The Inverse Association of Body Mass Index with Lung Cancer: Exploring Residual Confounding, Metabolic Aberrations and Within-Person Variability in Smoking

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ABSTRACT

Background: The inverse observational association between body mass index (BMI) and lung cancer risk remains unclear. We assessed whether the association is explained by metabolic aberrations, residual confounding, and within-person variability in smoking, and compared against other smoking-related cancers.

Methods: We investigated the association between BMI, and its combination with a metabolic score (MS) of mid-blood pressure, glucose, and triglycerides, with lung cancer and other smoking-related cancers in 778,828 individuals. We used Cox regression, adjusted and corrected for within-person variability in smoking (status/pack-years), calculated from 600,201 measurements in 221,958 participants.

Results: Over a median follow-up of 20 years, 20,242 smoking-related cancers (6,735 lung cancers) were recorded. Despite adjustment and correction for substantial within-person variability in smoking, BMI remained inversely associated with lung cancer [HR per standard deviation increase, 0.87 (95% confidence interval 0.85–0.89)]. Individuals with BMI less than 25 kg/m^2 and high MS had the highest risk [HR 1.52 (1.44–1.60) vs. BMI ≥25 with low MS]. These associations were weaker and nonsignificant among nonsmokers. Similar associations were observed for head and neck cancers and esophageal squamous cell carcinoma, whereas for other smoking-related cancers, we generally observed positive associations with BMI.

Conclusions: The increased lung cancer risk with low BMI and high MS is unlikely due to residual confounding and within-person variability in smoking. However, similar results for other cancers strongly related to smoking suggest a remaining, unknown, effect of smoking.

Impact: Extensive smoking-adjustments may not capture all the effects of smoking on the relationship between obesity-related factors and risk of smoking-related cancers.

Introduction

Body mass index (BMI), a surrogate measure of obesity, has been related to higher risks of many cancer forms with some of the strongest associations found for smoking-related cancers, especially esophageal (adenocarcinoma), renal cell, and liver cancer (1–3). In contrast, a consistent inverse association has been reported for lung cancer (1–5). As smoking is strongly related to both lung cancer and lower body weight (6, 7), the inverse association has been proposed to be caused by residual confounding by insufficient adjustment for smoking (3, 8). Mendelian randomization studies, which under certain assumptions estimate causal associations (9), have not supported the inverse association with lung cancer (10–12), and several large observational studies showed no association among nonsmokers (3, 5, 13). However, some studies did show an inverse association among nonsmokers (14), or among smokers even after accounting for detailed smoking information (4, 5). Therefore, as alternative explanation for the inverse relationship between BMI and lung cancer, Renehan and colleagues suggested larger measurement error of smoking than of BMI (8). To our knowledge, this has not yet been investigated.

In contrast to BMI, waist circumference has been positively related to lung cancer risk (4, 15). A large prospective study by Yu and colleagues showed the highest lung cancer risk for low BMI and high waist circumference combined (4). This phenotype was associated with heavy smoking, but it was suggested that central obesity with lower muscle mass, and therefore retained BMI, and more metabolic aberrations potentially associated with lung cancer, could underlie these findings (4, 15). Investigating BMI and metabolic aberrations jointly, with extensive control for smoking habits, could clarify whether the association between BMI and lung cancer is dependent on the presence of metabolic aberrations, and whether the increased lung cancer risk with low BMI could potentially be reflective of a sarcopenic phenotype with metabolic aberrations.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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In this study, we investigated the association between BMI and its combination with a metabolic score (MS) comprising mid-blood pressure and circulating triglycerides and glucose, with lung cancer and other smoking-related cancers. By leveraging serial measurements on BMI and smoking information, we corrected for within-person variability (including measurement-errors and short- and long-term within-person variability) (16). Our aim was to determine how metabolic aberrations, residual confounding and within-person variability in smoking influence associations between BMI and lung cancer and other smoking-related cancers.

Materials and Methods

Population

We focused our study on participants from Me-Can 2.0, constituting six population-based cohorts [Oslo study I, Norwegian Counties Study, Age 40-Programme, Västerbotten Intervention Project, Malmö Preventive Project, and Vorarlberg Health Monitoring and Prevention Programme (VHM&PP)], from Norway, Sweden, and Austria. Data were available from 843,531 individuals with 1,557,855 serial health examinations, collected during 1972 to 2014. Me-Can 2.0 is a continuation of Me-Can 1.0 that has been previously described in detail (17). Compared with Me-Can 1.0 (publications in 2009–2015), Me-Can 2.0 does not include Cohort of Norway, but it includes the full Oslo I, Norwegian Counties Study and 40-year programme, and additional individuals and observations in the Västerbotten Intervention Project from 2006 to 2014 and in the VHM&PP from 2003 to 2005. Measurement methods of anthropometrics and metabolic factors have been previously described (17). However, in the Västerbotten Intervention Project, the measurements for blood pressure and triglycerides changed on Sept 1, 2009. Before that date, blood pressure was measured in supine position, and was thereafter measured in sitting position. Serum triglycerides were measured on a Reflotron bench-top analyzer at the examining health care center before Sept 1, 2009, and were thereafter measured at the Clinical Chemistry department at the nearest hospital using standard enzymatic methods. Formula for transformation of blood pressure and triglyceride levels measured before versus after Sept 1, 2009 have been calculated (n individuals = 838 for triglycerides, and 648 for blood pressure), and these were applied in the present study. Triglyceride levels measured on Sept 1, 2009 onwards were converted to old measurement levels by: $0.177 + (0.932 \times \text{triglyceride level})$. Formula for blood pressure were age- and sex-specific (18).

