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CANCER

High body mass index and cancer risk—a Mendelian randomisation study

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Abstract High body mass index (BMI) has been associated with increased risk of some cancer. Whether these reflect causal associations is unknown. We examined this issue. Using a Mendelian randomisation approach, we studied 108,812 individuals from the general population. During a median of 4.7 years of follow-up (range 0–37), 8002 developed non-skin cancer, 3347 non-melanoma skin cancer, 1396 lung cancer, 637 other smoking related cancers, 1203 colon cancer, 159 kidney cancer, 1402 breast cancer, 1062 prostate cancer, and 2804 other cancers. Participants were genotyped for five genetic variants associated with BMI. Two Danish general population studies, the Copenhagen General Population and the Copenhagen City Heart Study. In observational analyses, overall risk of non-melanoma skin cancer was 35 % (95 % confidence interval 28–42 %) lower and risk of lung cancer 32 % (19–43 %) lower in individuals with a BMI $\geq$ 30 versus 18.5–24.9 kg/m^2. Corresponding risk of breast cancer was 20 % (0–44 %) higher in postmenopausal women. BMI was not associated with risk of colon, kidney, other smoking related cancers, prostate cancer, or other cancers. In genetic analyses, carrying 7–10 versus 0–4 BMI increasing alleles was associated with a 3 % higher BMI ($P < 0.001$), but not with risk of cancer. In instrumental variable analysis for a 10 kg/m^2 higher genetically determined BMI the odds ratio for any non-skin cancer was 1.16 (0.64–2.09), with a corresponding observational estimate of 0.94 (0.88–1.01). Using 108,812 individuals from the general population, we found that observationally high BMI was associated with lower risk of lung and skin cancer overall and with higher risk of breast cancer in postmenopausal women, but not with other types of cancer. BMI increasing alleles were not associated with risk of cancer, and results do not support causal associations. Power to test associations for some cancer sites was low.

Keywords Overweight · Obesity · Body mass index · Cancer · Epidemiology · Mendelian randomisation

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Introduction

High body mass index has been associated in various directions with risk of cancers (meta-analyzed in [1, 2]). However, whether these associations reflect causal associations is unclear. Indeed, the reported associations could be

due to confounding by factors simultaneously associated with elevated body mass index and cancer, i.e. low educational level or low physical activity. Also, some of the studies observing associations between body mass index and cancer have used participant reported information on height, weight, and cancer, rather than objectively collected data. Apart from confounding, reverse causation could also explain part of the association between body mass index and cancer in retrospective or cross-sectional studies, i.e. early lung cancer stages or preclinical cancers [3] may lead to lower body mass index.

Mendelian randomisation is an epidemiological approach that aims to circumvent confounding and reverse causation by use of genetic variation in populations [4, 5]. Due to the random assortment of genetic variants at conception, variants with effect on a modifiable exposure of interest, i.e. body mass index, are randomly distributed in relation to potential confounders. Furthermore, because genetic variants are determined at conception and remain constant throughout life, Mendelian randomisation is not influenced by reverse causation, since cancer cannot change the germline genotype of an individual. Thus, genetic variants that are associated with body mass index can be used as largely unconfounded instruments free of reverse causation to study the effect of body mass index on cancer. If body mass index truly is a causal risk factor in the development of cancer, genetic variants that change body mass index would be expected also to increase risk of cancer.

Using a Mendelian randomisation design, we tested the hypothesis that there is a causal association between body mass index and risk of cancer (Fig. 1, arrows #1–4). First, we tested whether body mass index at baseline was associated prospectively with increased risk of cancer (Fig. 1, #1); second, whether an allele score of body mass index increasing alleles of *FTO*(rs9939609), *MC4R*(rs17782313), and *TMEM18*(rs6548238), *BDNF*(rs10767664), and *GNPDA2*(rs10938397), five common genetic variants with the largest known effects on the entire distribution of body mass index in the population [6, 7], was associated with body mass index as expected (Fig. 1, #2); third, whether body mass index increasing alleles were associated directly with risk of cancer (Fig. 1, #3); and fourth, whether the causal effect of body mass index-increasing alleles on risk of cancer, using instrumental variable analysis, was consistent with the observational association between body mass index and risk of cancer (Fig. 1, #4 compared with #1). As a positive control of the Mendelian randomisation design and to verify study power, we included similar estimates for the *CHRNA3* genotype known to be associated with self-reported smoking and thus expected to be associated with risk of smoking related cancers.

Methods

Participants

We included participants in two similar prospective studies of the Danish general population, The Copenhagen General Population Study ($N = 89{,}988$) and The Copenhagen City Heart Study ($N = 18{,}829$) [8–10]. The two studies combined comprised a total of 108,817 participants of whom 8002 developed non-skin cancer, 3347 non-melanoma skin cancer, 1396 lung cancer, 637 other smoking related cancers, 1203 colon cancer, 159 kidney cancer, 1402 breast cancer, 1062 prostate cancer, and 2804 developed other cancers during up to 37 years of follow-up. Studies were approved by institutional review boards and Danish ethical committees (KF-100.2039/91, KF-01-144/01, H-KF-01-144/01). Written informed consent was obtained from participants. All participants were white and of Danish descent, and none were included in more than one study.

The Copenhagen General Population Study

The Copenhagen General Population Study was initiated in 2003 with ongoing enrolment [8–10]. Individuals were selected based on the national Danish Civil Registration System to reflect the adult Danish population aged 20–100 years. Data were obtained from a self-administered questionnaire reviewed together with an investigator at the day of attendance, a physical examination, and from blood samples including DNA extraction.

The Copenhagen City Heart Study

The Copenhagen City Heart Study [8–10] is a prospective study of the Danish general population initiated in 1976–1978 with follow-up examinations in 1981–1983, 1991–1994, and 2001–2003. Participants were recruited and examined exactly as in the Copenhagen General Population Study. Baseline was considered the first examination an individual participated in, where height and weight were measured. Blood samples for DNA extraction were drawn at the 1991–1994 and 2001–2003 examinations.

