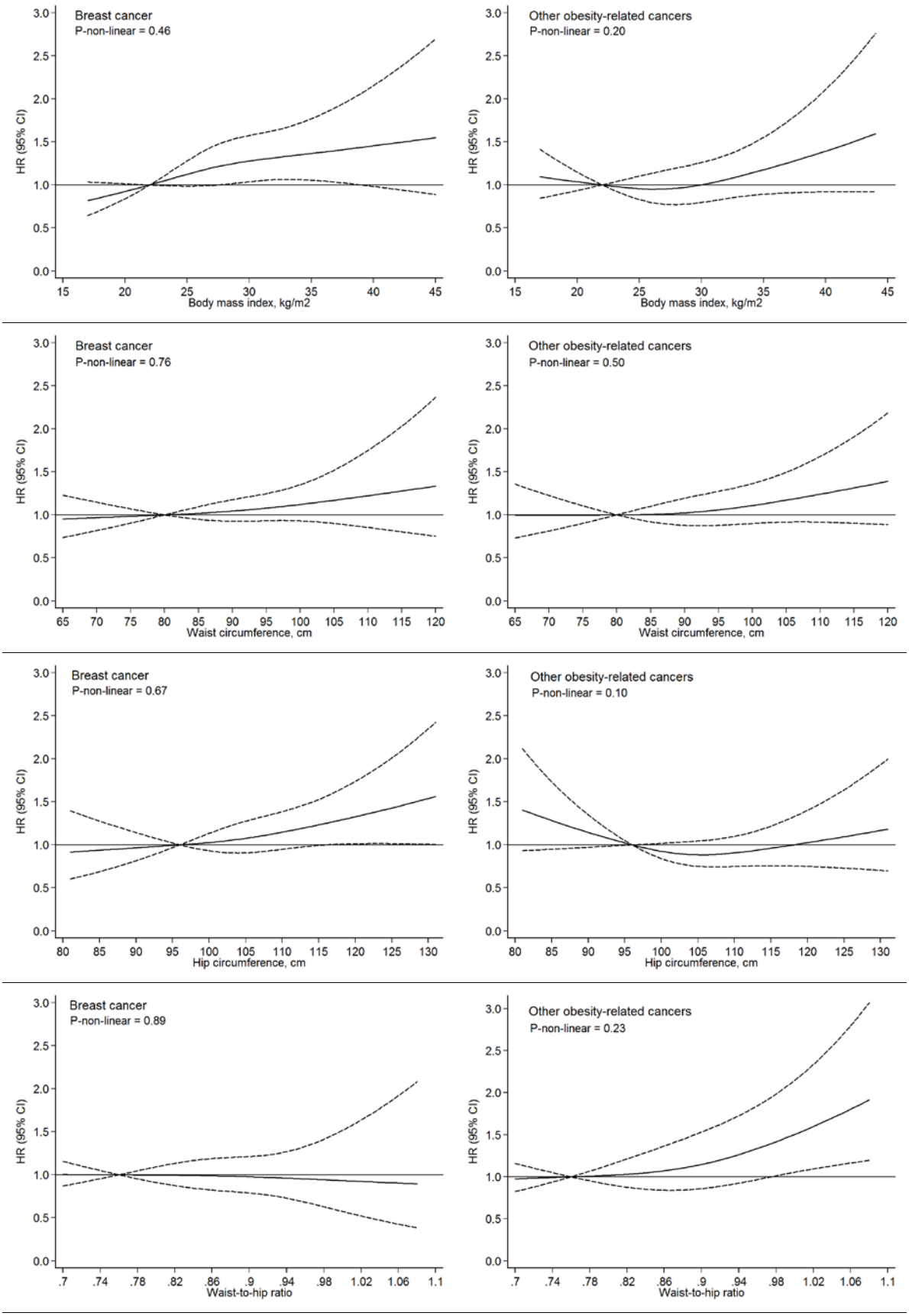
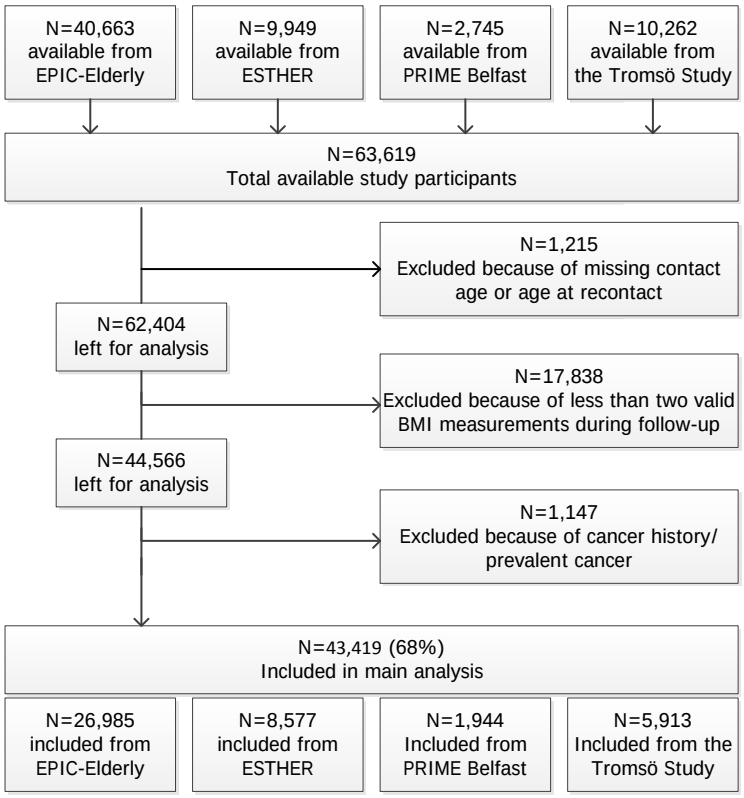