Data on smoking status were included in Me-Can, and further information on tobacco smoking, including frequency and number of years smoking, were added to the Me-Can 2.0 database. In the Norwegian and Swedish cohorts, smoking information was retrieved from questionnaires. In the VHM&PP, smoking habits were requested orally by the physician performing the health examination, but the recording did not distinguish between missing information and nonsmoker status. This likely led to a weaker association between baseline smoking and lung cancer risk in the VHM&PP than in other cohorts (Supplementary Fig. S1). Consequently, participants in the VHM&PP cohort were excluded from subgroup analyses of nonsmokers.

The study was conducted in accordance with the Declaration of Helsinki, and was approved by ethical committees in each country.

Follow-up

Linkages of participants were performed with the respective national or regional (VHM&PP) cancer register, the national cause of death register, and the national total population register (Norway and Sweden) for information on cancer diagnoses, deaths, and emigration, including the year 2012 in Norway and 2014 in Sweden and Austria.

Categorization of smoking-related cancers

Smoking-related cancers were defined as those listed by the International Agency for Research on Cancer (monograph 83 in 2004; ref 19 and additions in 2012; ref 20) as probably caused by smoking and with a relative risk of smokers compared with nonsmokers of at least 1.2. *In situ* cancers were excluded except urothelial carcinoma *in situ*, which were included because they frequently progress to higher stage (21). We used International Classification of Diseases (ICD) codes to categorize cancers by topography (Supplementary Table S1), and morphology or histology codes were used if necessary for further subgrouping. In our population, the hazard ratio (HR) of cancer in smokers compared with nonsmokers was 7.4 or higher for cancers of the lung, larynx, and esophageal squamous cell carcinoma (SCC) and 3.4 or lower for all other cancers.

Selection criteria

To be eligible for the study, participants had to have information on BMI, smoking status and pack-years, and no baseline history of a malignant cancer [excluding basalioma and *in situ* tumors, but including blood cancers (ICD-7 200–209) of uncertain or unknown behavior], resulting in 778,828 individuals with 1,264,393 serial measurements. For the combined analysis of BMI and metabolic score, we further analyzed a subset of individuals with additional information on blood pressure, triglycerides, and glucose (488,659 individuals with 876,618 serial measurements).

Our aim was to determine how metabolic aberrations, residual confounding, and within-person variability in smoking influence associations between BMI and lung cancer and other smoking-related cancers.

Statistical analysis

The specific analyses performed to investigate how (i) metabolic aberrations, (ii) residual confounding and (iii) within-person variability in smoking influence associations between BMI and lung cancer and other smoking-related cancers are outlined in Supplementary Table S2, and are described in further detail below.

HR of cancer by BMI level was calculated using Cox regression with follow-up from baseline until the first cancer diagnosis, emigration, death, or end of follow-up- whichever came first. We used attained age as time-scale, stratified by cohort, sex and birth decade, with adjustment for baseline age, fasting time, smoking status (nonsmoker, smoker, and ex-smoker) and pack-years. There was no evidence of violation of the proportional hazards assumption, which was tested by including time interactions with the exposures. To assess possible reverse causation, we repeated the analyses excluding the first 5 to 20 years of follow-up. We assessed between study heterogeneity by performing analyses separately by cohort and with the I^2 statistic (22). We investigated effect modification by sex and baseline smoking status with Wald tests for interaction. To further visualise BMI-smoking interactions, we calculated associations between categories of BMI (<20, 20–22.49, 22.5–24.99, 25–27.49,

27.5–29.99, ≥30 kg/m^2) and smoking (status/pack-years) jointly in relation to cancer risk.

To correct for within-person variability in BMI and smoking status and pack-years, we estimated long-term average levels ("usual levels") using multi-level regression calibration and information from up to 600,201 serial assessments in up to 230,454 individuals. This was achieved using linear mixed effects models, by regressing repeat measurements on baseline measures, adjusted for duration of follow-up and baseline levels of age, sex, fasting time (as appropriate), and for baseline levels of BMI, smoking status and pack-years (when not the independent variable) with random effects for cohort and repeat measurement (16, 23). The regression dilution ratio (RDR), i.e., the calibration slope, which measures the overall extent of within-person variability, was extracted from the calibration model. Further analyses allowing for age-dependent RDR corrections produced similar results and are not reported. Estimated usual levels of BMI, smoking status and pack-years were used directly in the Cox regression models to calculate corrected HRs.

We assessed the shape of the association with lung cancer by calculating HRs within tenths of BMI and plotted them against mean usual (and baseline) levels within each group. We estimated 95% confidence intervals (CI) for each group (including the reference group) that corresponded to the amount of information underlying each group (24, 25). For each cancer outcome we determined the best fitting 1st or 2nd order fractional polynomial (FP) to describe the relationship with BMI at baseline (using a 1% significance level as evidence for a 2nd order FP over a 1st order FP) using Cox regression models stratified by sex, cohort, and birth decade (26). We also analyzed BMI assuming a linear relationship with cancer, expressing results per SD in BMI levels.