Ascertainment of a diagnosis of cancer

Diagnoses of cancer from 1947 through December 26th 2012 were obtained from the Danish Cancer Registry, which identifies 98 % of all cancers diagnosed in Denmark [11, 12]. Information on cancer deaths was obtained from the national Danish Causes of Death Registry. Cancer diagnoses in both registries were classified according to the World Health Organization (WHO) International

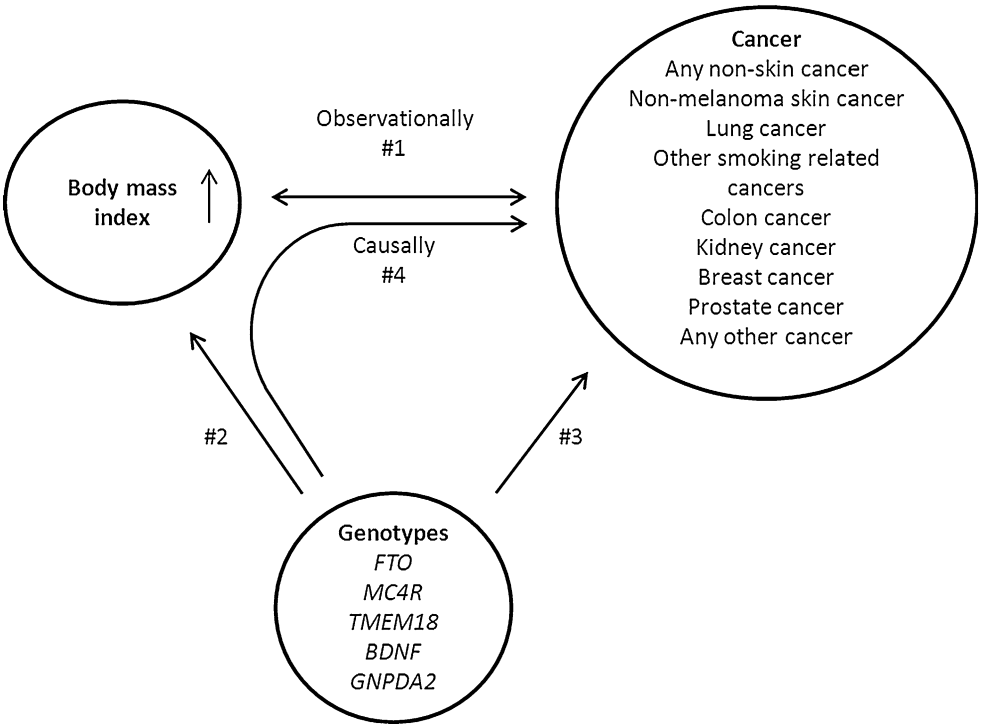

Fig. 1 Schematic representation of the Mendelian randomisation design underlying the present study. If evidence #1–3 is all documented, the interpretation would be that the data are compatible with a causal relationship between elevated body mass index and risk of cancer. This is then tested directly using instrumental variable analysis (#4, causal association) which is compared with the observational estimate (#1). If evidence #1 and #2 are present, but not #3 and #4, the interpretation would be that the association #1 is likely due to confounding or reverse causation

Classification of Diseases, Seventh Revision (ICD-7) [13] and Tenth Revision (ICD-10) [14] codes as follows: any non-skin cancer (ICD-7:140–171, 174–205; ICD-10:C00–C42, C45–C96); non-melanoma skin cancer (ICD-7:173; ICD-10:C44); lung cancer (including less than 1 % cancers in trachea, bronchia, and pleura: ICD-7:162–163; ICD-10:C33–34); colon cancer (ICD-7:153; ICD-10:C18); kidney cancer (ICD-7:189.09; ICD-10:C64); other smoking related cancers, that is oral, larynx and bladder cancer (ICD-7:140–149, 188; ICD-10:C00–C14, C67); breast cancer (ICD-7:174; ICD-10:C50); prostate cancer (ICD-7:185; ICD-10:C61); and other cancers including all other cancer diagnoses than the former.

Follow-up time for cancer for each participant in either study began at the first inclusion into a study. Follow-up ended at the date of death, occurrence of event, emigration ($N = 24$), or on December 26th 2012 (corresponding to the end of follow-up for the least updated register), whichever came first. Individuals with an endpoint before inclusion were excluded from analyses. No individual was lost to follow-up. Median follow-up was 4.7 years (range 0–37).

Body mass index

Weight was measured without shoes and in light clothing to the nearest 0.1 kg on Soehnle Professional scales. Height was measured to the nearest 0.1 cm with a Seca stadiometer. Body mass index was measured weight (kg) divided by measured height squared (m^2).

Covariates

Hypertension was systolic blood pressure ≥140 mmHg (≥135 mmHg for diabetics), diastolic blood pressure ≥90 mmHg (≥85 mmHg for diabetics), and/or use of antihypertensive medication prescribed specifically for hypertension [15]. Diabetes mellitus was self-reported disease, nonfasting plasma glucose >11.0 mmol/L, medication prescribed for diabetes, and/or hospitalisation or death due to diabetes (ICD8:249–250; ICD10:E10–11, E13–14) [16]. Participants also reported on smoking, amount smoked and ages of starting and quitting, which was used to calculate pack-years smoked; alcohol consumption in units per week (1 unit = 12 g alcohol); work and leisure time physical activity (coded as low for 0–2 h moderate activity, intermediate for 2–4 h activity, and high for more than 4 h moderate or vigorous activity per week during either work or leisure time); education (<10, 10 to <13, or ≥13 years of completed education); and for women also menopausal status. Missing data varied from 0 to 1 % for any individual variable.

Genotyping and biochemical analysis

An ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and Taqman based assays were used to genotype for body mass index associated genotypes *FTO*(rs9939609), *MC4R*(rs17782313), *TMEM18*(rs6548238), *BDNF*(rs10767664), and

GNPDA2(rs10938397), and smoking associated genotype *CHRNA3*(rs1051730). The five former polymorphisms were selected as those with the largest known common effect sizes for association with body mass index in European populations [6], accounting for ~51 % (0.74 % of 1.45 %) of the variation in body mass index so far accounted for by 32 known genetic variants, and the latter as a genotype known to be associated with smoking [17], and was included as a positive control for the known causal association between smoking and selected cancer types. To act as an aggregate instrument for body mass index, a simple allele score of 0–10 alleles was constructed as the sum of body mass index-increasing alleles across the five genotypes [8]. To ensure a linear relationship between the allele score and body mass index, and a sufficiently large number of individuals in each group, individuals with, respectively, 0–4 and 7–10 body mass index-increasing alleles were combined into groups used in Cox regression analyses. Genotypes were available on 89,988 participants in the Copenhagen General Population Study and on 10,600 participants in the Copenhagen City Heart Study. High-sensitivity C-reactive protein was measured by nephelometry or turbidimetry (Dako, Glostrup, Denmark, or Dade Behring, Deerfield, IL, USA) [18].

