Received: 16 November 2020 | Revised: 25 January 2021 | Accepted: 8 February 2021

DOI: 10.1002/ijc.33530

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Metabolic factors and the risk of small intestine cancers: Pooled study of 800 000 individuals in the metabolic syndrome and cancer project

Gabriele Nagel[1,2] | Tone Bjørge[3,4] | Andrea Jaensch[1] | Raphael S. Peter[1] | Christel Häggström[5,6] | Alois Lang[2] | Anders Engeland[3,7] | Stanley Teleka[8] | Karin Jirström[8] | David Lindquist[9] | Pär Stattin[6] | Hanno Ulmer[10] | Hans Concin[2] | Tanja Stocks[8]

[1]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

[2]Agency for Preventive and Social Medicine (aks), Bregenz, Austria

[3]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[4]Cancer Registry of Norway, Oslo, Norway

[5]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[6]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

[7]Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway

[8]Department of Clinical Sciences Lund, Lund University, Lund, Sweden

[9]Department of Clinical Sciences, Umeå University, Umeå, Sweden

[10]Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria

Correspondence
Gabriele Nagel, Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, 89081 Ulm, Germany.
Email: gabriele.nagel@uni-ulm.de

Abstract

To explore the largely unknown etiology of small intestine cancer, we examined metabolic factors and risk of small intestine cancer overall and by subtypes. Among 404 220 women and 403 265 men in six European cohorts, we applied Cox regression with adjustment for smoking and body mass index (BMI), to calculate sex-specific hazard ratios (HRs) of small intestine cancer by levels of BMI, mean arterial pressure (MAP) and plasma total cholesterol, triglycerides and glucose. We also calculated HRs for these factors combined (metabolic score; MetS) and used Wald test statistics to investigate pairwise interactions between metabolic factors on risk. We also performed analyses separately per subtype (neuroendocrine tumors [NETs] and adenocarcinomas). During a median follow-up of 16.9 years, 144 women and 195 men were diagnosed with small intestine cancer, including 184 NETs and 99 adenocarcinomas. Among men, no main associations or interactions between metabolic factors were observed in relation to the risk of small intestine cancer. Among women, triglycerides were positively and linearly associated with risk (HR per standard deviation [SD]: 1.23, 95% confidence interval [CI]: 1.04-1.46), and a positive association was also observed for the MetS (HR per SD: 1.25, 95% CI: 1.02-1.52). Positive interactions were observed among women between triglycerides and cholesterol (P = .0005), and between MAP and glucose (P = .009), on risk. Glucose was positively associated with adenocarcinomas among women. This large, prospective study suggests that elevated triglycerides, and metabolic factors in interaction, confer an increased risk of small intestine cancer among women, but not among men.

Abbreviations: 40-y, The Age 40-program; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases-Oncology; log, logarithms naturalis; MAP, mean arterial pressure; Me-Can, Metabolic syndrome and Cancer project; MetS, metabolic score; MPP, Malmö Preventive Project; NCS, The Norwegian County Study; Oslo, The Oslo study I cohort; siNETs, small intestine neuroendocrine tumors; VHM&PP, The Vorarlberg Health Monitoring and Prevention Program; VIP, The Västerbotten Intervention Project.

KEYWORDS
Mecan, metabolic factors, risk factors, small intestine cancer

1 | INTRODUCTION

Rare cancers make up approximately 20% to 25% of all incident cancers,[1,2] but the incidence of each specific cancer is very low. Small intestine cancer is one such cancer, for which the incidence rates has increased during the past decades in high-income countries.[3] However, the type of tumors primarily driving the increase varies between countries. In the United States, the increase has primarily been seen for small intestine neuroendocrine tumors (siNETs) (previously carcinoid tumors),[4] whereas in the Netherlands there has been an increase primarily of adenocarcinomas.[5] Moreover, cancer of the small intestine is often detected at a late stage with a poor prognosis, and the 5-year overall survival was only 48% to 65% in 2012 to 2016 in the Nordic countries.[6] This urges for more knowledge about the causes of small intestine cancer, which is currently very limited. There is, however, some evidence that genetic and lifestyle factors may be related to risk.[3]

Obesity and related metabolic factors have been associated with increased risks of many cancer forms.[7-10] About 4% to 6% of all cancers worldwide, and 13% of obesity-related cancers in adults, have been attributed to high body mass index (BMI, kg/m^2).[11] In relation to cancer of the small intestine, one large prospective study with 1162 incident cases, showed an increased risk for overweight and obesity among men, but not among women.[12] Other prospective studies have been much smaller ($n_{events} \leq 237$)[13-18] and in a recent umbrella review of obesity and cancer risk, evidence was considered insufficient to make any conclusions for cancer of the small intestine.[19] Additionally, cardiometabolic risk factors, summarized as the metabolic syndrome, could be independent risk factors or on the pathway between obesity and small intestine cancer. During the past years evidence was accumulating for an association between cancer and metabolic syndrome; a constellation of obesity and insulin resistance, hypertension and dyslipidemia,.[9,10] However, there are virtually no studies on the relationship between these factors and cancer of the small intestine altogether, or in histopathological subtypes.

The aim of our study was to investigate single metabolic factors and a combined metabolic score (MetS) in relation to the risk of small intestine cancer overall and separately for adenocarcinoma and siNET in a large pooled European cohort study with long follow-up.

What's new?