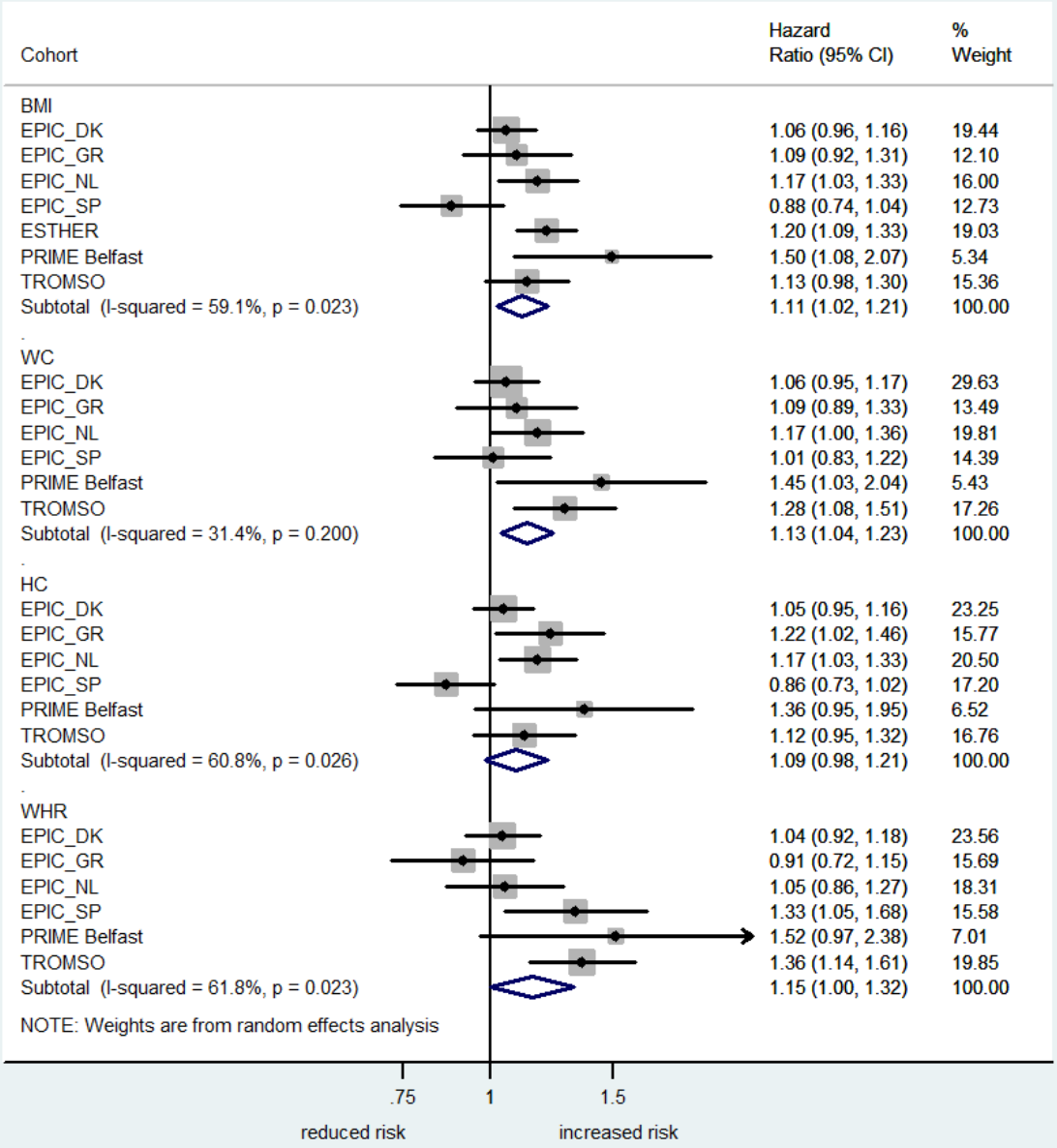