Statistical analyses

Data were analysed using Stata/IC 12.1. For genotypes, a deviation from Hardy–Weinberg equilibrium was tested using a Pearson Chi squared test. For Cox regression analyses, the allele score was categorized as 1 (0–4 alleles), 2 (5 alleles), 3 (6 alleles), and 4 (7–10 alleles) to obtain a sufficiently large reference group and body mass index in categories of <18.5, 18.5–24.9 kg/m^2 (reference group), 25–29.9, and ≥30 kg/m^2.

A schematic representation of the Mendelian randomisation design underlying the present study is shown in Fig. 1. We tested the following four hypotheses: (1) Whether elevated body mass index is associated observationally with an increased risk of cancer in a prospective design using Cox regression models with age as time scale and left truncation (delayed entry). Analyses were conducted from baseline corresponding to the first entry into one of the studies through 2012. Participants with a diagnosis of the cancer of interest before or at baseline were excluded. Risk of cancer was estimated as a function of body mass index in categories adjusted multifactorially for age, gender, C-reactive protein concentrations, self-reported smoking in pack-years, physical activity, alcohol consumption, education, year of birth, and for women also menopausal status. Adjustment for year of birth was done to accommodate changes in diagnostic criteria and treatment over calendar time. Observational risk of cancer as a function of categories of body mass index was shown for all participants; subsequently, participants with a body mass index <18.5 kg/m^2 were excluded from further analyses because these individuals may have a low body mass index due to preclinical cancer or other competing diseases. Trends across categories of elevated body mass index (participants with a body mass index <18.5 kg/m^2 excluded) were tested using the nonparametric Cuzic extension of a Wilcoxon rank-sum test. (2) The association between genotypes as an allele score and elevated body mass index was tested using linear regression. Logistic regression was used to assess whether observational body mass index, the allele score, or cancer were associated with potential confounders (age, gender, C-reactive protein concentrations, smoking, physical activity, alcohol consumption, education, and for women menopausal status). (3) The direct association between the allele score and cancer was tested using Cox regression models multifactorially adjusted for age, gender, and year of birth. (4) A potential causal relationship between genetically increased body mass index and risk of cancer was assessed by instrumental variable analysis by two-stage least squares regression, using the user-written *ivreg2* and *ivpois* commands in Stata. In the first stage, we performed least squares regression of body mass index on the allele score. In the second stage, we performed least squares regression of cancer on the predicted values from the first regression. The predicted values are the means of body mass index within each allele score [19, 20]. Strength of the instrument, that is, the strength of the association of the allele score with body mass index, was confirmed by an F-statistics of 43 from the first-stage regression, where $F > 10$ indicates sufficient strength to ensure a statistically valid instrumental variable analysis [4]. Power to exclude a causal risk of cancer (odds ratio) at a two-sided α of 0.05 and β of 80 % was calculated using an online power calculation tool (https://sb452.shinyapps.io/power/) for instrumental variable analysis in Mendelian Randomization studies with binary outcomes [21]. As a sensitivity analysis, the instrumental variable analyses were performed using a weighted sum of risk alleles across the five genotypes applying a weight equal to the effect of each variant on body mass index reported by a previous genome wide association study [6]. Also, because the *BDNF*(rs10767664) genotype has been associated with both higher body mass index and smoking in schizophrenia [22], instrumental variable analyses were performed omitting this variant as an instrument.

Results

The distribution of body mass index in the population is shown in Supplementary Figure 1. Of the entire study population 1.1 % were underweight (body mass index <18.5 kg/m^2), 44.5 % normal weight (18.5–24.9 kg/m^2),

38.8 % overweight (25.0–29.9 kg/m^2), and 15.6 % were obese or morbidly obese (≥30 kg/m^2). Participants with a body mass index ≥25 versus 18.5–24.9 kg/m^2 were older and more likely to be male, had higher C-reactive protein concentrations, smoked less, were less physically active, consumed more alcohol, and had less years of education. Also, women were more likely to be premenopausal (Table 1 and by gender in Supplementary Table 1). *FTO*(rs9939609), *MC4R*(rs17782313), *TMEM18*(rs6548238), *BDNF*(rs10767664), *GNPDA2*(rs10938397), and *CHRNA3*(rs1051730) genotypes were in Hardy–Weinberg equilibrium (all $P > 0.25$).

Body mass index and cancer: observational estimates (Fig. 1, #1)

Increasing body mass index categories were associated with stepwise lower risk of non-melanoma skin cancer and lung cancer, and higher risk of breast cancer in postmenopausal women, but not with other smoking related cancers, colon cancer, kidney cancer, breast cancer in premenopausal women, prostate cancer, or other cancers (Fig. 2). During a median follow-up of 4.7 years (range 0–37) multifactorial adjusted risk of non-melanoma skin cancer was 35 % (95 % confidence interval: 28–42 %) lower and risk of lung cancer 32 % (19–43 %) lower in individuals with a body mass index ≥30 kg/m^2 compared to those with a body mass index of 18.5–24.9 kg/m^2. Postmenopausal women with a body mass index ≥30 kg/m^2 had, compared to those with a body mass index of 18.5–24.9 kg/m^2 a 20 % (0–44 %) higher risk of breast cancer.

Allele score and body mass index (Fig. 1, #2)

An increasing number of alleles were associated with a stepwise mean increase in body mass index of 0.20 kg/m^2 per allele (Fig. 3). Carrying 7–10 versus 0–4 body mass index increasing alleles was associated with 3 % higher body mass index. The allele score explained 0.4 % of the variation in body mass index.

Confounding factors

Age, gender, C-reactive protein concentrations, smoking, physical activity, alcohol consumption, educational level, and for women also menopausal status were all strongly associated with both body mass index and/or with risk of cancer (Supplementary Figure 2), and may therefore confound the observational association. Allele score was however not associated with any of the potential confounders, except for a known association with concentrations of C-reactive protein [23].