Little is known about the etiology of small intestine cancer. In this study, there was little evidence for an association of body mass index with small intestine cancer. However, strong positive associations were found for triglycerides and a metabolic score in women, and glucose was further positively associated with adenocarcinoma of the small intestine in women. A healthy lifestyle preventing metabolic aberrations may prevent small intestine cancer in women. Cancers of the small intestine are often detected at a late stage with a poor prognosis. Thus it would be helpful to understand etiological factors that lead to these cancers. In this large, prospective study, the authors found strong positive associations between small intestine cancer and triglycerides, glucose, or metabolic scores—but only among women. BMI had little effect in either sex. These results indicate that lifestyle changes that reduce metabolic aberrations may help reduce the risk of small intestine cancer in women.

2 | MATERIALS AND METHODS

2.1 | Study population

The Metabolic syndrome and Cancer project (Me-Can) 2.0 is an expansion of Me-Can 1.0, which has previously been described in detail.[20] Me-Can 2.0 pools data from six cohorts in Austria (Vorarlberg Health Monitoring and Prevention Program [VHM&PP], 1985-2005), Norway (Norwegian Counties Study, 1974-1988; Age 40 Program [40y], 1985-1999; Oslo Study I [Oslo I], 1972-1973) and Sweden (Västerbotten Intervention Project [VIP], 1985-ongoing; Malmö Preventive Project [MPP], 1974-1992). Compared to Me-Can 1.0, on which Me-Can publications in 2009 to 2015 are based, Me-Can 2.0 includes one less cohort (Cohort of Norway) but additional individuals and health observations in the VIP between the years 2006 and 2014, and in the VHM&PP between the years 2003 and 2005. All participants have undergone one or more health examination(s), which included measurements of height, weight, blood pressure, and plasma concentrations of glucose, total cholesterol and triglycerides, as previously described in detail.[20,21] Data on smoking status were collected by questionnaires, except in the VHM&PP, where data was recorded during interview.

The selection of the study population is shown in Figure S1. Out of 843 531 individuals with 1 557 855 health examinations (observations) in Me-Can 2.0, we excluded 36 046 individuals (141 227 observations), with the majority of exclusions (133 031 observations, 94%) performed due to a prevalent cancer at the time of health examination, a nonfasting status with unknown fasting time in the VHM&PP before the year 1988, or missing fasting status. Among the remaining 807 485 individuals (1 416 628 observations), we selected the first observation for our study.

2.2 | Exposures

We calculated BMI as weight (kg)/height^2 (m) and mean arterial pressure (MAP) as (systolic blood pressure + 2 × diastolic blood

pressure)/3. These factors, total cholesterol and log-transformed values of triglycerides and glucose, were divided into quartiles and were also standardized by (individual level-mean level)/SD into z-scores with a mean value of zero and a SD of one. The creation of quartiles and z-standardization were performed separately by cohort, sex and fasting time. A MetS was constructed by standardizing the sum of component-wise z-scores, similar to previous Me-Can studies.

2.3 | Outcomes

Cancer cases and deaths were identified through linkages with national cancer and cause of death registries.[20] For identification of emigration status (except in Austria), the cohorts were linked to the respective national population register. Follow-up ended on 31 December 2012, in Norway, and on 31 December 2014, in Sweden and Austria.

Cancer cases were coded according to the International Classification of Diseases (ICD) codes. Cancers of the small intestine were defined as ICD-7 152 and ICD-10 C17. The subtype adenocarcinoma was defined as ICD-Oncology (O)-3 codes 8140, 8145, 8210, 8261, 8263, 8480, 8482 and 8490, and siNETs were defined as 8156, 8240, 8241, 8246 and 8249.[16]

2.4 | Statistical analysis

Due to a differential association by sex between BMI and the risk of small intestine cancer in the largest study to date,[12] we performed all analyses separately by sex. All Norwegian individuals included in our study were also included in Reference 12, but with shorter follow-up. Cox regression models with age as the time metric were fitted to obtain hazard ratios (HRs) with 95% confidence intervals (95% CIs) for metabolic factors in quartiles and for these factors and the MetS per

TABLE 1 Baseline characteristics of the 807 485 individuals in the study

	Men		Women	
	Cases	Total cohort	Cases	Total cohort
Individuals, N	195	403 265	144	404 220
Age at baseline, years, mean (SD)	46.4 (8.6)	43.0 (8.8)	48.0 (9.7)	42.9 (9.6)
Cohort, N (%)				
OSLO	12 (6.2%)	17 708 (4.4%)	—	—
NCS	25 (12.8%)	44 136 (10.9%)	22 (15.3%)	42 490 (10.5%)
40-y	84 (43.1%)	191 393 (47.5%)	50 (34.7%)	207 710 (51.4%)
VHM&PP	27 (13.9%)	80 957 (20.1%)	38 (26.4%)	94 023 (23.3%)
VIP	18 (9.2%)	48 941 (12.1%)	18 (12.5%)	50 373 (12.5%)
MPP	29 (14.9%)	20 130 (5.0%)	16 (11.1%)	9624 (2.4%)
Fasting time, hours, N (%)				
<8	118 (60.5%)	246 150 (61.0%)	72 (50.0%)	244 842 (60.6%)
≥8	77 (39.5%)	157 115 (39.0%)	72 (50.0%)	159 378 (39.4%)
BMI, kg/m^2, mean (SD)	25.8 (3.2)	25.6 (3.4)	24.8 (4.1)	24.6 (4.3)
MAP, mm Hg, mean (SD)	100.9 (11.5)	98.7 (11.3)	96.6 (12.7)	93.5 (12.1)
Glucose, mmol/L, median (IQR)	5.3 (4.9-5.8)	5.2 (4.7-5.8)	5.2 (4.8-5.8)	5.1 (4.6-5.6)
Cholesterol, mmol/L, mean (SD)	5.9 (1.1)	5.8 (1.2)	5.8 (1.5)	5.5 (1.1)
Triglycerides, mmol/L, median (IQR)	1.7 (1.2-2.4)	1.6 (1.1-2.3)	1.3 (0.9-1.6)	1.1 (0.8-1.6)
Smoking status, N (%)				
Never	66 (33.9%)	155 746 (38.6%)	74 (51.4%)	194 719 (48.2%)
Former	57 (29.2%)	110 945 (27.5%)	35 (24.3%)	93 892 (23.2%)
Current	72 (36.9%)	136 574 (33.9%)	35 (24.3%)	115 609 (28.6%)
Histology, N (%)				
Neuroendocrine tumors (NETs)	107 (54.9%)		77 (53.5%)	
Adenocarcinoma	52 (26.7%)		47 (32.6%)	
Other	36 (18.5%)		20 (13.9%)	