We further investigated the associations with cancer risk for BMI combined with a MS comprising mid-blood pressure [(systolic+ diastolic blood pressure)/2], triglycerides, and glucose. Each metabolic factor was standardized by cohort, sex, and fasting time (except mid-blood pressure), before being summed up into a metabolic score. Four categories were analyzed with the division of BMI at 25 kg/m^2 and the MS at the median value, using high BMI with low MS as reference to mimic the analysis of BMI and waist circumference by Yu *et al*[4]. Because statistical power was reduced in this analysis due to the smaller dataset with complete information on metabolic factors and the division of the exposure into four categories, we combined cancers as relevant based on our findings for BMI.

Analyses using Stata (version 14) involved 2-sided *p*-values and 95% CIs.

Results

Among the 778,828 participants in the study, the mean age at baseline was 44 years (SD = 9) and 382,853 (49%) were men (**Table 1**). At baseline, 357,146 (46%) participants were categorized as nonsmokers, 182,858 (23%) as ex-smokers, 181,244 (23%) as light-moderate–smokers (defined as <20 pack-years), and 57,579 (7%) as heavy smokers (defined as ≥20 pack-years). On average, ex-smokers had higher BMI levels whereas heavy smokers had higher levels of metabolic factors. A larger proportion of smokers than nonsmokers and ex-smokers had a BMI below 25 kg/m^2 with high MS.

Participants with repeated measurements were younger and were more likely to be nonsmokers than those without repeated measurements (Supplementary Table S3). The RDR was 0.95 (95% CI, 0.94–0.95) for BMI and 0.43 (0.37–0.49), 0.23 (0.32–0.44), and 0.51 (0.46–0.57) for smoking, ex-smoking and pack-years, respectively (Supplementary Fig. S2).

During a median follow-up of 20 years, 20,242 individuals were diagnosed with a smoking-related cancer, of which 6,735 (33%) were lung cancer. In relation to lung cancer risk, there was an inverse and curvilinear association with BMI, with the lowest risk for those with a BMI around 30 kg/m^2 (**Fig. 1**). These associations attenuated but persisted after adjustment for smoking, and did not further attenuate after correction for within-person variability in smoking. Exclusion of the first 5 to 20 years of follow-up did not change the results. The HR of lung cancer per SD higher BMI was 0.87 (95% CI, 0.85–0.89) in fully adjusted models.

Associations between BMI and other smoking-related cancers than lung cancer generally attenuated after adjustment for smoking and correction for within-person variability, but to a lesser degree than seen for lung cancer. In fully-adjusted FP analyses of BMI and specific smoking-related cancers, BMI was inversely associated with cancers of the lung, larynx, esophageal SCC, pharynx, and oral cavity, i.e., cancers that are most strongly related to smoking and head and neck cancers, and was positively associated with cancer of the liver, pancreas, esophageal adenocarcinoma, stomach-cardia, cervix uteri SCC, renal cell carcinoma, and myeloid leukemia (Supplementary Fig. S3).

Baseline smoking status modified the associations between BMI and several smoking-related cancers (**Fig. 2**). For all smoking-related cancers combined, there was a positive association with BMI among nonsmokers [HR per SD higher BMI, 1.14 (95% CI, 1.10–1.18)], but an inverse association among smokers [HR 0.94 (0.92–0.96), p for interaction < 0.001]. Inverse associations were observed for lung cancer, head and neck cancer, and esophageal SCC and were restricted to smokers. Interaction analyses of BMI categories and smoking in greater detail showed interaction for head and neck cancers and esophageal SCC combined (P for interaction < 0.001), but not for lung cancer (P for interaction = 0.09; **Fig. 3**). To explore whether the interaction was general for body size, we repeated the analysis for height, but found no interaction with smoking (Supplementary Fig. S4).

The relationships between BMI and risk of cancers were generally similar for men and women, except for cancers of the stomach noncardia, large cell lung cancer, and urinary bladder (Supplementary Fig. S5).

A BMI below 25 kg/m^2 combined with a high metabolic score was associated with an increased lung cancer risk compared with a BMI above 25 kg/m^2 and a low metabolic score [HR 1.52 (95% CI, 1.44–1.60); **Fig. 4**]. Cancers of the head and neck and esophageal SCC combined, but not other cancers combined, showed a similar pattern of association for the metabolic score by BMI level to that observed for lung cancer. The pattern of association for lung cancer was similar for men and women and did not change after exclusion of the first 5 to 20 years of follow-up (Supplementary Fig. S6). Among nonsmokers, however, the association was weak and non-significant after excluding the VHM&PP [HR 1.21 (95% CI, 0.91–1.63)].

Discussion

The main finding of this pooled cohort study confirms an inverse and curvilinear association between BMI and lung cancer risk, which persisted after extensive adjustment for smoking information and correction for within-person variability in smoking, and after

Table 1. Baseline characteristics of participants in the Metabolic syndrome and Cancer project 2.0, overall and by categories of smoking.