Table 1 Baseline characteristics of participants by body mass index category

	Body mass index (kg/m^2)				*P* trend	All
	<18.5	18.5–24.9	25–29.9	≥30		
No. of individuals (%)	1162 (1.1 %)	48,387 (44.5 %)	42,242 (38.8 %)	17,021 (15.6 %)		108,812 (100 %)
Body mass index (kg/m^2)	17.9 (17.3–18.3)	22.9 (21.5–24.0)	27.0 (26.0–27.3)	32.3 (31.0–34.7)		25.4 (23.0–28.3)
Age (years)	53.6 (44.2–64.0)	54.0 (42.0–63.9)	58.2 (48.5–67.2)	59.0 (49.5–67.0)	<0.001	56.3 (46.5–65.9)
Women	65 %	84 %	44 %	52 %	<0.001	55 %
C-reactive protein (mg/L)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.5 (1.1–2.5)	2.3 (1.5–4.1)	<0.001	1.5 (1.0–2.4)
Current smokers	29 %	50 %	24 %	22 %	<0.001	27 %
Smoking, pack-years (smokers only)	21 (11–34)	20 (11–32)	25 (14–39)	26 (14–40)	<0.001	23 (12–37)
Physical activity						
Low	45 %	59 %	46 %	49 %	<0.001	46 %
Intermediate	46 %	34 %	45 %	43 %	<0.001	45 %
High	9 %	7 %	9 %	8 %	<0.001	9 %
Alcohol consumption, units per week	6.0 (2.0–13)	3.5 (0–9.0)	8.0 (3.0–15)	6.0 (2.0–13)	<0.001	7.0 (2.0–14)
Education						
<10 years	21 %	23 %	30 %	37 %	<0.001	27 %
10–13 years	54 %	43 %	50 %	45 %	<0.001	51 %
13 years or more	18 %	17 %	14 %	11 %	<0.001	15 %
Postmenopausal, women only	37 %	52 %	31 %	37 %	<0.001	35 %

Continuous values are median and interquartile range and categorical values are in percent. 1 unit alcohol = 12 g

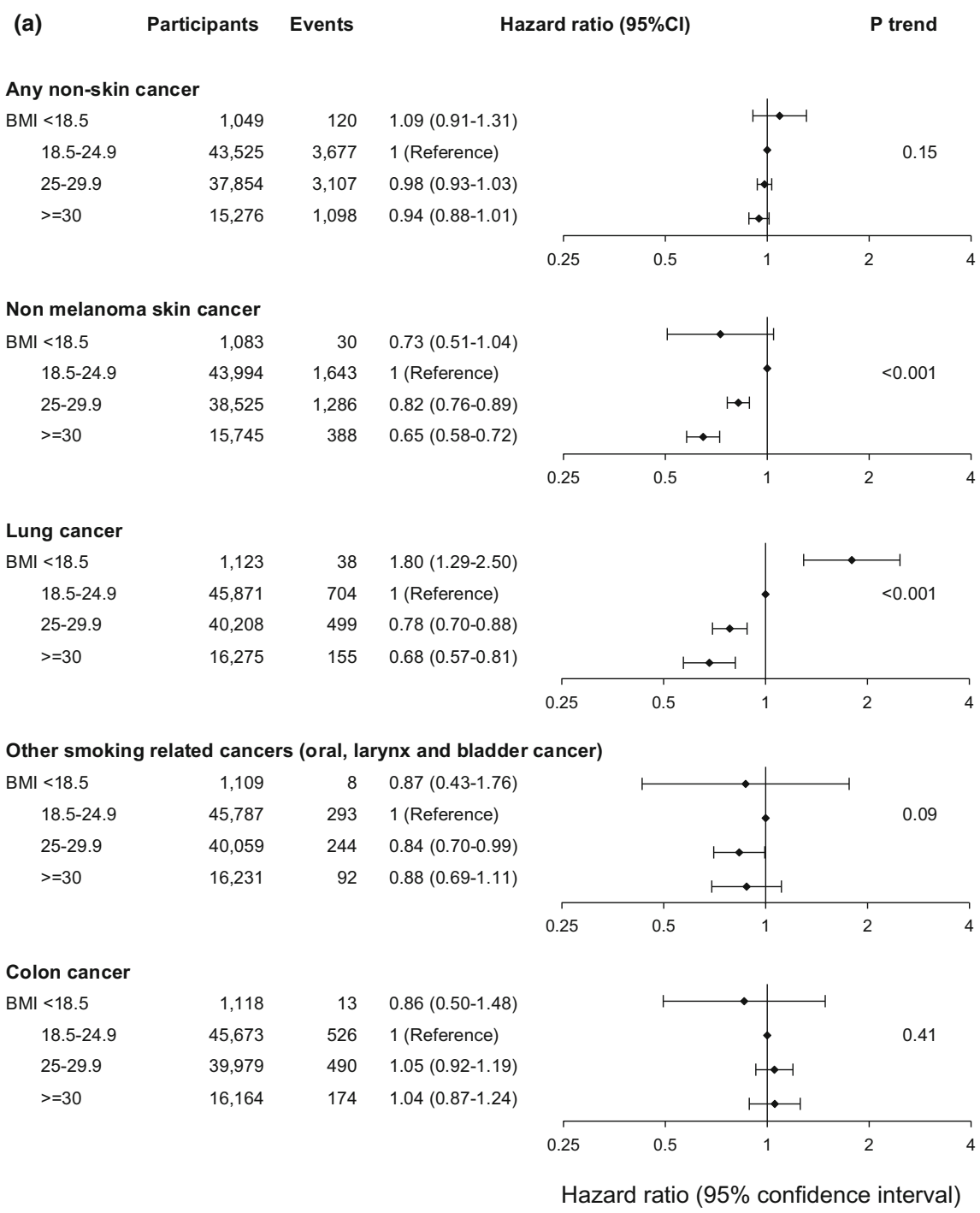

Fig. 2 Prospective risk of cancer as a function of baseline categories of body mass index. Risk estimates were adjusted for age, gender, C-reactive protein concentrations, smoking in pack-years, physical activity, alcohol consumption, education, birth year, and for women menopausal status. Risk of breast cancer is shown in women only, and risk of prostate cancer in men only. *P* values are for trend of hazard ratios across body mass index categories 18.5–24.9, 25–29.9, and ≥30 kg/m^2. Hazard ratios for participants with a body mass index <18.5 kg/m^2 were not included in the trend test. *BMI* body mass index, *CI* confidence interval

Allele score and cancer: genetic estimates (Fig. 1, #3)

Age, gender, and year of birth adjusted risks of all non-skin cancers combined, non-melanoma skin cancer, lung cancer, other smoking related cancers, colon cancer, kidney cancer, breast cancer, prostate cancer, or other cancers were not different among individuals with 5, 6, or 7–10 body mass index increasing alleles compared to individuals with 0–4 body mass index increasing alleles (Fig. 4).