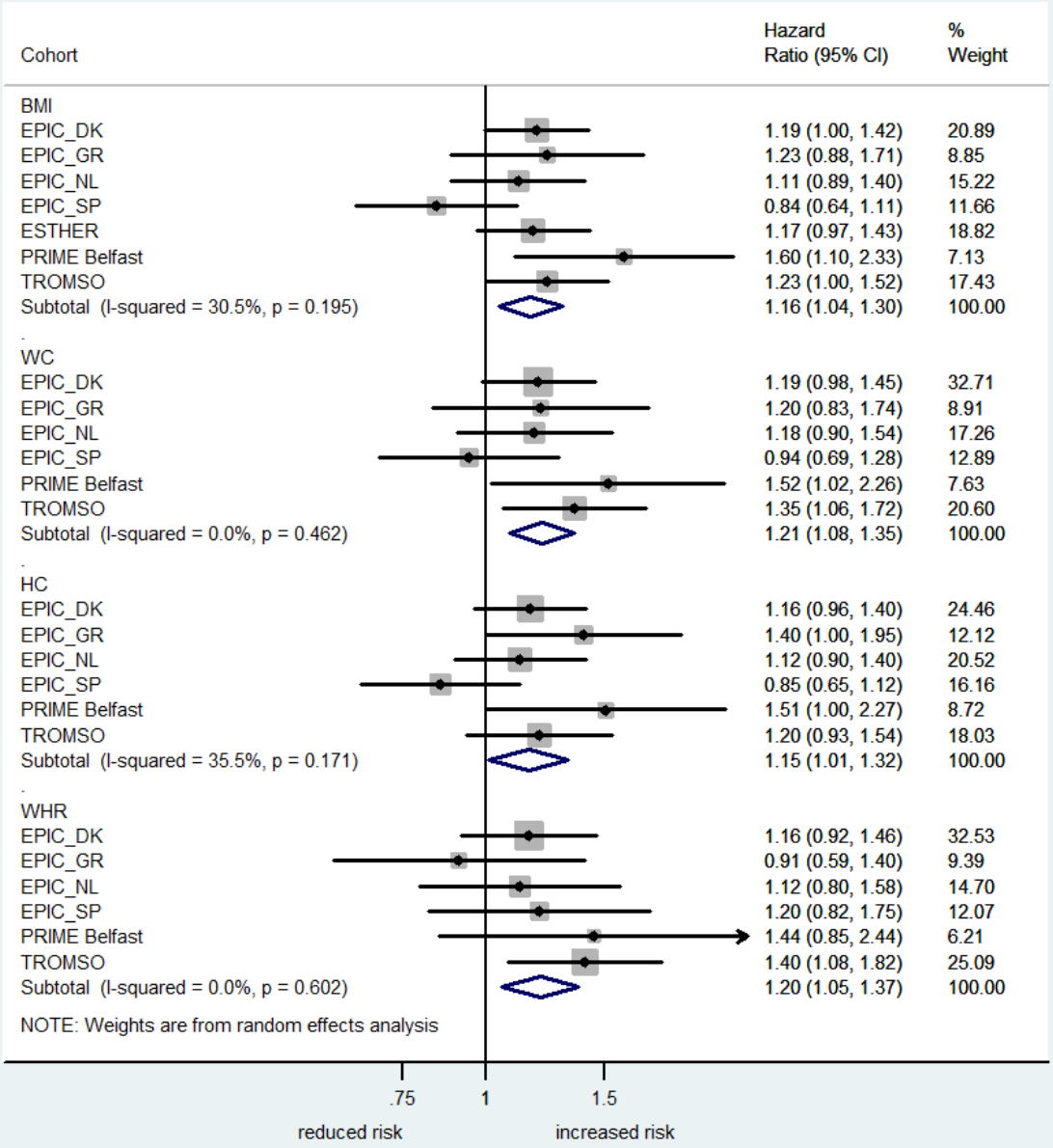
Figure S3. Association of different obesity indicators with postmenopausal breast cancer and with 'other obesity-related cancers'[a], allowing for non-linear effects.