Characteristics	Overall (n = 778,828)	Nonsmoker (n = 357,147)	Ex-smoker (n = 182,858)	Smoker, <20 pack-years (n = 181,244)	Smoker, ≥20 pack-years (n = 57,579)
Cohort, *n* (%)					
VHM&PP	161,232 (21)	129,949 (36)	0 (0)	23,246 (13)	7,947 (14)
VIP	94,205 (12)	60,328 (17)	19,366 (12)	10,062 (6)	4,449 (8)
MPP	20,971 (3)	11,634 (3)	0 (0)	4,005 (2)	5,332 (9)
40-y	394,722 (51)	119,435 (34)	142,219 (78)	102,067 (56)	31,001 (54)
Oslo	17,039 (2)	3,576 (1)	4,227 (2)	6,724 (4)	2,512 (4)
NCS	90,659 (12)	32,225 (9)	16,956 (9)	35,140 (19)	6,338 (11)
Age, mean (SD) years	44 (9)	44 (11)	46 (6)	42 (6)	47 (7)
Male, *n* (%)	382,853 (49)	159,024 (44)	96,453 (53)	87,485 (48)	39,891 (69)
Decade of birth, *n* (%)					
1890–1930	62,034 (8)	32,623 (9)	9,520 (5)	12,074 (7)	7,817 (14)
1930–1950	299,957 (39)	138,251 (39)	52,400 (29)	80,256 (44)	29,050 (50)
1950–1970	383,530 (49)	159,450 (44)	119,783 (66)	83,807 (46)	20,490 (36)
1970–1990	33,307 (4)	26,823 (8)	1,155 (1)	5,107 (3)	222 (<1)
BMI, mean (SD) kg/m^2	25.0 (3.9)	25.0 (4.1)	25.6 (3.7)	24.4 (3.7)	25.2 (3.8)
BMI category, kg/m^2, *n* (%)					
<20	47,069 (6)	22,971 (6)	5,782 (3)	15,029 (8)	3,288 (6)
20–22.49	200,814 (26)	91,384 (26)	40,082 (22)	55,301 (31)	14,047 (24)
22.5–24.99	181,630 (23)	80,799 (23)	44,327 (24)	43,099 (24)	13,405 (23)
25–27.49	178,351 (23)	79,265 (22)	47,839 (26)	37,553 (21)	13,694 (24)
27.5–29.99	92,765 (12)	42,945 (12)	25,237 (14)	17,198 (9)	7,385 (13)
≥30	78,199 (10)	39,783 (11)	19,591 (11)	13,064 (7)	5,761 (10)
MS, mean (SD)	−0.05 (1.99)	−0.09 (1.99)	−0.01 (1.92)	−0.16 (1.93)	0.36 (2.23)
BMI-MS category[a], *n* (%)					
BMI < 25 kg/m^2-high MS	93,941 (19)	45,061 (18)	21,957 (19)	20,054 (23)	6,869 (24)
BMI < 25 kg/m^2-low MS	165,776 (34)	89,631 (35)	34,251 (30)	34,014 (38)	7,880 (27)
BMI ≥ 25 kg/m^2-high MS	147,523 (31)	77,108 (31)	38,158 (33)	22,249 (25)	10,008 (35)
BMI ≥ 25 kg/m^2-low MS	77,977 (16)	40,104 (16)	21,116 (18)	12,703 (14)	4,054 (14)
Mid-blood pressure, mean (SD) mmHg[b]	105 (13)	106 (13)	107 (12)	104 (12)	107 (13)
Serum triglycerides, mean (SD) mmol/L[b,c]	1.4 (1.0)	1.3 (1.0)	1.5 (0.9)	1.5 (1.1)	1.7 (1.3)
Serum glucose, mean (SD) mmol/L[b,d]	5.4 (1.2)	5.4 (1.2)	5.4 (1.0)	5.3 (1.0)	5.6 (1.3)
Diabetes[e], *n* (%)	6,007 (1)	2,262 (1)	1,921 (1)	1,205 (1)	619 (1)

Abbreviations: MPP, Malmö Preventive Project; NCS, Norwegian Counties Study; Oslo, Oslo study I; VIP, Västerbotten Intervention Project; 40-y, Age 40-Programme.

[a]The MS is a sum of z scores for mid-blood pressure, triglycerides, and glucose, each standardized by cohort, sex, and fasting time (except mid-blood pressure), calculated for 485,217 (62%) individuals. The median was used as cut-point for low/high MS.

[b]Mean and SD calculated separately by cohort and then combined using random effects meta-analysis.

[c]Based on 286,249 (37%) individuals with eight hours or more of fasting.

[d]Based on 260,038 (33%) individuals with eight hours or more of fasting and with glucose measured in serum or plasma (excludes the MPP where glucose was measured in whole blood).

[e]Self-reported diabetes. Excludes the VHM&PP that lacked the information.

excluding initial years of follow-up. Further, we found diverse associations for smokers and nonsmokers such that higher BMI among nonsmokers and lower BMI among smokers were associated with higher risks of combined smoking-related cancers. This inverse association among smokers was found for cancers of the lung, head and neck, and esophageal SCC. The highest risk of these cancers, but not of other cancers combined, was observed for low BMI combined with a high metabolic score.

BMI has been consistently shown to be inversely associated with lung cancer risk (1–5), but the lack of a biological explanation and a weak or no association among nonsmokers have led some to suspect bias from residual confounding in smoking. However, in two large prospective studies (4, 5), the inverse association among smokers persisted after adjustment for smoking in detail, which questions the possibility of confounding bias due to insufficient adjustment for smoking. In 2012, Renehan and colleagues showed with data simulation that greater measurement error of smoking than of BMI might explain the association (8). However, despite correction for the substantial within-person variability in smoking information in our study, the curvilinear and inverse association between BMI and lung cancer risk persisted, probably due to a weak relationship between BMI and smoking. Additionally, consistent with other studies (4, 5), excluding up to 20 years of follow-up showed no evidence of reverse causation in the observed associations.