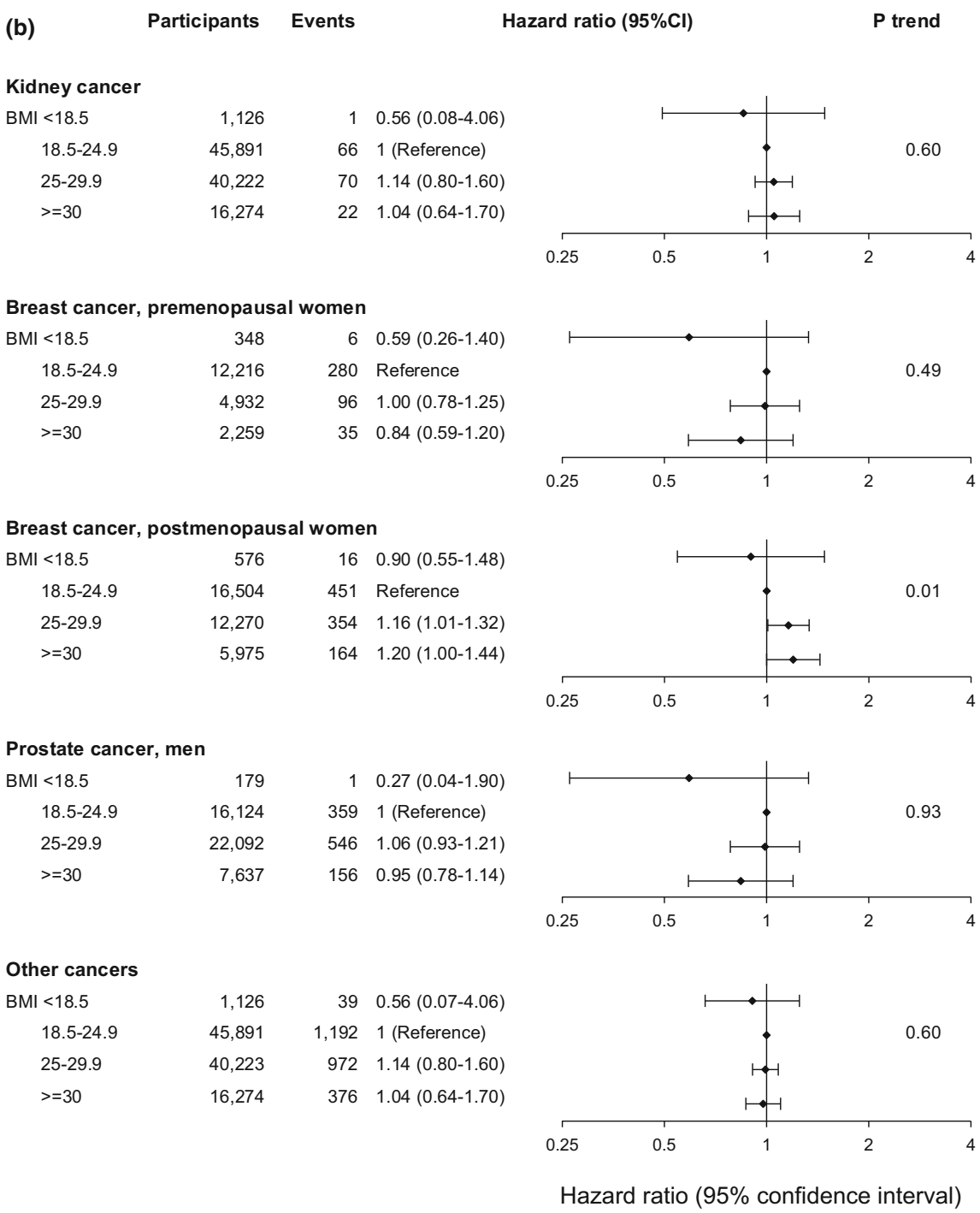

Fig. 2 continued

Body mass index and cancer: causal estimates (Fig. 1, #4)

In instrumental variable analysis for a 10 kg/m^2 increase in genetically determined body mass index the odds ratio for any non-skin cancer was 1.16 (95 % CI 0.64–2.09), with a corresponding observational estimate of 0.94 (0.89–0.99). The observational multifactorially adjusted risk of non-melanoma skin cancer was reduced by 37 % (30–42 %) and for lung cancer by 36 % (26–45 %), and for breast cancer in postmenopausal women increased by 14 % (0–32 %), for a 10 kg/m^2 higher body mass index; however, the causal genetic risk was not increased or decreased for any of the cancers and did not support causal

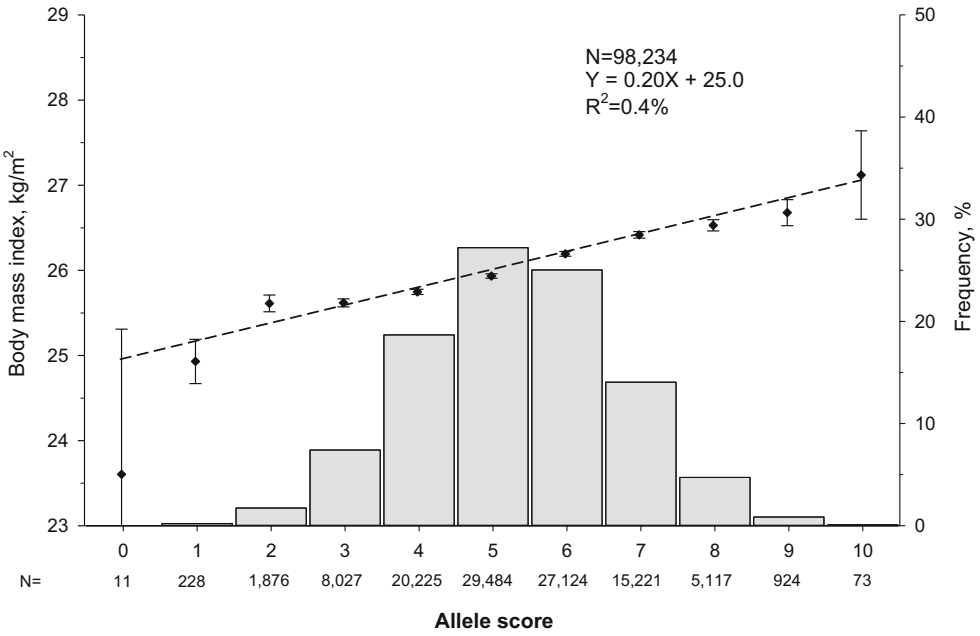

Fig. 3 Mean body mass index and standard error of the mean by an allele score of the number of body mass index increasing alleles of the *FTO*(rs9939609), *MC4R*(rs17782313), *TMEM18*(rs6548238), *BDNF*(rs10767664), and *GNPDA2*(rs10938397) genotypes, and the distribution of this allele score in the general population. R^2 = percent contribution of the allele score to the variation in body mass index