Notes: Glucose, cholesterol and triglycerides are all in mmol/L. Glucose and triglycerides are log-transformed.
Abbreviations: 40-y, The Age 40-program; BMI, body mass index (kg/m^2); MAP, mean arterial pressure = [(systolic blood pressure + diastolic blood pressure*2)/3] (mm Hg); MPP, The Malmö Preventive Project; NCS, The Norwegian County Study; Oslo, The Oslo study I cohort; VHM&PP, The Vorarlberg Health Monitoring and Prevention Program; VIP, The Västerbotten Intervention Project.

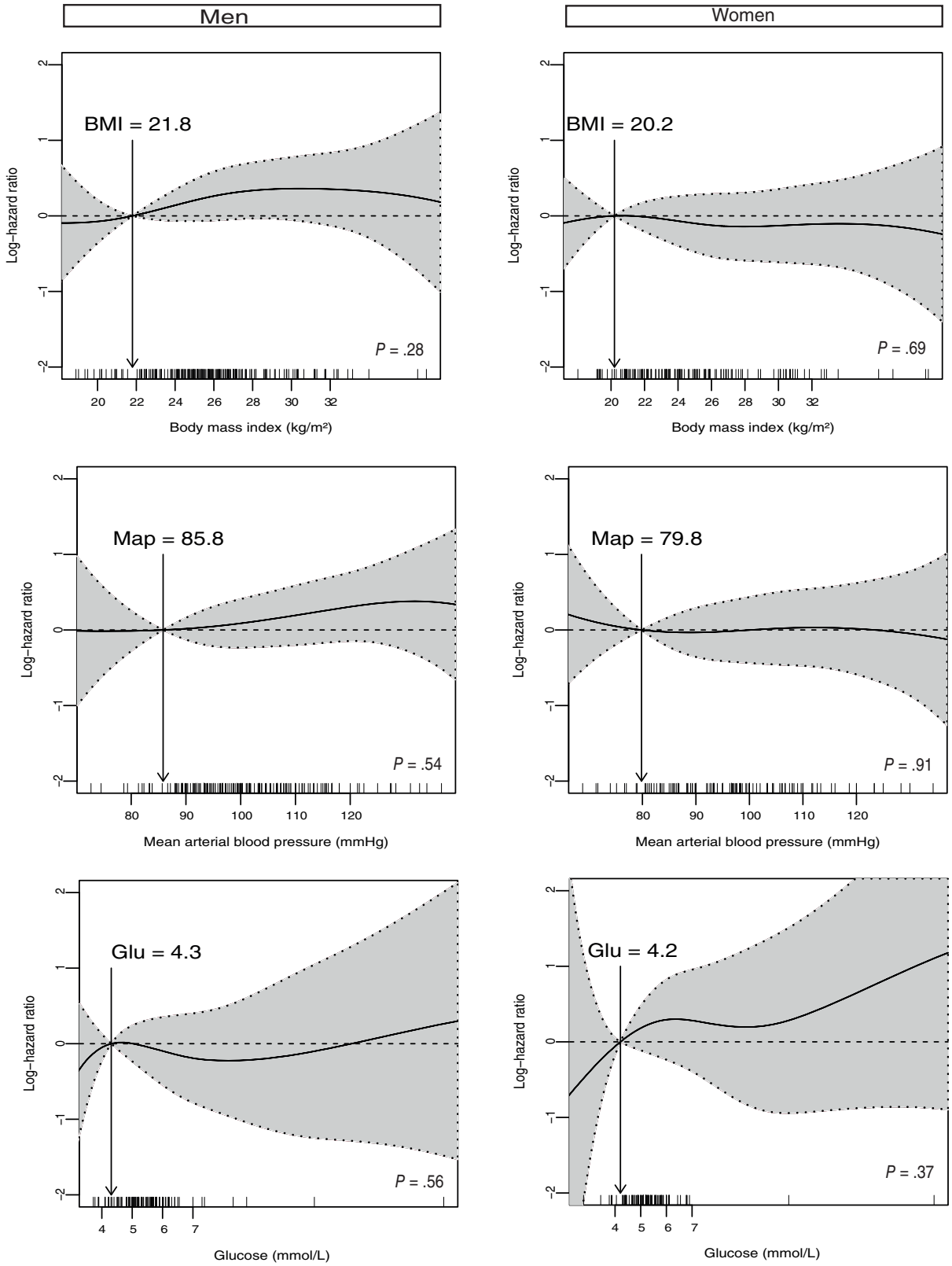

FIGURE 1 Hazard ratio (95% confidence interval) of small intestine cancer (N = 214) across levels of metabolic factors, by sex. The models were adjusted for smoking status and fasting status, stratified by cohort and categories of birth year