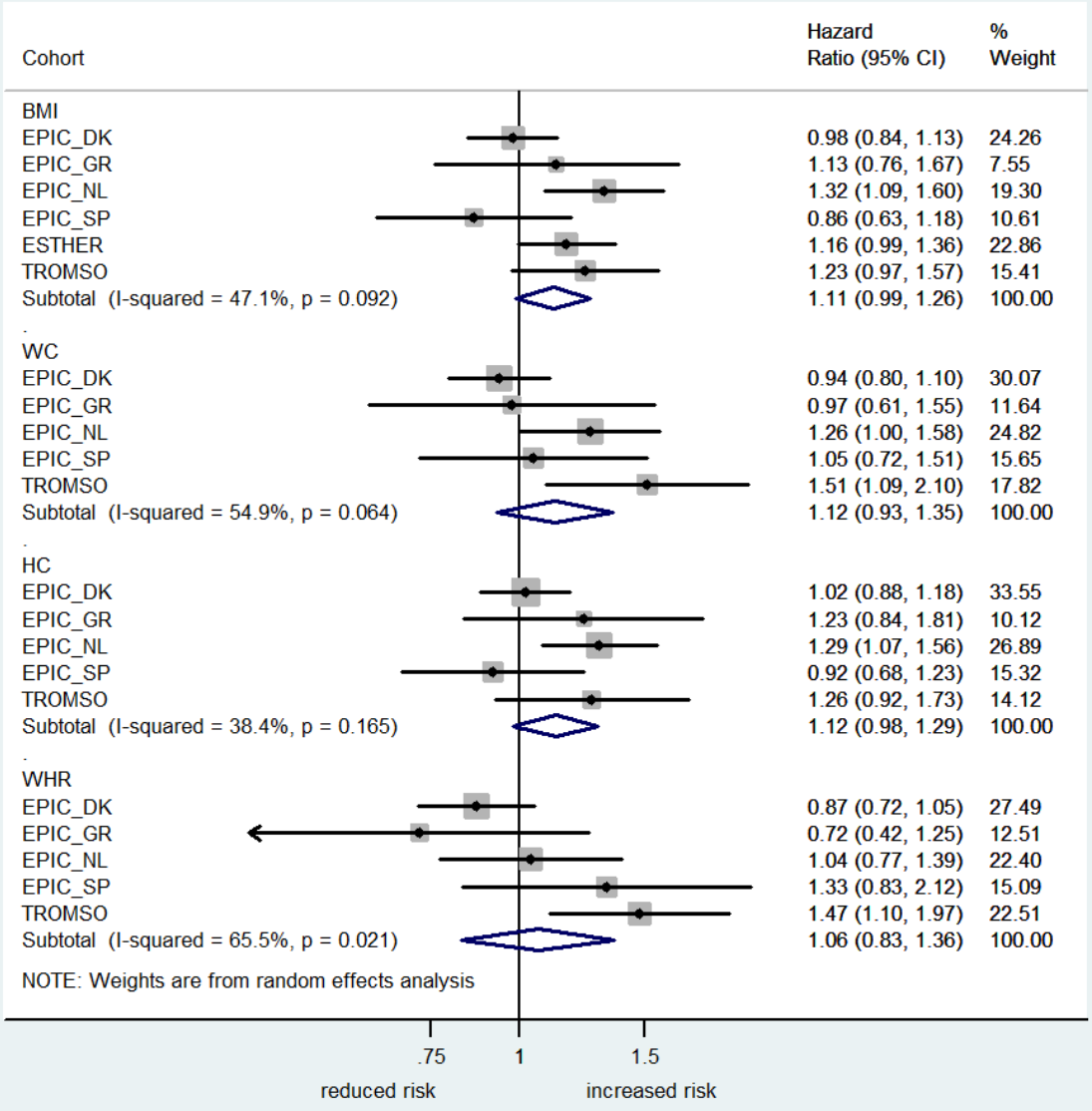
[a] First primary cancers of the lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