associations between body mass index and cancer (Fig. 5). Stratifying analyses by gender gave similar results (Supplementary Figure 3) and using a weighted sum of risk alleles across the five genotypes applying a weight equal to the effect of each variant on body mass index reported by a previous genome wide association study [6] likewise gave similar results (Supplementary Figure 4). To reduce potential risk of pleiotropy from the *BDNF*(rs10767664) genotype, instrumental variable analyses were performed omitting this variant as an instrument, giving similar results (Supplementary Figure 5).

As a positive control of statistical power and the Mendelian randomisation design, results on the *CHRNA3*(rs1051730) genotype were included. This genotype is known to be associated with both smoking status, smoking intensity and the amount smoked [17], and may thus be associated with higher risk of lung cancer and other smoking related cancers [24]. In the present study, a one pack-year higher tobacco consumption was associated with a 2.6 % (2.4–2.8 %) higher observational risk of lung cancer and a one pack-year higher tobacco consumption associated with the *CHRNA3*(rs1051730) genotype with a 8.5 % (7.1–9.9 %) higher genetic risk of lung cancer. Corresponding risks of other smoking related cancers were a 1.5 % (1.2–1.8 %) higher observational risk and an 4.7 % (3.7–5.6 %) higher genetic risk (Fig. 5). The effect sizes for the genetic estimates for *CHRNA3* genotype may be overestimated because self-reported smoking may underestimate the increase in tobacco consumption caused by the genotype [25, 26].

Discussion

Using 108,812 individuals from the general population, we found that observationally high body mass index was associated with lower risk of lung and skin cancer overall, and higher risk of breast cancer in postmenopausal women, but not with other types of cancer. Because body mass index increasing alleles were not associated with risk of cancer, the present results suggest that previous observational associations might to some extent be explained by confounding and/or reverse causation.

Some previous observational studies have reported associations between high body mass index and high risk of esophageal adenocarcinoma, thyroid cancer, renal cancer [27], colon cancer [28, 29], breast cancer [30], and prostate cancer (meta-analyzed in [1, 2]). From these reports, two general links between body mass index and cancer have been suggested [31]: (1) increased insulin like growth potentially stimulating cancer growth; and (2) a high body mass index resulting in lower plasma concentration of adiponectin, a hormone suggested to have anti-angiogenic and anti-inflammatory effects. In the present study we confirmed previously reported observational findings of associations between high body mass index and a low observational risk of skin [32] and lung [1] cancer overall and a high risk of breast cancer in postmenopausal women; although, these associations did not appear to be causal. The most likely explanation for these associations is confounding and behavioural influences. Thus, a lower body mass index may be associated with a preclinical