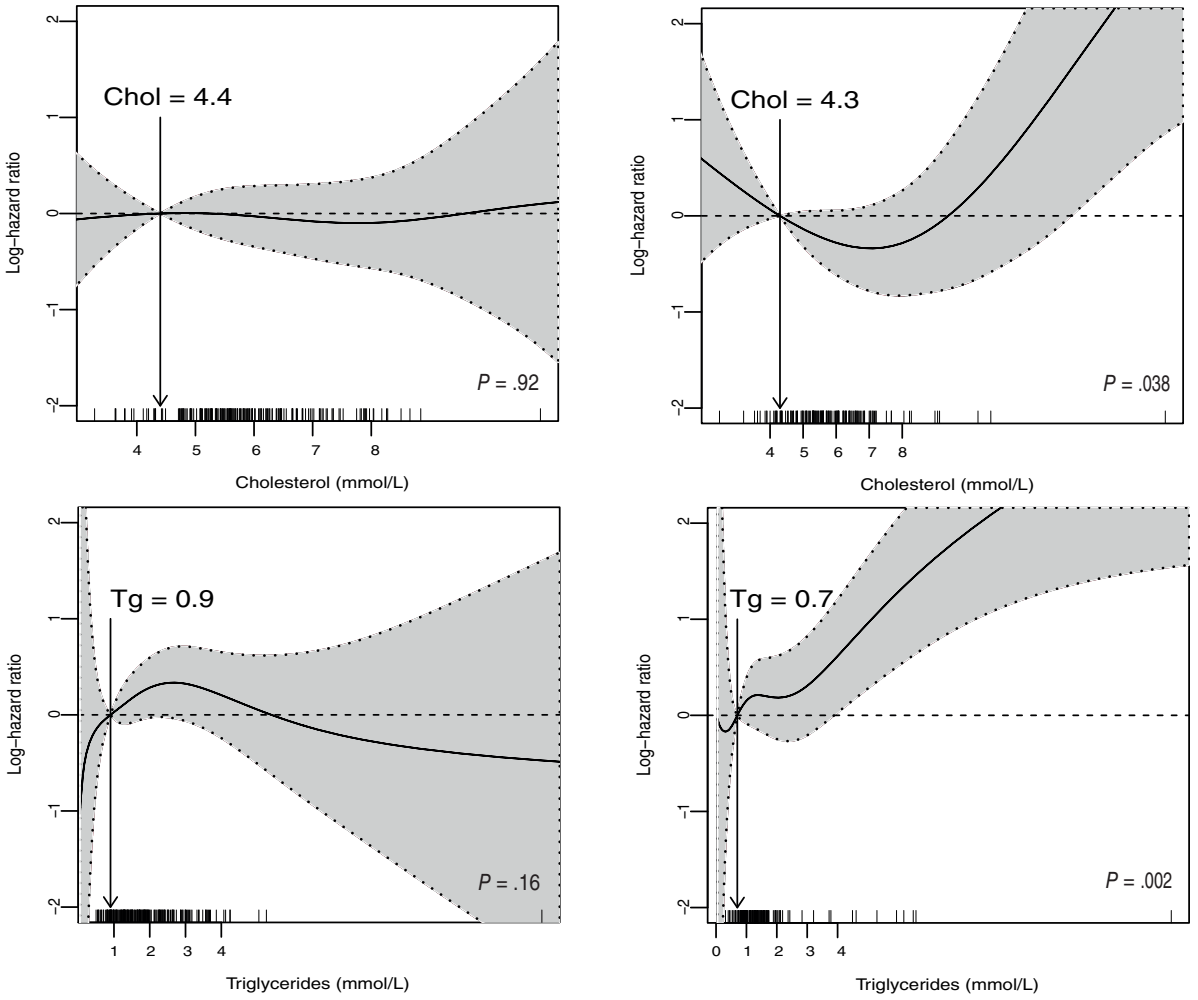

FIGURE 1 (Continued)

SD increment. Participants were followed from baseline until their first cancer diagnosis, emigration or death, whichever occurred first. All models were stratified by cohort and categories of birth year, and adjusted models additionally included BMI (except when BMI or the MetS was the exposure) and smoking status (never, former, current smokers) as covariables. *P*-values for linear trends across quartiles of metabolic factors were derived from Wald test statistics for each metabolic factor included as a continuous quartile variable (ranked 1-4) in the model. We also investigated the shape of the association across the full exposure range of each metabolic factor using penalized splines with three degrees of freedom, and the same strata and adjustments as previously described.

We evaluated cohort and smoking interactions with metabolic factors and the MetS in relation to risk of small intestine cancer, using the Wald statistics of product terms of cohort and each metabolic factor or the MetS as z-score. As the HR for the MetS and small intestine cancer among women appeared greater than the sum of each individual component, we also performed Wald tests of interaction for the product term of each pairwise combination of metabolic factors as continuous z-scores. Furthermore, subtypes were analyzed in a similar way as above. The results for adenocarcinoma and siNETs by sex are presented.