In contrast to BMI, waist circumference has been positively related to the risk of lung cancer (4, 15). Yu and colleagues observed the highest risk for low BMI combined with high waist circumference (4), which in our study was observed for the combination of low BMI and a high metabolic score. A sarcopenic phenotype of central obesity with lower muscle mass, but with more metabolic aberrations, could explain this BMI-waist controversy (4, 15). However, low BMI combined with high waist circumference in Yu et al, or with high metabolic score in

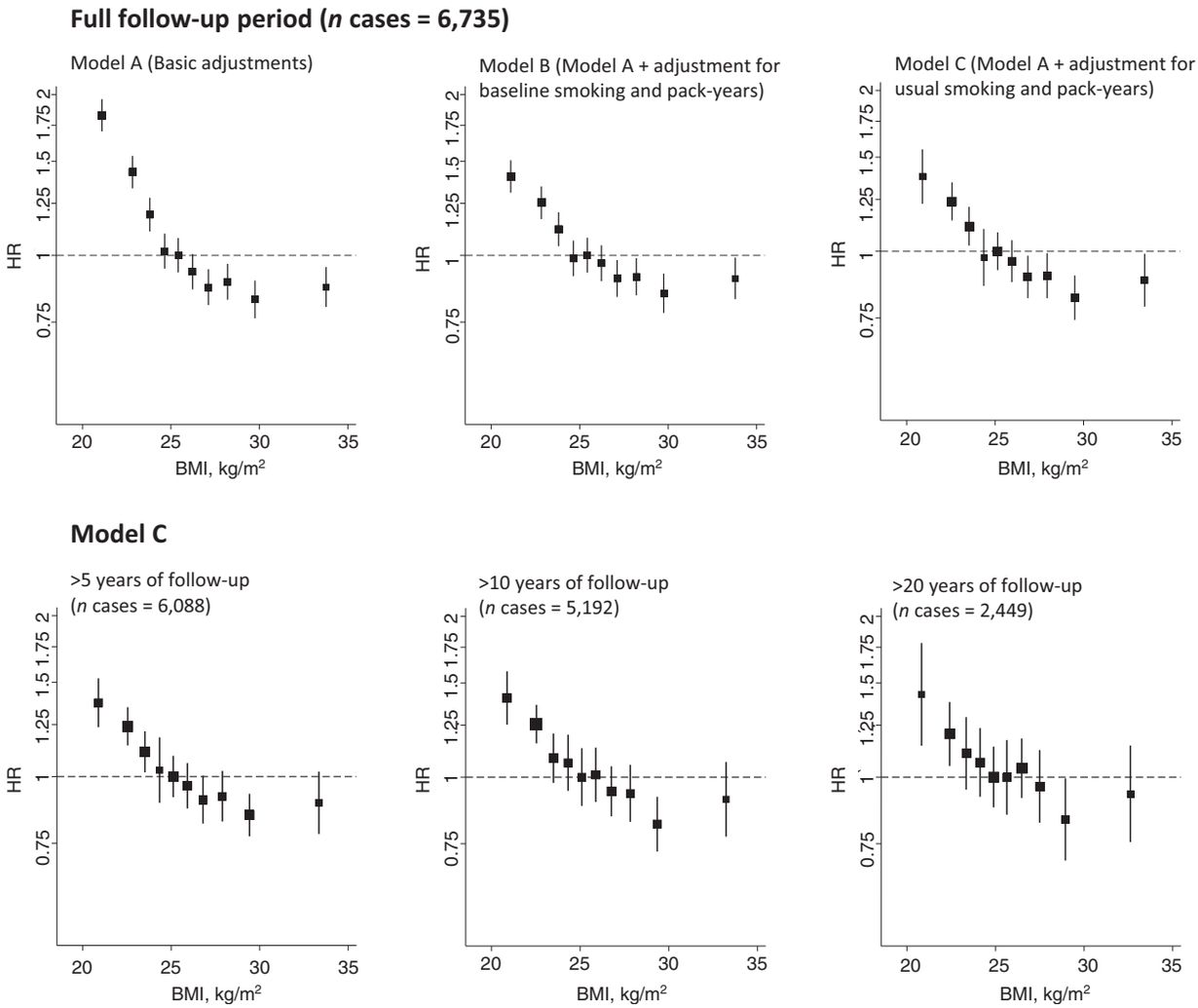

Figure 1.
HR (95% CI) of lung cancer by usual BMI levels in deciles (*n* participants = 778,828) by use of different models and follow-up periods. Model A shows HRs from Cox regression with attained age as time-scale, stratified by cohort, sex, and birth decade, and adjusted for baseline age and fasting time. The fifth decile is the referent group.