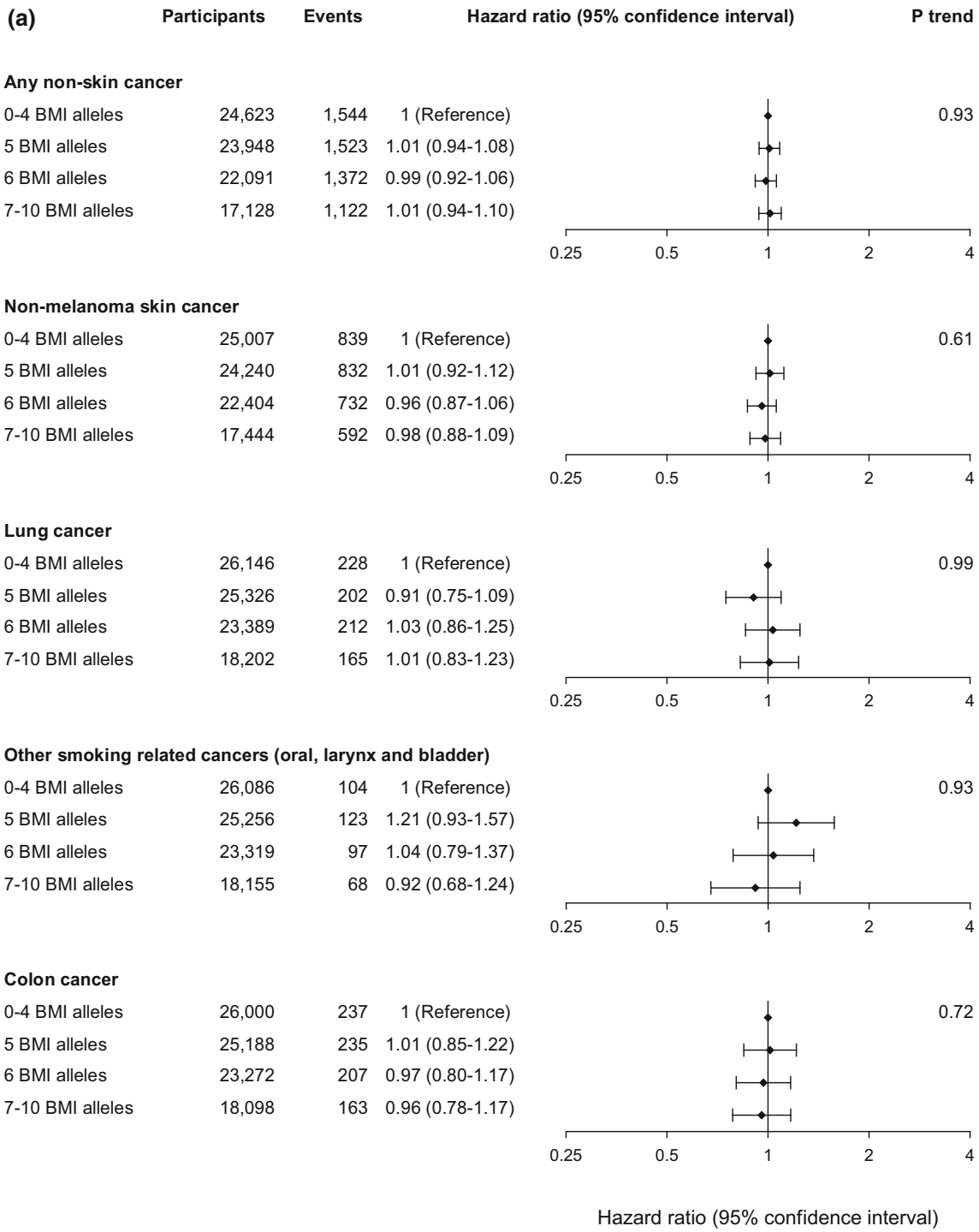

Fig. 4 Prospective risk of cancer as a function of an allele score of the number of body mass index increasing alleles of the *FTO*(rs9939609), *MC4R*(rs17782313), *TMEM18*(rs6548238), *BDNF*(rs10767664), and *GNPDA2*(rs10938397) genotypes. The group of participants with 0–4 body mass index increasing alleles is the reference group. *P* values are from tests for trend of hazard ratios across ordered allele scores

cancer [3]. Likewise, sun exposure is known to be associated with increased risk of skin cancer [32], and overweight and obese persons may be less active outdoor, do less sun-bathing, and thus have a lower accumulated sun exposure. Two previous Mendelian randomization studies have examined the causal association between body mass index and risk of cancer; one examining the association with colorectal cancer in 10,226 colorectal cancer cases

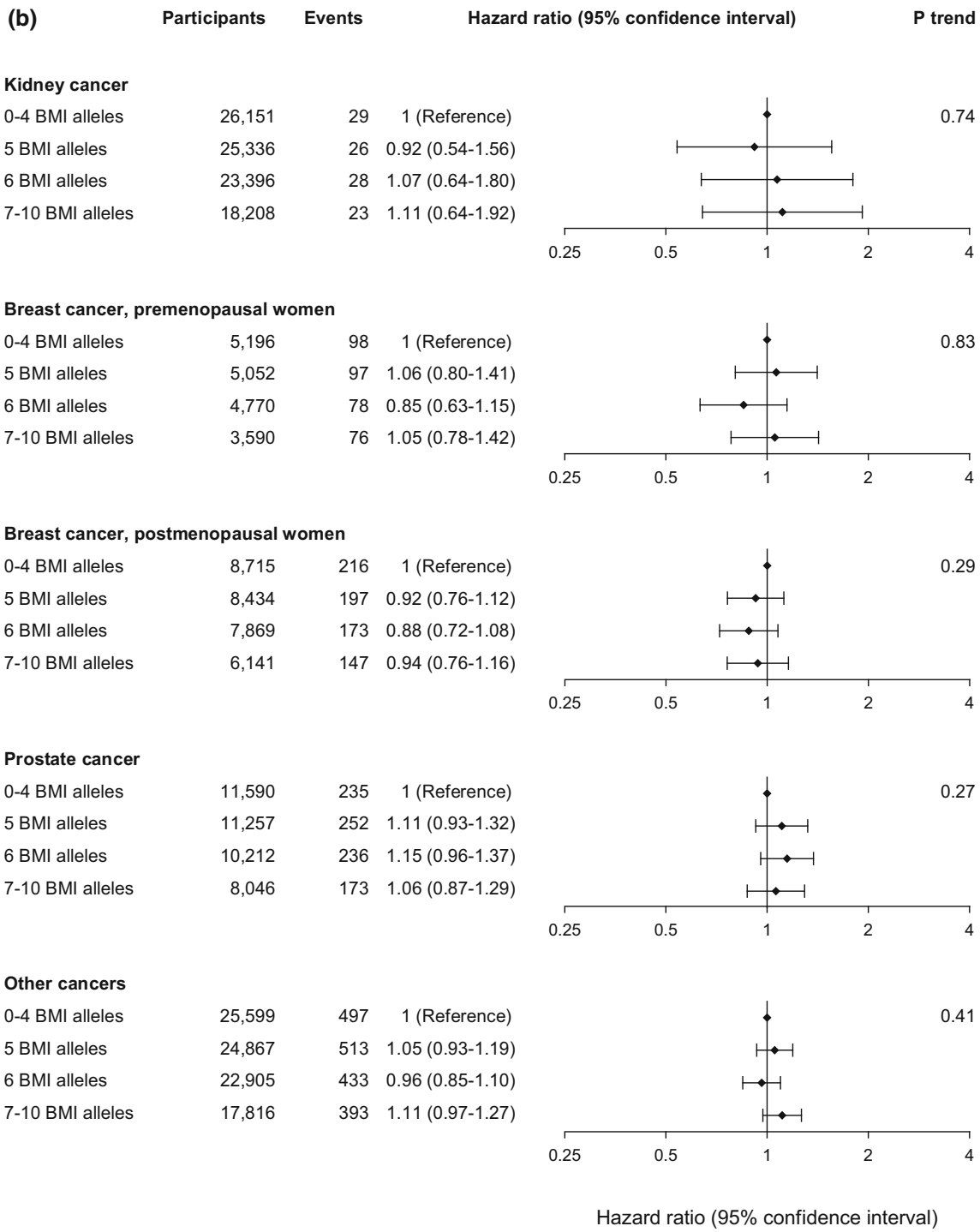

Fig. 4 continued

and 10,286 population based controls and observed an 82 % increased risk of colorectal cancer for a 5 kg/m^2 higher body mass index in women, but no increase in risk in men [33]; and another examining the association with prostate cancer in 20,848 prostate cancer cases and 20,214 controls, observing no increase in risk of prostate cancer [34]. Our findings for prostate cancer were similar; however, we could not confirm increased risk of colon cancer as a function of genetically higher body mass index.