The data were analyzed using the statistical software package SAS release 9.4 (SAS Institute, Cary, NC), and spline analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

The 403 265 men in the study were on average 43.0 (SD 8.8) years old and had a mean BMI of 25.6 (SD 3.4) kg/m^2 at baseline, and the 404 220 women were on average 42.9 (SD 9.6) years old and had a mean BMI of 24.6 (4.3) kg/m^2 (Table 1). During a median 16.9 years of follow-up, 195 men and 144 women were diagnosed with a cancer of the small intestine; 184 with siNET, 99 with adenocarcinoma and 56 with small intestine cancer of other or unknown type.

Analysis of the shape of the association between metabolic factors and the risk of small intestine cancer virtually showed no associations across the range of exposures, with the exception of a u-shaped association for cholesterol among women, and a positive linear association for triglycerides among women (Figure 1). Triglycerides were also positively associated with small intestine cancer among women in

TABLE 2 Hazard ratio (95% confidence interval) of cancer of the small intestine related to different metabolic risk factors categorized in quintiles in 403 265 men and 404 220 women

		Men				Women			
Exposure in quintiles		Mean (SD)	Cases, N	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Mean (SD)	Cases, N	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]
BMI, kg/m^2	1	21.8 (1.3)	38	Reference	Reference	20.2 (1.2)	29	Reference	Reference
	2	24.3 (0.7)	43	1.07 (0.69-1.66)	1.08 (0.70-1.67)	22.7 (0.7)	41	1.20 (0.75-1.94)	1.21 (0.75-1.95)
	3	26.3 (0.8)	63	1.52 (1.01-2.28)	1.53 (1.02-2.29)	25.0 (1.0)	38	0.98 (0.60-1.61)	0.99 (0.60-1.61)
	4	30.1 (2.7)	51	1.30 (0.85-1.98)	1.31 (0.86-2.00)	30.4 (3.7)	36	0.90 (0.54-1.48)	0.90 (0.55-1.49)
P trend				0.090	0.084			0.44	0.46
Mean arterial pressure, mmHg	1	85.8 (4.7)	40	Reference	Reference	79.7 (4.5)	24	Reference	Reference
	2	94.6 (2.3)	48	1.10 (0.72-1.67)	1.08 (0.71-1.64)	89.0 (2.7)	37	1.20 (0.72-2.02)	1.22 (0.73-2.04)
	3	101.1 (2.6)	46	1.01 (0.66-1.55)	0.98 (0.63-1.50)	95.8 (2.8)	36	1.11 (0.65-1.87)	1.13 (0.67-1.92)
	4	113.4 (8.2)	60	1.22 (0.81-1.84)	1.15 (0.75-1.75)	109.3 (9.1)	47	1.08 (0.64-1.81)	1.12 (0.66-1.92)
P trend				0.41	0.62			0.95	0.82
Glucose, mmol/L	1	4.3 (0.6)	30	Reference	Reference	4.2 (0.5)	16	Reference	Reference
	2	5.0 (0.4)	25	0.83 (0.49-1.41)	0.82 (0.48-1.40)	4.8 (0.4)	24	1.48 (0.79-2.79)	1.49 (0.79-2.81)
	3	5.5 (0.4)	40	1.27 (0.79-2.05)	1.25 (0.78-2.01)	5.3 (0.4)	24	1.43 (0.76-2.69)	1.45 (0.77-2.73)
	4	6.7 (1.8)	28	0.89 (0.53-1.50)	0.86 (0.51-1.45)	6.3 (1.5)	32	1.79 (0.98-3.28)	1.85 (1.00-3.41)
P trend				0.88	0.99			0.080	0.066
Cholesterol, mmol/L	1	4.4 (0.5)	39	Reference	Reference	4.3 (0.5)	29	Reference	Reference
	2	5.4 (0.3)	56	1.29 (0.86-1.95)	1.27 (0.84-1.91)	5.1 (0.3)	35	1.01 (0.61-1.65)	1.01 (0.61-1.65)
	3	6.1 (0.3)	51	1.11 (0.73-1.69)	1.07 (0.70-1.63)	5.8 (0.3)	38	0.93 (0.57-1.53)	0.94 (0.57-1.54)
	4	7.3 (0.8)	49	1.01 (0.66-1.54)	0.95 (0.62-1.46)	7.0 (0.8)	42	0.81 (0.49-1.33)	0.81 (0.49-1.34)
P trend				0.75	0.55			0.35	0.36
Triglycerides, mmol/L	1	0.9 (0.2)	40	Reference	Reference	0.7 (0.1)	21	Reference	Reference
	2	1.4 (0.3)	48	1.16 (0.76-1.77)	1.13 (0.74-1.73)	1.0 (0.1)	34	1.55 (0.90-2.67)	1.57 (0.91-2.71)
	3	1.9 (0.4)	53	1.28 (0.85-1.93)	1.22 (0.81-1.86)	1.3 (0.2)	42	1.78 (1.05-3.01)	1.83 (1.07-3.13)
	4	3.6 (1.7)	53	1.31 (0.87-1.98)	1.22 (0.79-1.88)	2.3 (1.0)	45	1.75 (1.03-2.98)	1.88 (1.09-3.26)
P trend				0.17	0.35			0.042	0.026
MetS	1	−1.2 (0.4)	7	Reference	Reference	−1.2 (0.4)	27	Reference	Reference
	2	−0.4 (0.2)	19	0.75 (0.43-1.31)	0.75 (0.43-1.30)	−0.4 (0.2)	24	2.25 (0.94-5.38)	2.25 (0.94-5.37)
	3	0.2 (0.2)	34	0.86 (0.51-1.45)	0.85 (0.51-1.44)	0.2 (0.2)	31	3.49 (1.52-8.00)	3.47 (1.51-7.97)
	4	1.3 (0.7)	34	1.06 (0.64-1.76)	1.05 (0.63-1.73)	1.4 (0.7)	39	2.75 (1.17-6.45)	2.74 (1.17-6.42)
P trend				0.62	0.66			0.026	0.027

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a]Calculated from Cox regression models, with age as time scale, stratified by cohort and categories of birth year.