our study, were associated with smoking. Furthermore, the strikingly similar findings in our study for BMI, with and without the metabolic score, in relation to lung cancer and other cancers strongly related to smoking and of organs directly smoke-exposed at inhalation, i.e., cancers of the head and neck and esophageal SCC, suggest that smoking may be at play even after extensive control for it. Moreover, in joint analysis of BMI and smoking, cancers of the head and neck and esophageal SCC combined were more strongly related to smoking for each lower BMI category, which is supported by a study of head and neck cancers, larger than ours, which additionally adjusted for alcohol intake (27). We speculated this to reflect higher per-cigarette concentration of tobacco carcinogens in persons of small than large body and organ size, which could have a larger impact on organs directly exposed to smoke at inhalation than on more distant organs. As these organs typically grow lengthwise, such theory would be supported by a similar interaction between height and smoking, which we did not observe, but was found in the aforementioned study (27) and in a pooled analysis of case-control studies of head and neck cancers (28). We conclude that it is difficult to find an explanation that accommodates both a differential association with lung cancer risk between waist circumference and BMI, and the uniform results in our study for the cancers strongly related to smoking and head and neck cancers.

Our study's access to individual-participant data from large cohort studies with linkage to high-quality cancer registers (29–31), and extensive follow-up of study participants enabled us to investigate rarer cancers, cancer subtypes, and nonsmokers separately. The simultaneous investigation of lung cancer with other cancers further clarified the understanding of this common cancer. To correct for misclassification and within-person variability in smoking information and BMI, we also used extensive information on serial assessments, from which we could refute the hypothesis of large measurement error of smoking influencing the results of BMI and lung cancer (8). To limit and assess reverse causality, we focused on

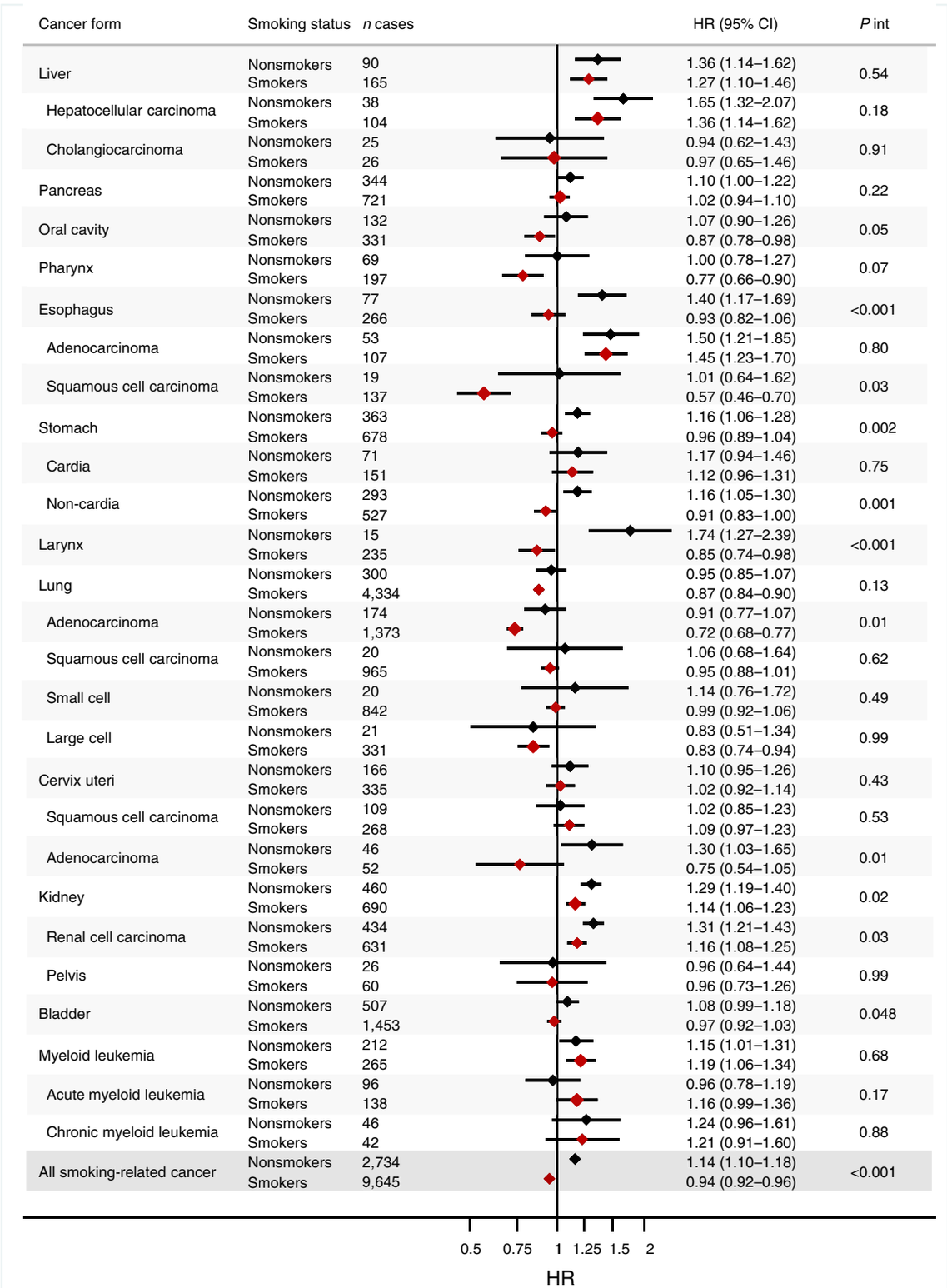

Figure 2.