Our study is the largest prospective study to date comprising a population of homogenous ethnicity with stringent height and weight measures, extensive information on

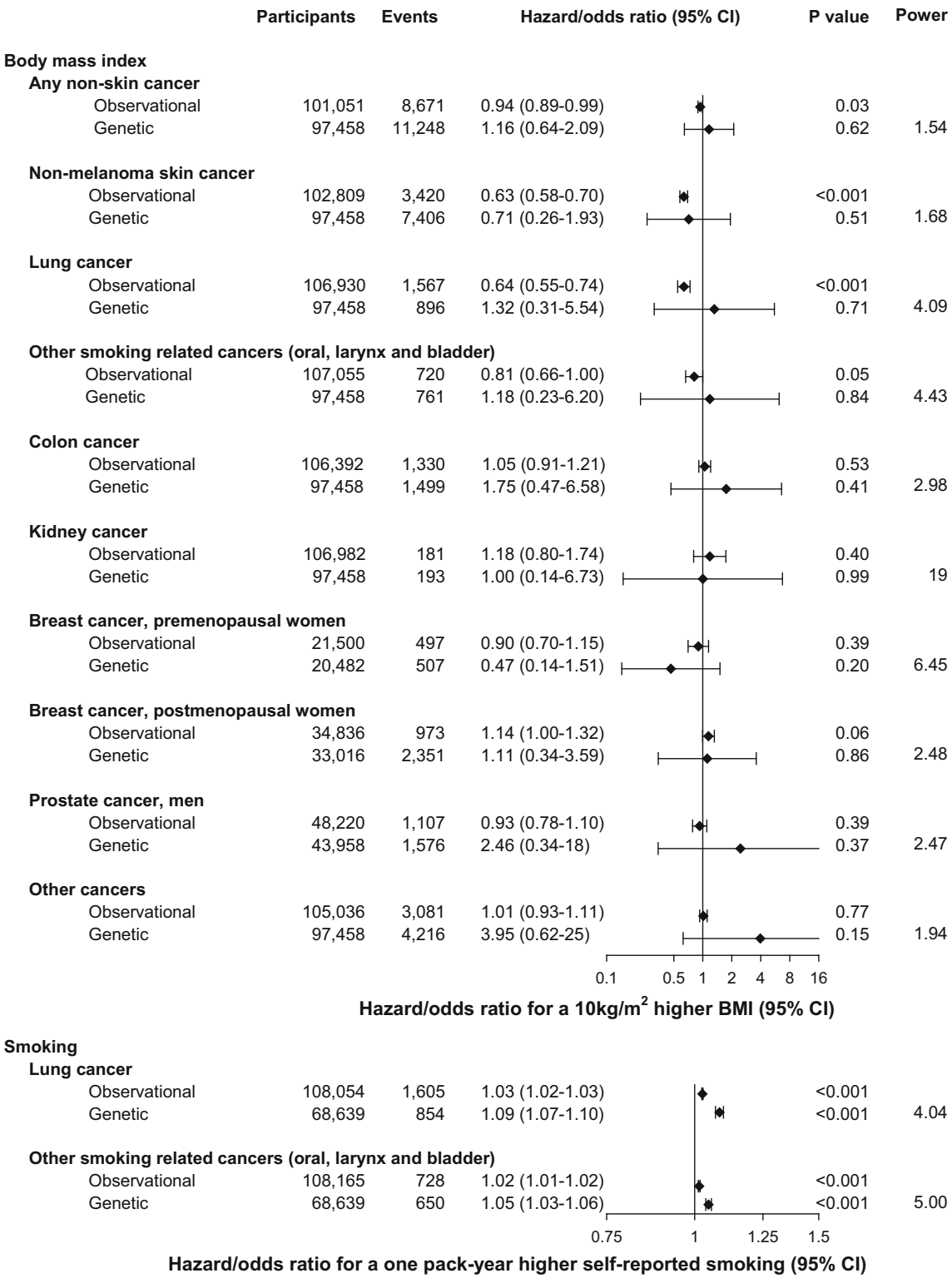

Fig. 5 Risk of cancer for a 10 kg/m^2 higher observational and causal genetically determined body mass index. The hazard ratio for a 10 kg/m^2 higher observational body mass index was calculated using Cox regression. Odds ratios for genetically higher body mass index were derived from instrumental variable analysis. Power denotes the odds ratio that can be excluded at a two-sided α of 0.05 and β of 80 %. Observational and genetic estimates for self-reported smoking in pack years and risk of lung cancer and other smoking related cancers were included as a positive control of the study design and study power. *P* values are for significance of hazard ratios and odds ratios. *CI* confidence interval, *BMI* body mass index

confounders, and validated cancer diagnoses, thus reducing risk of bias due to misclassification. It is also the first study to use a Mendelian randomisation design to estimate the causal associations between body mass index and risk of all cancer types. Because we were not able to confirm previously reported associations between high body mass index and risk of cancer, we included observational and genetic data on smoking and risk of lung cancer and other smoking related cancers as positive controls. These data showed the expected observational and causal associations between smoking and increased risk of lung cancer and other smoking related cancers, confirming that we have statistical power to detect known causal associations and confirming the validity of the Mendelian randomisation design. However, statistical power is limited for some of the rare cancers and for this reason we also report the causal risk of cancer (odds ratio from instrumental variable analyses) that can be excluded with 80 % power at a two-sided α of 0.05 for each endpoint.

The Mendelian randomisation approach is a way of circumventing confounding and reverse causation seen in observational epidemiology; however, some limitations apply. The most important for this study is pleiotropy, which is when the genetic variant used as an instrument for a risk factor is associated with yet other risk factors. To minimize influence from pleiotropy, we carefully selected genetic instruments and used genetic variants located in five different genes combined in an allele score for body mass index, making it unlikely that the genetic variants in the allele score have the same pleiotropic effects [4]. That the genotypes did not associate with known confounders or had pleiotropic effects were confirmed in the present study. Also, because the *BDNF*(rs10767664) genotype has been associated with both higher body mass index and smoking in schizophrenia [22], instrumental variable analyses were performed omitting this variant as an instrument, giving similar results as when including all five genotypes. Another limitation of this study is that all participants are white and our results may not necessarily apply to other races or ethnicities; however, we are not aware of data suggesting that our results should not apply to most races and countries where obesity is prevalent. Furthermore, using a weighted sum of risk alleles across the five genotypes applying a weight equal to the effect of each variant on body mass index reported in previous genome wide association studies including several ethnicities [6], gave similar causal estimates, suggesting that our results may largely apply to other ethnicities.

In conclusion, using 108,812 individuals from the general population, we found that observationally high body mass index was associated with lower risk of lung and skin cancer overall and with higher risk of breast cancer in postmenopausal women, but not with other types of cancer. Because body mass index increasing alleles were not associated with risk of cancer, the present results do not support causal associations; however, for some cancers statistical power was limited.

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