[b]Additionally adjusted for smoking status and BMI (except BMI and MetS quartiles).

TABLE 3 Hazard ratio (95% confidence interval) of cancer of the small intestine for continuous z-score of metabolic factors, single and combined (MetS) in 403 265 men and 404 220 women

	Men (N = 195 cases)		Women (N = 144 cases)	
Exposure	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]
BMI	1.11 (0.96-1.28)	1.11 (0.97-1.28)	0.96 (0.81-1.14)	0.96 (0.81-1.15)
Mean arterial pressure	1.09 (0.95-1.26)	1.07 (0.93-1.24)	0.99 (0.84-1.17)	1.00 (0.84-1.20)
Log Glucose	0.98 (0.82-1.18)	0.97 (0.80-1.16)	1.13 (0.94-1.35)	1.14 (0.95-1.37)
Cholesterol	0.99 (0.86-1.14)	0.97 (0.84-1.12)	0.95 (0.81-1.13)	0.96 (0.81-1.13)
Log Triglycerides	1.08 (0.94-1.25)	1.05 (0.90-1.22)	1.19 (1.02-1.40)	1.23 (1.04-1.46)
MetS	1.07 (0.88-1.28)	1.06 (0.88-1.28)	1.25 (1.02-1.52)	1.25 (1.02-1.52)

Abbreviations: BMI, body mass index; CI, confidence interval; MetS, metabolic score; HR, hazard ratio.
[a]Calculated from Cox regression models, with age as time scale, stratified by cohort and categories of birth year.
[b]Additionally adjusted for smoking status and BMI (except z-score of BMI and MetS).

adjusted analyses of quartiles (HR, fourth vs first quartile, 1.88, 95% CI 1.09-3.26, *P* for trend = .03) (Table 2) and z-scores (HR per SD, 1.23, 95% CI 1.04-1.46) (Table 3). Despite the lack of association between other single metabolic factors and risk among women, a strong positive association was found for the MetS in the continuous model (HR per SD, 1.25, 95% CI 1.02-1.52) and by quartiles (HR, fourth vs first quartile, 2.74, 95% CI 1.17-6.42, *P* for trend = .03). Pairwise interaction tests between z-scores of single metabolic factors showed significant positive associations between triglycerides and cholesterol (*P* = .0005) and between glucose and MAP (*P* = .009) in women (Table S1). There were no associations between single metabolic factors or the MetS and risk of small intestine cancer among men.

The associations between metabolic factors and small intestine cancer risk did not differ by cohort or smoking status (*P* for interaction ≥.05 for all).

In relation to subtypes, glucose concentrations were positively associated with adenocarcinoma in women (HR per SD, 1.39, 95% CI 1.07-1.79 and in trend for the MetS (1.31, 95% CI 0.93-1.85) (Table 4; Tables S2 and S3). No other associations were observed in relation to adenocarcinoma or siNETs in women or men.

4 | DISCUSSION

This large prospective cohort study of metabolic factors and small intestine cancer showed a positive linear association between triglyceride levels and the risk of small intestine cancer in women. Moreover, triglycerides and total cholesterol, and MAP and glucose, interacted positively in women, resulting in a strong positive association between the MetS and risk of small intestine cancer. The MetS and glucose were further positively associated with adenocarcinoma of the small intestine in women. No associations were observed among men.

Apart from BMI, we are not aware of other studies investigating the relation between metabolic factors and risk of small intestine cancer. A rare cancer, such as small intestine cancer, requires a large sample size and/or long follow-up to acquire a sufficient number of events, which we did have through the pooling of six European cohorts. Follow-up for cancer incidence and mortality was long and virtually complete in our study through record linkages with high-quality national registers.[20] Yet, the modest number of small intestine cancers, histological subtypes in particular, remains the main limitation of our study, which resulted in limited statistical power and potentially false positive or negative findings. For example, the positive associations for glucose among women, and BMI among men, were fairly linear and nearly reached statistical significance, supporting potentially true positive associations, as previously reported for BMI among men.[12] Moreover, although we accounted for smoking and BMI (where appropriate) in our analyses, the results might still be confounded by other factors such as lifestyle and sociodemographic factors not available to us. In lack of more specific markers of body fatness and lipoproteins, respectively, our study was limited to the use of BMI and total cholesterol level.

Among women, we found a positive association between triglyceride levels and risk of small intestine cancer. Such association does find some support in experimental studies. For example, Min mice feature high concentration of serum triglycerides, and these have been found to accumulate lipids in intestinal polyps,[22] and oxidant-related triglycerides in these mice have been found to be increased in the course of intestinal polyp formation.[23] However, the biological reason for a positive association between triglycerides and small intestine cancer among women, but not among men, is unclear. In our study, cholesterol was not associated with the risk of small intestine cancer, but interacted positively with triglycerides on risk among women. Sex differences in lipid and lipoprotein metabolism contribute to sex differences in cardio-vascular risk. Complex mechanisms including hormonal effects mediated by genes on X chromosome are involved.[24] These sex-specific mechanisms may also be involved in cancer risk. We speculate that sex hormones may partially underlie the observed interaction between cholesterol and triglycerides among women, and a differential association between triglycerides and small intestine cancer between men and women. However, the sex differences observed in our study require further investigation.