HR (95% CI) of cancer per SD of usual BMI (3.9 kg/m^2) among nonsmokers (n = 227,198) and smokers (n = 207,630), respectively. The analysis of nonsmokers excludes the VHM&PP. HRs were calculated using Cox regression with attained age as time-scale, stratified by cohort, sex, and birth decade, and adjusted for baseline age, fasting time, usual smoking status, and usual pack-years. *P* int denotes the *P* value for interaction between BMI and smoking status (smoking vs. nonsmoking).

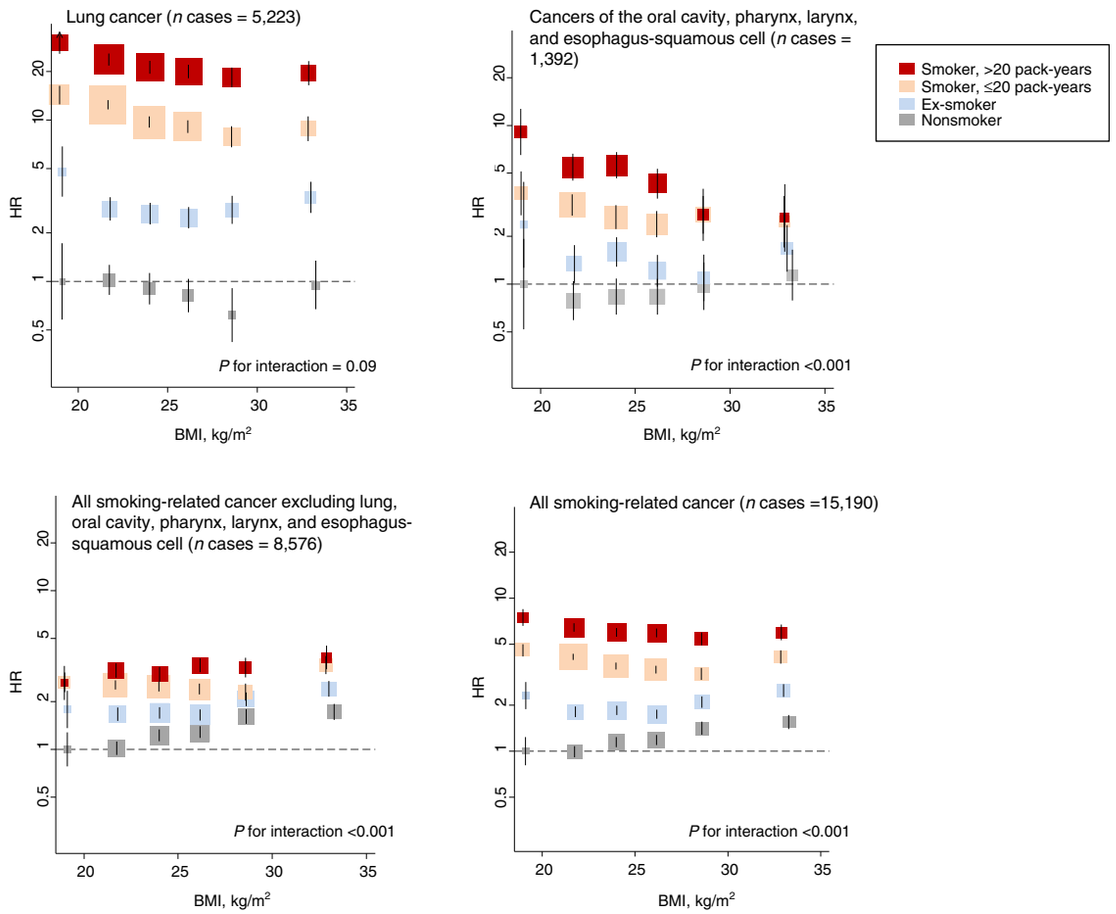

Figure 3.

HR (95% CI) of cancer across categories of baseline BMI in subgroups of smoking (*n* participants = 617,596), excluding VH&PP. HRs were calculated using Cox regression with attained age as time-scale, stratified by cohort, sex, and birth decade, and adjusted for baseline age, fasting status, usual smoking status, and usual pack-years. Nonsmokers with BMI below 20 kg/m^2 are the referent group. *P* for interaction denotes the *P* value for the difference in linear trends of HR across BMI level between smoking groups.

individuals without baseline cancer and investigated omittance of the initial periods of follow-up.

Nevertheless, our study has some limitations. We lacked data on potentially important confounders such as socioeconomic factors, physical activity, diet, alcohol intake, medications, and specific infections, such as helicobacter pylori in relation to stomach cancer and human papillomavirus in cervix cancer. Self-reported smoking data are prone to bias and are challenging to harmonize across studies that used varying methods to record such data. We made substantial efforts to validate the smoking data, which led to exclusion of one cohort with ambiguous data on nonsmokers. We have not accounted for competing risks and although it is possible that our results are influenced by censoring high-risk individuals with premature deaths from non-cancer causes, this does not explain the differential associations across the smoking-related cancers. Because some individuals who reduced their BMI due to health complications are included in our analysis, we cannot fully exclude the effects of reverse causation. Therefore, additional study designs such as nonlinear Mendelian randomization studies will be important to establish causal associations with particular emphasis on effect modification by smoking (9). So far, Mendelian randomization studies have refuted an inverse linear association between BMI and lung cancer risk (10–12) and have supported a positive association between BMI and renal cell (32) and pancreatic cancer (33, 34).