The figures show a 3-knot restricted cubic spline model at Harrell's default percentiles (i.e. 10th [reference point], 50th, and 90th) allowing for non-linear effects and are stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height. *P*-values are from Wald-test evaluating the linearity hypothesis.


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
the Tromsö Study
N=63,619
Total available study participants
N=1,215
Excluded because of missing contact
age or age at recontact
N=62,404
left for analysis
N=17,838
Excluded because of less than two valid
BMI measurements during follow-up
N=44,566
left for analysis
N=1,147
Excluded because of cancer history/
prevalent cancer
N=43,419 (68%)
Included in main analysis
N=26,985
included from
EPIC-Elderly
N=8,577
included from
ESTHER
N=1,944
Included from
PRIME Belfast
N=5,913
Included from the
Tromsö Study


Cohort
Hazard Ratio (95% CI)
% Weight
BMI
EPIC_DK 1.06 (0.96, 1.16) 19.44
EPIC_GR 1.09 (0.92, 1.31) 12.10
EPIC_NL 1.17 (1.03, 1.33) 16.00
EPIC_SP 0.88 (0.74, 1.04) 12.73
ESTHER 1.20 (1.09, 1.33) 19.03
PRIME Belfast 1.50 (1.08, 2.07) 5.34
TROMSO 1.13 (0.98, 1.30) 15.36
Subtotal (I-squared = 59.1%, p = 0.023) 1.11 (1.02, 1.21) 100.00
WC
EPIC_DK 1.06 (0.95, 1.17) 29.63
EPIC_GR 1.09 (0.89, 1.33) 13.49
EPIC_NL 1.17 (1.00, 1.36) 19.81
EPIC_SP 1.01 (0.83, 1.22) 14.39
PRIME Belfast 1.45 (1.03, 2.04) 5.43
TROMSO 1.28 (1.08, 1.51) 17.26
Subtotal (I-squared = 31.4%, p = 0.200) 1.13 (1.04, 1.23) 100.00
HC
EPIC_DK 1.05 (0.95, 1.16) 23.25
EPIC_GR 1.22 (1.02, 1.46) 15.77
EPIC_NL 1.17 (1.03, 1.33) 20.50
EPIC_SP 0.86 (0.73, 1.02) 17.20
PRIME Belfast 1.36 (0.95, 1.95) 6.52
TROMSO 1.12 (0.95, 1.32) 16.76
Subtotal (I-squared = 60.8%, p = 0.026) 1.09 (0.98, 1.21) 100.00
WHR
EPIC_DK 1.04 (0.92, 1.18) 23.56
EPIC_GR 0.91 (0.72, 1.15) 15.69
EPIC_NL 1.05 (0.86, 1.27) 18.31
EPIC_SP 1.33 (1.05, 1.68) 15.58
PRIME Belfast 1.52 (0.97, 2.38) 7.01
TROMSO 1.36 (1.14, 1.61) 19.85
Subtotal (I-squared = 61.8%, p = 0.023) 1.15 (1.00, 1.32) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5
reduced risk
increased risk


Cohort
Hazard Ratio (95% CI)
% Weight
BMI
EPIC_DK 1.19 (1.00, 1.42) 20.89
EPIC_GR 1.23 (0.88, 1.71) 8.85
EPIC_NL 1.11 (0.89, 1.40) 15.22
EPIC_SP 0.84 (0.64, 1.11) 11.66
ESTHER 1.17 (0.97, 1.43) 18.82
PRIME Belfast 1.60 (1.10, 2.33) 7.13
TROMSO 1.23 (1.00, 1.52) 17.43
Subtotal (I-squared = 30.5%, p = 0.195) 1.16 (1.04, 1.30) 100.00
WC
EPIC_DK 1.19 (0.98, 1.45) 32.71
EPIC_GR 1.20 (0.83, 1.74) 8.91
EPIC_NL 1.18 (0.90, 1.54) 17.26
EPIC_SP 0.94 (0.69, 1.28) 12.89
PRIME Belfast 1.52 (1.02, 2.26) 7.63
TROMSO 1.35 (1.06, 1.72) 20.60
Subtotal (I-squared = 0.0%, p = 0.462) 1.21 (1.08, 1.35) 100.00
HC
EPIC_DK 1.16 (0.96, 1.40) 24.46
EPIC_GR 1.40 (1.00, 1.95) 12.12
EPIC_NL 1.12 (0.90, 1.40) 20.52
EPIC_SP 0.85 (0.65, 1.12) 16.16
PRIME Belfast 1.51 (1.00, 2.27) 8.72
TROMSO 1.20 (0.93, 1.54) 18.03
Subtotal (I-squared = 35.5%, p = 0.171) 1.15 (1.01, 1.32) 100.00
WHR
EPIC_DK 1.16 (0.92, 1.46) 32.53
EPIC_GR 0.91 (0.59, 1.40) 9.39
EPIC_NL 1.12 (0.80, 1.58) 14.70
EPIC_SP 1.20 (0.82, 1.75) 12.07
PRIME Belfast 1.44 (0.85, 2.44) 6.21
TROMSO 1.40 (1.08, 1.82) 25.09
Subtotal (I-squared = 0.0%, p = 0.602) 1.20 (1.05, 1.37) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5
reduced risk
increased risk