The by far largest prospective study to date on BMI and risk of small intestine cancer (n = 1162), which had some overlap with

TABLE 4 Hazard ratio (95% confidence interval) for subtypes of cancer of the small intestine for continuous z-score of metabolic factors, single and combined (MetS) in 403 265 men and 404 220 women

	Adenocarcinomas (N = 99)				Neuroendocrine tumors (NETs) (N = 184)			
	Men (N = 52)		Women (N = 47)		Men (N = 107)		Women (N = 77)	
Exposure	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]
BMI	0.99 (0.74-1.31)	0.99 (0.74-1.32)	0.93 (0.68-1.26)	0.93 (0.68-1.27)	1.17 (0.97-1.40)	1.17 (0.97-1.41)	0.99 (0.79-1.25)	0.99 (0.79-1.25)
Mean arterial pressure	0.84 (0.63-1.13)	0.84 (0.62-1.14)	0.85 (0.62-1.15)	0.86 (0.63-1.18)	1.12 (0.94-1.35)	1.09 (0.89-1.32)	1.04 (0.82-1.30)	1.05 (0.82-1.33)
Log glucose	1.03 (0.75-1.40)	1.05 (0.77-1.43)	1.34 (1.04-1.72)	1.39 (1.07-1.79)	1.03 (0.80-1.31)	1.00 (0.78-1.29)	1.10 (0.85-1.42)	1.09 (0.84-1.42)
Cholesterol	0.91 (0.69-1.21)	0.91 (0.68-1.21)	0.98 (0.73-1.31)	0.98 (0.73-1.32)	0.99 (0.82-1.20)	0.96 (0.79-1.17)	0.99 (0.79-1.25)	0.99 (0.79-1.25)
Log Triglycerides	0.89 (0.67-1.19)	0.89 (0.66-1.21)	1.18 (0.89-1.56)	1.24 (0.92-1.66)	1.20 (0.99-1.44)	1.15 (0.94-1.40)	1.19 (0.96-1.48)	1.22 (0.96-1.54)
MetS[4]	0.90 (0.63-1.28)	0.89 (0.63-1.27)	1.32 (0.93-1.86)	1.31 (0.93-1.85)	1.11 (0.86-1.43)	1.10 (0.85-1.42)	1.26 (0.95-1.67)	1.25 (0.95-1.66)

Abbreviations: CI, confidence interval; BMI, body mass index; HR, hazard ratio; MetS, metabolic score.
[a]Calculated from Cox regression models, with age as time scale, stratified by cohort and categories of birth year.
[b]Additionally adjusted for smoking status and BMI (except BMI and MetS).

participants of the current study, showed a positive association in men, but not in women, similar to the pattern observed in our study as well as for studies of colorectal cancer.[12] Another cohort study with 237 cases of small intestine cancer showed a positive association overall, but did not investigate the association separately among men and women.[16] That study, like ours, suggested a positive, albeit non-significant, association between BMI and carcinoid tumors only. Other prospective studies have been substantially smaller.[13-18] The mechanistic pathways that would potentially link obesity to small intestine cancers, specifically among men and for carcinoid tumors, are unclear. Possible mechanisms include changes in underlying pathogenetic pathways including metabolic factors, hormones, including sex-hormones and inflammatory factors.[25] Obesity leads to a number of pathophysiologic changes including dyslipidemia, hyperglycemia and inflammation,[26-28] which have been suggested to promote tumor development and growth.[28] In colon cancer, the largest proportion of the association of adiposity was mediated by high-density lipoprotein cholesterol, non-high-molecular-weight adiponectin and soluble leptin receptor.[29] Differences in the association between men and women were attributed to reactive oxygen metabolites and C-peptide.[29] However, a mechanistic pathway through lipids and glucose specifically among men are not supported by our results.

Despite that, no other metabolic factor than triglycerides was positively associated with small intestine cancer among women, a strong positive association was observed for the MetS, suggesting synergistic positive effects of individual metabolic factors. Interaction tests showed pairwise interactions between four of the metabolic factors on risk, which has never been observed before in relation to any cancer form investigated in the Me-Can project. Future studies will show whether these findings apply also to other populations.

In conclusion, in this large prospective cohort study, increasing triglyceride levels and a MetS comprising five metabolic factors were associated with an increased risk of small intestine cancer in women. Positive interactions were observed between several metabolic factors on risk among women. In contrast, no associations were observed among men. Our findings are novel, and further studies are warranted.

ACKNOWLEDGMENTS

We thank all participants of the cohorts. In Norway, we thank the screening team of the former National Health Screening Service of Norway, now the Norwegian Institute of Public Health. We also thank all scientists and organizations behind the VIP cohort and Åsa Ågren and her team at the department of biobank research for coordinating the VIP data. In the MPP, we thank Anders Dahlin, database manager of the cohort. In the VHM&PP, we thank Elmar Stimpfl and Karin Parschalk for excellent technical support as well as Markus Wallner, Christian Bernhard, and Gabriela Dür from the Vorarlberg State Government.

CONFLICT OF INTEREST

There are no competing financial interests in relation to this work.

ETHICS APPROVAL

The study including informed consent was approved by ethical committees in Norway, Sweden and Austria.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from cohort committees and national registers of the cohorts and countries involved. Restrictions apply to the availability of these data, which were used under license for this study. Data are available after contact with the corresponding author conditional on permission from the involved cohort committees and national registers.