In conclusion, our study shows inverse and curvilinear associations between BMI and lung cancer risk despite extensive adjustment and correction for within-person variability in smoking habits. The highest lung cancer risk was observed for low BMI and high metabolic score combined. However, these associations were more evident among smokers, and similar associations were observed for cancers of the head and neck and esophageal SCC, but not for cancers less strongly related to smoking. From our investigation, we conclude that (i) completely controlling for the effect of smoking on cancers of the lung, head and neck, and esophageal SCC in an observational analysis appears difficult even with detailed and repeat smoking information, (ii) the remaining influence of smoking on the association between obesity, metabolic

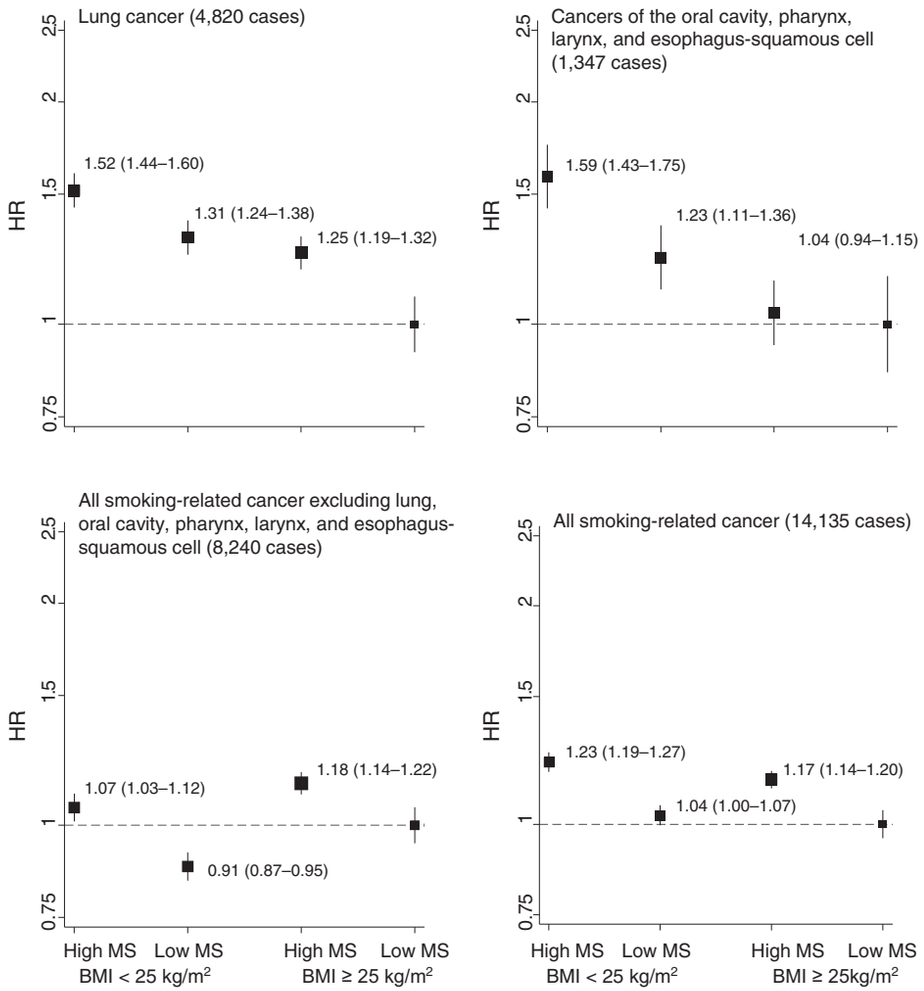

Figure 4.

HR (95% CI) of cancer by level of BMI and MS combined (*n* participants = 503,167). The MS comprises mid-blood pressure, serum triglycerides and glucose, each standardized by cohort, sex, and fasting time (except mid-blood pressure) before being summed up and divided at the median (high/low MS). HRs were calculated using Cox regression with attained age as time-scale, stratified by cohort, sex, and birth decade, and adjusted for baseline age, usual smoking status, and usual pack-years. BMI ≥ 25 kg/m^2 with low MS is the referent group.

factors, and these cancer forms remains unclear, and (iii) with the available methodology to date, these associations may be best investigated by Mendelian randomization, ideally incorporating non-linear associations.

Authors' Disclosures

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Authors' Contributions

A.M. Wood: Conceptualization, data curation, formal analysis, investigation, writing–original draft, writing–review and editing. **H. Jonsson:** Investigation, writing–review and editing. **G. Nagel:** Data curation, investigation, writing–review and editing. **C. Häggström:** Investigation, writing–review and editing. **J. Manjer:** Investigation, writing–review and editing. **H. Ulmer:** Investigation, writing–review and editing. **A. Engeland:** Data curation, investigation, writing–review and editing. **E. Zitt:** Investigation, writing–review and editing. **S.H.J. Jochems:** Investigation, writing–review and editing. **S. Ghaderi:** Investigation, writing–review and editing. **P. Stattin:** Investigation, writing–review and editing. **T. Bjørge:** Data curation, investigation, writing–review and editing. **T. Stocks:** Conceptualization, data curation, funding acquisition, investigation, writing–original draft, writing–review and editing.

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