Cohort
Hazard Ratio (95% CI)
% Weight
BMI
EPIC_DK 0.98 (0.84, 1.13) 24.26
EPIC_GR 1.13 (0.76, 1.67) 7.55
EPIC_NL 1.32 (1.09, 1.60) 19.30
EPIC_SP 0.86 (0.63, 1.18) 10.61
ESTHER 1.16 (0.99, 1.36) 22.86
TROMSO 1.23 (0.97, 1.57) 15.41
Subtotal (I-squared = 47.1%, p = 0.092) 1.11 (0.99, 1.26) 100.00
WC
EPIC_DK 0.94 (0.80, 1.10) 30.07
EPIC_GR 0.97 (0.61, 1.55) 11.64
EPIC_NL 1.26 (1.00, 1.58) 24.82
EPIC_SP 1.05 (0.72, 1.51) 15.65
TROMSO 1.51 (1.09, 2.10) 17.82
Subtotal (I-squared = 54.9%, p = 0.064) 1.12 (0.93, 1.35) 100.00
HC
EPIC_DK 1.02 (0.88, 1.18) 33.55
EPIC_GR 1.23 (0.84, 1.81) 10.12
EPIC_NL 1.29 (1.07, 1.56) 26.89
EPIC_SP 0.92 (0.68, 1.23) 15.32
TROMSO 1.26 (0.92, 1.73) 14.12
Subtotal (I-squared = 38.4%, p = 0.165) 1.12 (0.98, 1.29) 100.00
WHR
EPIC_DK 0.87 (0.72, 1.05) 27.49
EPIC_GR 0.72 (0.42, 1.25) 12.51
EPIC_NL 1.04 (0.77, 1.39) 22.40
EPIC_SP 1.33 (0.83, 2.12) 15.09
TROMSO 1.47 (1.10, 1.97) 22.51
Subtotal (I-squared = 65.5%, p = 0.021) 1.06 (0.83, 1.36) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5
reduced risk
increased risk