ORCID

Gabriele Nagel https://orcid.org/0000-0001-6185-8535
Tone Bjørge https://orcid.org/0000-0002-9096-5257
Christel Häggström https://orcid.org/0000-0001-6808-4405
Anders Engeland https://orcid.org/0000-0001-5620-9207
Stanley Teleka https://orcid.org/0000-0002-9343-8399
Tanja Stocks https://orcid.org/0000-0002-0904-0557

REFERENCES

1. DeSantis CE, Kramer JL, Jemal A. The burden of rare cancers in the United States. *CA Cancer J Clin*. 2017;67:261-272.
2. Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol*. 2017;18:1022-1039.
3. Barsouk A, Rawla P, Barsouk A, Thandra KC. Epidemiology of cancers of the small intestine: trends, risk factors, and prevention. *Med Sci (Basel)*. 2019;7:46.
4. Pan SY, Morrison H. Epidemiology of cancer of the small intestine. *World J Gastrointest Oncol*. 2011;3:33-42.
5. Legué LM, Bernards N, Gerritse SL, et al. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: a population-based study in the Netherlands. *Acta Oncol*. 2016;55:1183-1189.
6. NORDCAN. Cancer stat fact sheets Nordic countries - Small intestineMal. http://www-dep.iarc.fr/NORDCAN/english/StatsFact.asp?cancer=100&country=0
7. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Arch Physiol Biochem*. 2008;114:71-83.
8. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet*. 2014;384:755-765.
9. Stocks T, Bjørge T, Ulmer H, et al. Metabolic risk score and cancer risk: pooled analysis of seven cohorts. *Int J Epidemiol*. 2015;44:1353-1363.
10. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35:2402-2411.
11. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol*. 2015;16:36-46.
12. Bjørge T, Tretli S, Engeland A. Height and body mass index in relation to cancer of the small intestine in two million Norwegian men and women. *Br J Cancer*. 2005;93:807-810.
13. Bennett CM, Coleman HG, Veal PG, Cantwell MM, Lau CCL, Murray LJ. Lifestyle factors and small intestine adenocarcinoma risk: a systematic review and meta-analysis. *Cancer Epidemiol*. 2015;39:265-273.
14. Boffetta P, Hazelton WD, Chen Y, et al. Body mass, tobacco smoking, alcohol drinking and risk of cancer of the small intestine—a pooled analysis of over 500,000 subjects in the Asia Cohort Consortium. *Ann Oncol*. 2012;23:1894-1898.
15. Samanic C, Chow W-H, Gridley G, Jarvholm B, Fraumeni JF Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*. 2006;17:901-909.
16. Cross AJ, Hollenbeck AR, Park Y. A large prospective study of risk factors for adenocarcinomas and malignant carcinoid tumors of the small intestine. *Cancer Causes Control*. 2013;24:1737-1746.
17. Lu Y, Cross AJ, Murphy N, et al. Comparison of abdominal adiposity and overall obesity in relation to risk of small intestinal cancer in a European Prospective Cohort. *Cancer Causes Control*. 2016;27:919-927.
18. Pang Y, Kartsonaki C, Guo Y, et al. Adiposity and risks of colorectal and small intestine cancer in Chinese adults: a prospective study of 0.5 million people. *Br J Cancer*. 2018;119:248-250.
19. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ*. 2017;356:j477.
20. Stocks T, Borena W, Strohmaier S, et al. Cohort profile: the metabolic syndrome and cancer project (Me-Can). *Int J Epidemiol*. 2010;39:660-667.
21. Häggström C, Jonsson H, Bjørge T, et al. Linear age-course effects on the associations between body mass index, triglycerides, and female breast and male liver cancer risk: an internal replication study of 800,000 individuals. *Int J Cancer*. 2020;146:58-67.
22. Mutoh M, Komiya M, Teraoka N, et al. Overexpression of low-density lipoprotein receptor and lipid accumulation in intestinal polyps in Min mice. *Int J Cancer*. 2009;125:2505-2510.
23. Ikeda K, Mutoh M, Teraoka N, Nakanishi H, Wakabayashi K, Taguchi R. Increase of oxidant-related triglycerides and phosphatidylcholines in serum and small intestinal mucosa during development of intestinal polyp formation in Min mice. *Cancer Sci*. 2011;102:79-87.
24. Palmisano BT, Zhu L, Eckel RH, Stafford JM. Sex differences in lipid and lipoprotein metabolism. *Mol Metab*. 2018;15:45-55.
25. Donohoe CL, Lysaght J, O'Sullivan J, Reynolds JV. Emerging concepts linking obesity with the hallmarks of cancer. *Trends Endocrinol Metab*. 2017;28:46-62.
26. Allott EH, Hursting SD. Obesity and cancer: mechanistic insights from transdisciplinary studies. *Endocr Relat Cancer*. 2015;22:R365-R386.
27. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev*. 2015;16:1-12.
28. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: tumor microenvironment and inflammation. *J Clin Oncol*. 2016;34:4270-4276.
29. Aleksandrova K, Drogan D, Boeing H, et al. Adiposity, mediating biomarkers and risk of colon cancer in the European prospective investigation into cancer and nutrition study. *Int J Cancer*. 2014;134:612-621.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Nagel G, Bjørge T, Jaensch A, et al. Metabolic factors and the risk of small intestine cancers: Pooled study of 800 000 individuals in the metabolic syndrome and cancer project. *Int. J. Cancer*. 2021;1–9. https://doi.org/10.1002/ijc.33530