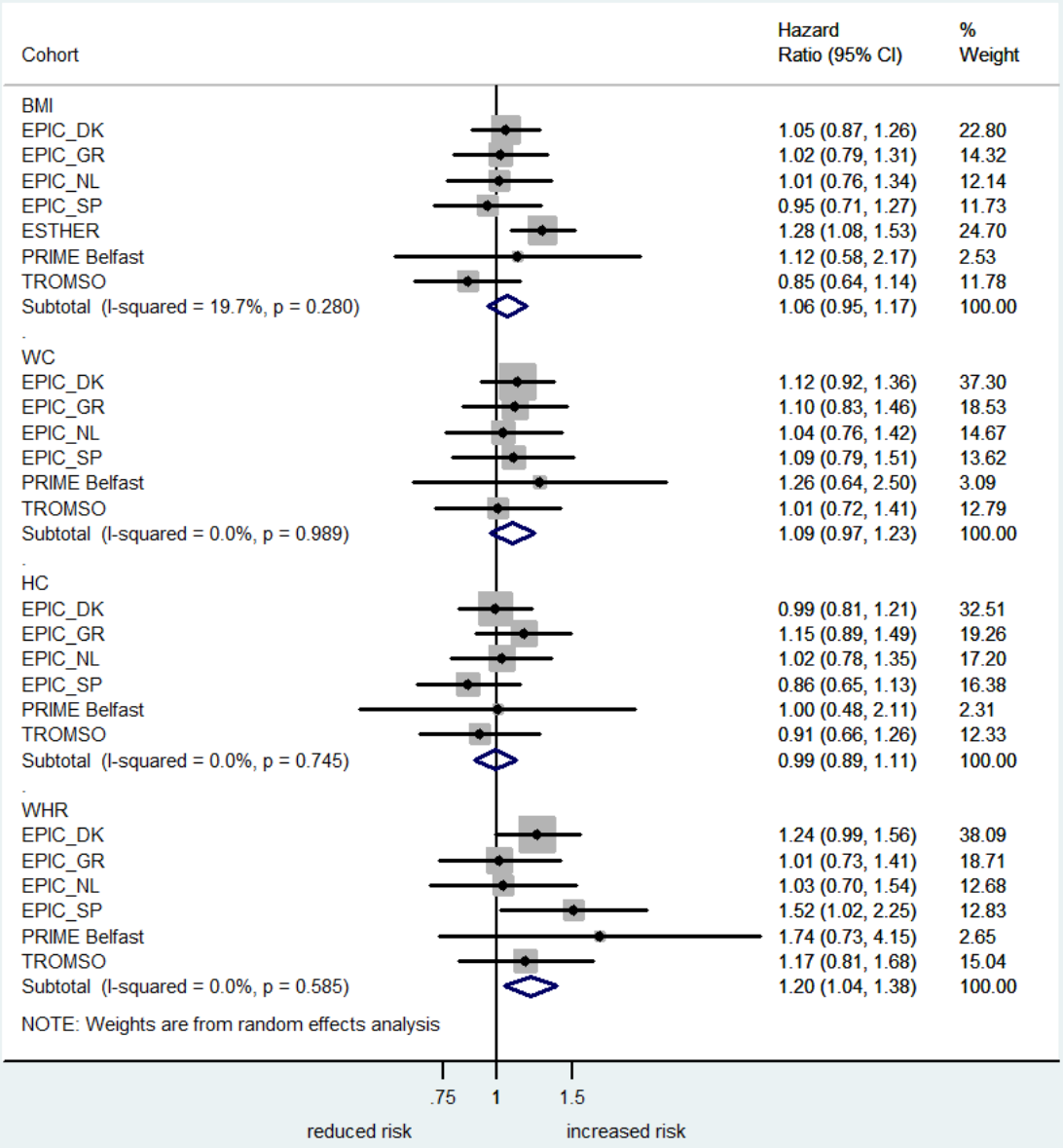

Cohort
Hazard Ratio (95% CI)
% Weight
BMI
EPIC_DK 1.05 (0.87, 1.26) 22.80
EPIC_GR 1.02 (0.79, 1.31) 14.32
EPIC_NL 1.01 (0.76, 1.34) 12.14
EPIC_SP 0.95 (0.71, 1.27) 11.73
ESTHER 1.28 (1.08, 1.53) 24.70
PRIME Belfast 1.12 (0.58, 2.17) 2.53
TROMSO 0.85 (0.64, 1.14) 11.78
Subtotal (I-squared = 19.7%, p = 0.280) 1.06 (0.95, 1.17) 100.00
WC
EPIC_DK 1.12 (0.92, 1.36) 37.30
EPIC_GR 1.10 (0.83, 1.46) 18.53
EPIC_NL 1.04 (0.76, 1.42) 14.67
EPIC_SP 1.09 (0.79, 1.51) 13.62
PRIME Belfast 1.26 (0.64, 2.50) 3.09
TROMSO 1.01 (0.72, 1.41) 12.79
Subtotal (I-squared = 0.0%, p = 0.989) 1.09 (0.97, 1.23) 100.00
HC
EPIC_DK 0.99 (0.81, 1.21) 32.51
EPIC_GR 1.15 (0.89, 1.49) 19.26
EPIC_NL 1.02 (0.78, 1.35) 17.20
EPIC_SP 0.86 (0.65, 1.13) 16.38
PRIME Belfast 1.00 (0.48, 2.11) 2.31
TROMSO 0.91 (0.66, 1.26) 12.33
Subtotal (I-squared = 0.0%, p = 0.745) 0.99 (0.89, 1.11) 100.00
WHR
EPIC_DK 1.24 (0.99, 1.56) 38.09
EPIC_GR 1.01 (0.73, 1.41) 18.71
EPIC_NL 1.03 (0.70, 1.54) 12.68
EPIC_SP 1.52 (1.02, 2.25) 12.83
PRIME Belfast 1.74 (0.73, 4.15) 2.65
TROMSO 1.17 (0.81, 1.68) 15.04
Subtotal (I-squared = 0.0%, p = 0.585) 1.20 (1.04, 1.38) 100.00
NOTE: Weights are from random effects analysis
.75
1
1.5
reduced risk
increased risk

Table 1. Study and participants characteristics by cohort in the CHANCES consortium of middle-aged and older adults

Characteristic	EPIC Elderly								Germany (ESTHER)		Northern Ireland (PRIME Belfast)		Norway (Tromsø)	
	Denmark		Greece		Netherlands		Spain							
Recruitment year, range	1993-1997		1994-1999		1993-1997		1992-1996		2000-2003		1991-1994		1994-1995	
Age at entry, years (SD)	62.5	1.5	66.9	4.4	64.3	2.7	62.5	1.7	61.9	6.6	54.2	2.8	59.4	6.9
Sex														
Men, n (%)	5072	46.4	2882	40.1	210	4.9	1949	42.5	3849	44.9	1944	100	2762	46.7
Women, n (%)	5853	53.6	4299	59.9	4085	95.1	2635	57.5	4728	55.1	0	0	3151	53.3
Education														
Low, n (%)	4193	38.4	6539	91.1	1303	30.3	3927	85.7	6197	72.3	15	0.8	3033	51.3
Medium, n (%)	4889	44.8	398	5.5	2451	57.1	320	7.0	1757	20.5	1677	86.3	1726	29.2
High, n (%)	1827	16.7	220	3.1	521	12.1	287	6.3	415	4.8	252	13.0	1118	18.9
Unknown, n (%)	16	0.2	24	0.3	20	0.5	50	1.1	208	2.4	0	0.0	36	0.6
BMI at baseline, kg/m^2 (SD)	26.2	3.9	29.3	4.3	25.8	3.9	29.5	4.0	27.6	4.2	26.1	3.2	26.1	3.7
Underweight, n (%)	62	0.6	19	0.3	46	1.1	4	0.1	33	0.4	8	0.4	44	0.7
Normal weight, n (%)	4421	40.5	1114	15.5	1947	45.3	493	10.8	2323	27.1	723	37.2	2377	40.2
Overweight, n (%)	4861	44.5	3125	43.5	1745	40.6	2167	47.3	4064	47.4	998	51.3	2661	45.0
Obese, n (%)	1581	14.5	2923	40.7	557	13.0	1920	41.9	2157	25.2	215	11.1	831	14.1
WC at baseline, cm (SD)	89.1	12.4	95.9	11.4	84.2	10.3	97.1	10.7	-	-	90.9	9.1	90.1	10.9
HC at baseline, cm (SD)	101.2	7.8	106.3	9.1	103.8	8.3	107.9	8.5	-	-	96.8	6.4	103.5	7.3
WHR at baseline, ratio (SD)	0.88	0.10	0.90	0.09	0.81	0.07	0.90	0.08	-	-	0.94	0.05	0.87	0.08
Height at baseline, cm (SD)	168.8	8.8	158.2	8.7	163.8	6.5	159.5	8.6	167.3	8.4	174.2	6.8	168.2	9.4
Vigorous physical activity														
No, n (%)	1752	16.0	5566	77.5	1669	38.9	4311	94	4853	56.6	1689	86.9	3528	59.7
Yes, n (%)	5135	47.0	1506	21.0	2480	57.7	242	5.3	3704	43.2	255	13.1	2324	39.3
Unknown, n (%)	4038	37.0	109	1.5	146	3.4	31	0.7	20	0.2	0	0.0	61	1.0
Alcohol intake, grams/d (SD)	19.0	19.8	7.5	15.4	7.8	11.9	13.0	22.2	6.8	9.4	20.3	30.4	3.6	5.1
Smoking status														
Never daily smoker, n (%)	3625	33.2	4891	68.1	2052	47.8	3109	67.8	4191	48.9	792	40.7	1950	33.0
Former daily smoker, n (%)	4078	37.3	1285	17.9	1532	35.7	732	16.0	2772	32.3	637	32.8	2127	36.0
Current daily smoker, n (%)	3201	29.3	805	11.2	694	16.2	740	16.1	1389	16.2	491	25.3	1831	30.9
Unknown, n (%)	21	0.2	200	2.8	17	0.4	3	0.1	255	2.6	24	1.2	5	0.1
Median follow-up time, years	11.9		11.5		13.2		13.4		10.5		18.0		15.9	
N cancers cases														
N all obesity-related[a]	465		127		250		164		352		56		242	
N breast cancer (age>50, women only)	193		22		109		42		125		-		64	
N colorectal cancer	141		39		80		66		111		41		113	
N other obesity-related[b]	131		66		61		56		116		15		65	

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

[b] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.
Note: All values are means, except when stated otherwise.
Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

Table 2. Changes in risk discrimination for the risk of incident cancer in men and women combined after addition of anthropometric indicators to the null model

	Null model		BMI		WC		HC		WHR		BMI + WC + HC	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Obesity-related cancers[a]												
AIC	15826.6		15823.6		15820.6		15823.7		15823.4		15823.1	
C-index	0.688	0.676 - 0.699	0.687	0.675 - 0.698	0.663	0.649 - 0.677	0.663	0.650 - 0.677	0.664	0.651 - 0.678	0.663	0.650 - 0.677
Colorectal cancer												
AIC	5678.8		5672.8		5670.2		5674.8		5674.0		5673.5	
C-index	0.688	0.667 - 0.709	0.689	0.668 - 0.711	0.680	0.655 - 0.704	0.679	0.655 - 0.704	0.681	0.657 - 0.706	0.681	0.656 - 0.705
Breast cancer[b]												
AIC	5031.2		5030.3		5031.9		5032.0		5033.1		5032.9	
C-index	0.824	0.813 - 0.836	0.823	0.812 - 0.835	0.801	0.787 - 0.815	0.802	0.788 - 0.816	0.803	0.789 - 0.817	0.801	0.787 - 0.815
Other obesity-related cancers[c]												
AIC	4780.7		4782.7		4781.4		4782.2		4777.0		4780.6	
C-index	0.588	0.561 - 0.615	0.587	0.559 - 0.614	0.605	0.573 - 0.637	0.605	0.574 - 0.637	0.612	0.581 - 0.643	0.618	0.587 - 0.648

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.
[b] Women only.
[c] Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.
Note: Null model included sex, age, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.
Abbreviations: AIC, Akaike Information Criterion; BMI, body mass index; CI, confidence interval; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

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Figure 1. Flowchart of participant inclusion.

Figure 2. Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with 'obesity-related cancers'[a].

[a] First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

Figure 3. Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with colorectal cancer.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

Figure 4. Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with postmenopausal breast cancer.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

Figure 5. Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with 'other obesity-related cancers'[a].

[a] First primary cancers of the lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.